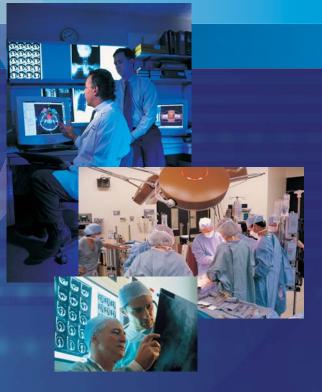
Canadian Agency for Drugs and Technologies in Health Agence canadienne des médicaments et des technologies de la santé

### TECHNOLOGY REPORT

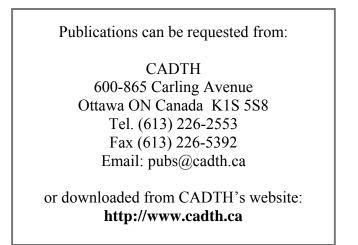


Long-Acting Beta<sub>2</sub>-Agonist and Inhaled Corticosteroid Combination Therapy for Adult Persistent Asthma: Systematic Review of Clinical Outcomes and Economic Evaluation



Supporting Informed Decisions

Until April 2006, the Canadian Agency for Drugs and Technologies in Health (CADTH) was known as the Canadian Coordinating Office for Health Technology Assessment (CCOHTA).



*Cite as:* Bond K, Coyle D, O'Gorman K, Coyle K, Spooner C, Lemière C, Vandermeer B, Tjosvold L, Rowe BH. *Long-Acting Beta*<sub>2</sub>-Agonist and Inhaled Corticosteroid Combination Therapy for Adult *Persistent Asthma: Systematic Review of Clinical Outcomes and Economic Evaluation*. [Technology report number 122]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.

Production of this report is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Prince Edward Island, Saskatchewan, and Yukon. The Canadian Agency for Drugs and Technologies in Health takes sole responsibility for the final form and content of this report. The views expressed herein do not necessarily represent the views of Health Canada or any provincial or territorial government.

Reproduction of this document for non-commercial purposes is permitted provided appropriate credit is given to CADTH.

CADTH is funded by Canadian federal, provincial, and territorial governments.

Legal Deposit – 2009 National Library of Canada ISBN: 978-926680-24-8 (print) ISBN: 978-1-926680-25-5 (online) H0480 – November 2009

PUBLICATIONS MAIL AGREEMENT NO. 40026386 RETURN UNDELIVERABLE CANADIAN ADDRESSES TO CANADIAN AGENCY FOR DRUGS AND TECHNOLOGIES IN HEALTH 600-865 CARLING AVENUE OTTAWA ON K1S 5S8 **Canadian Agency for Drugs and Technologies in Health** 

#### Long-Acting Beta<sub>2</sub>-Agonist and Inhaled Corticosteroid Combination Therapy for Adult Persistent Asthma: Systematic Review of Clinical Outcomes and Economic Evaluation

Kenneth Bond, BEd MA<sup>1</sup> Douglas Coyle, PhD<sup>2</sup> Kathleen O'Gorman, MPH<sup>1</sup> Kathryn Coyle, BScPharm MSc<sup>2</sup> Carol Spooner, BScN MSc<sup>1</sup> Catherine Lemière, MD MSc<sup>3</sup> Ben Vandermeer, MSc<sup>1</sup> Lisa Tjosvold, MLIS<sup>1</sup> Brian H. Rowe, MD MSc CCFP(EM) FCCP<sup>4</sup>

November 2009

<sup>&</sup>lt;sup>1</sup> Capital Health and University of Alberta Evidence-based Practice Centre, Edmonton, AB

<sup>&</sup>lt;sup>2</sup> Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON

<sup>&</sup>lt;sup>3</sup> Sacré-Coeur Hospital and Department of Medicine, University of Montreal, Montreal, QC

<sup>&</sup>lt;sup>4</sup> Department of Emergency Medicine, University of Alberta, Edmonton, AB

#### Reviewers

These individuals kindly provided comments on this report.

#### **External Reviewers**

D. W. Cockcroft, BSc MD FRCPC Professor, Respiratory Medicine University of Saskatchewan Saskatoon, SK

Carlo Marra, PharmD PhD Associate Professor Faculty of Pharmaceutical Sciences University of British Columbia Vancouver, BC Paul Hernandez, MDCM FRCPC Associate Professor of Medicine Dalhousie University Halifax, NS

Christopher J. Longo, BA (Economics) MSc (Physiology) PhD (Health Policy) Assistant Professor McMaster University School of Business Hamilton, ON

#### **CADTH Peer Review Group Reviewers**

Michelle L. McIsaac, MA Health Economist The University of Melbourne Parkville Victoria, AU Robert Dales, MD FRCPC MSc (Epidemiology) Professor of Medicine University of Ottawa Ottawa, ON

**Industry:** The following manufacturers were provided with an opportunity to comment on an earlier version of this report: Graceway Pharmaceuticals, GlaxoSmithKline Inc., Novartis Pharmaceuticals Canada Inc., Nycomed Canada Inc., and AstraZeneca Canada Inc. All comments that were received were considered when preparing the final report.

This report is a review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") that are available to CADTH. The accuracy of the contents of the source documentation on which this report is based is not warranted, assured, or represented in any way by CADTH, and CADTH does not assume responsibility for the quality, propriety, inaccuracies, or reasonableness of any statements, information, or conclusions contained in the source documentation.

CADTH takes sole responsibility for the final form and content of this report. The statements and conclusions in this report are those of CADTH and not of its Panel members or reviewers.

### Authorship

Kenneth Bond coordinated the project, selected trials, extracted data, performed quality assessment, summarized and interpreted data, and contributed to writing all sections of the report.

Douglas Coyle was the lead for the economic analysis; developed the methods for the economic analysis; selected studies; extracted, tabulated, analyzed, and interpreted the economic data; and contributed to writing the economic sections of the report.

Kathleen O'Gorman selected trials, extracted data, performed quality assessment, summarized and analyzed data, and contributed to writing the clinical sections of the report.

Kathryn Coyle assisted with the development of the methods for the economic analysis; selected studies; extracted, tabulated, and analyzed data; and contributed to writing the economic sections of the report.

Carol Spooner selected trials, extracted data, performed quality assessment, and contributed to writing and formatting the clinical sections of the report.

Catherine Lemière provided guidance on the development of the clinical review methods and was a content expert in clinical asthma management.

Ben Vandermeer performed the meta-analyses and other statistical analyses; provided methodological and statistical advice; and contributed to writing the analysis and results section of the report.

Lisa Tjosvold designed and executed the literature search strategies, wrote the search strategy section of the report and appendix, and managed the bibliographic information.

Brian H. Rowe was the overall research lead, assisted with the development of the clinical review methods; was a content expert in clinical asthma management; selected studies; tabulated, analyzed, and interpreted data; and contributed to writing all sections of the report.

All authors contributed to the revision of the report.

#### Acknowledgements

The authors are grateful to Mr. David Jones, Ms. Maria Ospina, and Ms. Jennifer Seida for their assistance with study selection, quality assessment, and data extraction for the clinical review. The authors thank Mr. Don Husereau (CADTH) for his guidance.

### **Conflicts of Interest**

Dr. Lemière has received funds from GlaxoSmithKline Inc. for an investigator-initiated study; consulting fees from GlaxoSmithKline Inc., AstraZeneca Canada Inc., and Novartis Pharmaceuticals Canada Inc.; and speaker fees from AstraZeneca Canada Inc., GlaxoSmithKline Inc., and Merck Frosst Canada Ltd.

Dr. Rowe has received funding from GlaxoSmithKline Inc. and AstraZeneca Canada Inc. for investigator-initiated studies and speaker fees from AstraZeneca Canada Inc. and GlaxoSmithKline Inc.

All other authors declare no conflicts of interest.

#### Long-Acting Beta<sub>2</sub>-Agonist and Inhaled Corticosteroid Combination Therapy for Adult Persistent Asthma: Systematic Review of Clinical Outcomes and Economic Evaluation

# **EXECUTIVE SUMMARY**

#### Issue

In 2005, 2.25 million Canadians aged 12 years or older were diagnosed with asthma (approximately 8.3% of the general population aged 12 years or older). Patients with asthma reported symptoms or attacks daily (14%) or several times per month (37%).

The Canadian Asthma Guidelines recommend the use of inhaled corticosteroid (ICS) and rescue short-acting beta<sub>2</sub>-agonist (SABA) agents in first-line medical management of chronic persistent asthma. The guidelines recommend add-on combination therapy of a long-acting beta<sub>2</sub>-agonist (LABA) with an ICS after failure to gain adequate control with ICS monotherapy. There are variations among provincial public drug plans in the criteria for reimbursement that stem from concerns about clinical care and the sustainability of drug funding given limited resources.

#### Objectives

This project aimed to evaluate the clinical efficacy, safety, and cost-effectiveness of LABA-ICS combination therapy for adults (12 years of age or older) who are diagnosed with persistent asthma. To achieve these objectives, the following research questions were proposed:

- What is the clinical efficacy of LABA plus ICS maintenance therapy compared with ICS monotherapy in steroid-naive patients with persistent asthma (ICS treatment-naive) aged 12 years or older?
- What is the clinical efficacy of LABA plus ICS maintenance therapy compared with ICS monotherapy in patients with persistent asthma aged 12 years or older who are being treated with an ICS?
- What is the comparative efficacy of salmeterol-fluticasone versus formoterol-budesonide maintenance therapy in patients with persistent asthma aged 12 years or older?
- Are there differences in adverse events between combination LABA-ICS treatment (for example, inhaled salmeterol-fluticasone and formoterol-budesonide combinations) and ICS monotherapy?
- Is there evidence that adding a LABA to an ICS allows for a reduction in the ICS dose (do LABAs have a steroid-sparing effect)?
- What is the cost-effectiveness of LABA plus ICS maintenance therapy compared with ICS monotherapy for ICS-naive patients and those uncontrolled on low- or medium-dose ICS monotherapy?
- What are the recommendations regarding LABA plus ICS use in Canadian, North American, and international (GINA) guidelines for the management of asthma?

#### **Clinical Review**

*Methods:* A systematic review was conducted to identify all randomized controlled trials (RCTs) that compared LABA-ICS with ICS monotherapy or another LABA-ICS combination therapy for the management of persistent adult asthma. Meta-analyses were performed when appropriate.

*Results:* Meta-analyses indicated that LABA-ICS has a clinically meaningful benefit compared with ICS monotherapy among steroid-naive adults in improving morning peak expiratory flow (PEF) and increasing the number of symptom-free days (SFDs). Assuming a study control-group

risk of exacerbation of approximately 50%, the number needed to treat to prevent one exacerbation was four (95% CI 3 to 24). This was based on one trial of 12 weeks' duration.

Thirty-seven RCTs evaluated the efficacy of LABA-ICS therapy compared with that of similardose ICS monotherapy. Meta-analyses showed that the use of LABA-ICS may have a clinically meaningful benefit compared with ICS monotherapy in improving morning and evening PEF and increasing the number of SFDs and days with optimal control. Assuming a study control-group risk of exacerbation of 27%, the number needed to treat to prevent one exacerbation was 19 (95% CI 13 to 38).

Thirty-one RCTs evaluated the efficacy of LABA-ICS therapy compared with that of higherdose ICS monotherapy. Meta-analyses indicated that the use of LABA-ICS may have a clinically meaningful benefit compared with ICS monotherapy in improving morning PEF, reducing the risk of an exacerbation and increasing the number of SFDs and days with optimal control. The results suggest that LABA-ICS is clinically equivalent to a higher-dose ICS in improving evening PEF, absolute and per cent-predicted forced expiratory volume in one second, reducing SABA use, and improving quality of life. Assuming a study control-group risk of exacerbation of 28%, the number needed to treat to prevent one exacerbation was 23 (95% CI 16 to 52).

Twelve RCTs evaluated the relative efficacy of various LABA-ICS therapies for adult persistent asthma. Meta-analyses indicated that there was no clinically meaningful benefit of using one LABA-ICS combination compared with another in improving pulmonary function, asthma symptom control, or health-related quality of life.

Twelve RCTs evaluated the potential steroid-sparing effects of LABA-ICS combination therapy compared with ICS monotherapy. Meta-analyses failed to indicate clinically meaningful differences between using LABA-ICS or ICS in any pulmonary function measures. The results suggest that a lower-dose LABA-ICS is equivalent to ICS in improving absolute and per cent-predicted forced expiratory volume in one second and reducing SABA use. The statistically significant differences favoured the use of LABA-ICS for an increase in SFDs and a reduction of mean ICS dose. Subgroup analyses indicated a statistically significant reduction in SABA use favouring the use of LABA-ICS for the step-down reduction of ICS. There was no clinically meaningful difference between the two treatments in health-related quality of life.

The safety of LABA-ICS combination therapy compared with that of ICS monotherapy was evaluated based on data from 79 RCTs. Among 10 key safety measures, worsening asthma was reduced by 22% (95% CI 34% to 10%) when LABA-ICS therapy was used. There were no statistically significant differences between the treatments for the remaining nine measures.

#### **Economic Analysis**

*Methods:* A systematic review of economic evaluations comparing the use of LABA-ICS combination therapy with ICS monotherapy in patients with asthma who were 12 years of age or older was conducted.

A Markov model was created to estimate the long-term costs and quality-adjusted life-years (QALYs) that were associated with four strategies relating to the optimum time to introduce

LABA in combination with ICS as initial therapy, after lack of control on low-dose ICS, after lack of control on medium-dose ICS, or after lack of control on high-dose ICS.

*Results:* The studies that were identified during the economic review had weaknesses in analysis, funding, and use of comparators. This supported the need for a full economic analysis from the Canadian context.

In comparing all four strategies, the incremental QALYs gained from introducing a LABA earlier are small at 12 weeks and one year. The total costs are higher the earlier a LABA is introduced. For treatment-naive patients, the incremental cost per QALY gained from treatment with LABA plus ICS instead of ICS monotherapy is \$3.3 million. For asthma that is uncontrolled on low-dose ICS, the incremental cost per QALY gained from treatment with LABA plus low-dose ICS instead of medium-dose ICS monotherapy is \$1.6 million. For asthma that is uncontrolled on medium-dose ICS, the incremental cost per QALY gained from treatment with LABA plus low-dose ICS instead of high-dose ICS monotherapy is \$1.6 million. For asthma that is uncontrolled on medium-dose ICS, the incremental cost per QALY gained from treatment with LABA plus medium-dose ICS instead of high-dose ICS monotherapy is \$190,000. The results were insensitive to changes in relevant parameters.

#### **Health Services Impact**

Based on data from British Columbia, in all scenarios, the forecasted expenditure for LABA-ICSs that are used by patients with asthma will increase during the next three years. Switching from the use of a low-dose LABA-ICS to a higher-dose ICS could produce cost savings of \$11,000 (0.1%) to \$44,000 (0.4%) per year. Switching from the use of a low- and medium-dose LABA-ICS to a higher-dose ICS could provide cost savings of \$125,000 (1.1%) to \$500,000 (4.6%) per year. If low- and medium-dose LABA-ICS combinations are switched to higher-dose ICS and patients on single-inhaler LABA-ICS therapy are given increased ICS, the cost savings range from \$270,000 (2.5%) to \$1.1 million (10%) per year. For these savings to be realized, it is necessary to delay the introduction of LABAs until a patient's asthma is uncontrolled on high-dose ICS monotherapy.

#### Conclusions

This review confirms that for most patients with persistent asthma, initial therapy and the only therapy that is needed is ICS. The LABA-ICS combination provides some benefit that is limited in the range of symptoms for which control is improved and in the clinical meaningfulness of the improvements. The efficacy and safety results suggest that there are often statistically significant but not clinically meaningful benefits from switching to combination therapy for the management of most asthma that is not controlled by the use of ICS. For asthma that is controlled on ICS, the addition of a LABA may help to reduce the amount of daily ICS used and may thereby reduce the risk that is associated with prolonged use of daily high- and moderate-dose ICS. In addition, the number and severity of exacerbations can be reduced with this management strategy. There are no clinically important differences between LABA-ICS combination therapies.

The cost-effectiveness analysis suggests that the introduction of a LABA before patients have tried high-dose ICS monotherapy may not be justified. The later a LABA is introduced into therapy, the more cost-effective the strategy becomes. The optimum strategy among the four that were considered occurred when patients started using a LABA after their asthma was uncontrolled by high doses of ICS. A sensitivity analysis revealed that these results were insensitive to changes in relevant parameters.

# **ACRONYMS AND ABBREVIATIONS**

AE	adverse event
AQLQ	Asthma Quality of Life Questionnaire
CI	confidence interval
CTS	Canadian Thoracic Society
$FEV_1$	forced expiratory volume in one second
GINA	Global Initiative for Asthma
GP	general practitioner
ICS	inhaled corticosteroid
IQR	interquartile range
LABA	long-acting beta2-agonist
MCID	minimal clinically important difference
min	minute
NAEPP	National Asthma Education and Prevention Program
PEF	peak expiratory flow
QALY	quality-adjusted life-year
RCT	randomized controlled trial
SABA	short-acting beta <sub>2</sub> -agonist
SFDs	symptom-free days

# TABLE OF CONTENTS

EXE	EXECUTIVE SUMMARYiv				
ACR	RONYI	MS AND ABBREVIATIONSv	'ii		
1	INTR 1.1 1.2 1.3	ODUCTION         Background and Setting in Canada         Current Clinical Practice         1.2.1 Clinical practice guidelines         Overview of Technology         1.3.1 Interventions         1.3.2 Patient group         1.3.3 Variation in Canadian provincial policies	1 2 3 4 4 4		
2	THE	SSUE	5		
3	OBJE	ECTIVES	6		
4	<b>CLIN</b> 4.1 4.2	CAL REVIEW         Methods         4.1.1       Literature searches         4.1.2       Selection criteria and method         4.1.3       Data extraction strategy.         4.1.4       Quality assessment         4.1.5       Data synthesis and analysis         1       Results         4.2.1       Quantity of research available         1       1.2.2         Study characteristics       1         4.2.3       Quality of included trials	7 7 9 0 1 3		
5	<b>ECOI</b> 5.1 5.2	NOMIC ANALYSIS3Review of Economic Studies35.1.1Methods35.1.2Results45.1.3Summary and discussion4Economic Evaluation45.2.1Objective45.2.2Methods45.2.3Results45.2.4Summary and Discussion4			
6	<b>HEAL</b> 6.1 6.2 6.3	TH SERVICES IMPACT	50 50		

7	DISC	JSSI	ON51
			mary of Results51
		7.1.1	
		7.1.2	2 Economic analysis
	7.2	Stre	ngths and Limitations of This Assessment
		7.2.′	1 Clinical review
		7.2.2	2 Economic analysis54
			eralizability of Findings55
	7.4	Kno	wledge Gaps55
8	CON	CLUS	SIONS
9	REFE	REN	ICES57
APP	ENDI	(1:	Literature Search Strategies
APP	ENDI	( 2:	Excluded Studies—Clinical Review
APP	ENDI	( 3:	Excluded Studies—Economic Review
APP	ENDI	( 4:	Forms
APP	ENDI>	( 5:	Methodological Quality of Studies Included in Clinical Review
APP	ENDI	6:	Characteristics of Studies Included in Clinical Review
APP	ENDI	(7:	Detailed Results of Clinical Review
APP	ENDI	( 8:	Appraisal of Canadian, North American, and International Clinical Practice
			Guidelines for the Use of Long-Acting Beta <sub>2</sub> -Agonist and Inhaled Corticosteroid
			Combination Therapy for Persistent Asthma
	ENDI		Quality Checklist for Evaluation of Economic Evaluations
			Characteristics of Economic Studies Not Reviewed in Main Report
			Review of Economic Studies Not Reviewed in the Main Report
			Characteristics of Economic Studies Reviewed in the Main Report
			Methodological Quality of Economic Studies Reviewed in Main Report
			Values for Economic Analysis
			Detailed Results of Economic Analysis
			Methods for Budget Impact Analysis
APP	ENDI	( 17:	Detailed Results of the Budget Impact Analysis

# **1** INTRODUCTION

# 1.1 Background and Setting in Canada

In 2005, 2.25 million Canadians who were aged 12 years or older (8.3% of the general population aged 12 years or older) were diagnosed with asthma.<sup>1</sup> Patients with asthma reported symptoms or attacks daily (14%) or several times per month (37%).<sup>2</sup> From 1998 to 2001 approximately 80,000 people were admitted to hospital because of asthma.<sup>2</sup>

Asthma is characterized by airway inflammation, variable expiratory airflow obstruction, and airway hyper-responsiveness. Many pharmacologic and non-pharmacologic treatments exist, but the control of asthma has been elusive for many patients.<sup>3</sup> After trigger avoidance and environmental control (for example, smoking cessation, air quality improvement, reduction of occupational exposures) and the reduction of allergen exposure, the first-line pharmacologic treatment of persistent asthma is inhaled corticosteroids (ICSs). According to clinical practice guidelines,<sup>4</sup> the use of ICS is the initial maintenance therapy for patients with asthma. There is insufficient evidence to recommend the initial use of combination therapy in steroid-naive patients who are diagnosed with mild asthma.<sup>5</sup>

Long-acting beta<sub>2</sub>-agonists (LABAs) are bronchodilators that relax muscles in the airways to improve breathing. They are effective when used with ICSs. They are not to be used as monotherapy for several reasons. LABA monotherapy has been shown to increase the number of severe and life-threatening asthma exacerbations and asthma-related deaths.<sup>6</sup> The combination therapy of a LABA and ICS effectively targets the pathophysiological processes in asthma by addressing inflammation and airway spasm. A synergistic effect seems to result from the combination of these two agents.<sup>7</sup>

Patients with asthma who have persistent symptoms need maintenance therapy with ICS.<sup>4,8</sup> The patients who continue to experience symptoms while on moderate-dose ICS therapy often have a second or third treatment added. These additions may include LABAs or leukotriene receptor antagonists. LABA-ICS combination therapy is recommended<sup>4,8,9</sup> and used most commonly in adults. LABAs and ICS are available and may be taken as individual medications (Table 1). Combination LABA-ICS medications are available in fixed-dose inhalers: salmeterol-fluticasone (Advair; GlaxoSmithKline Inc.) and formoterol-budesonide (Symbicort, AstraZeneca Canada Inc).

There are many controversies regarding the role of combination therapies in treating chronic and acute asthma. For example, formoterol-budesonide is marketed as a variable-dose treatment ("variable dose" is used here to refer to an adjustable maintenance dose of LABA-ICS with short-acting beta<sub>2</sub>-agonist [SABA] for relief and to a fixed maintenance dose of additional LABA-ICS for relief that can be adjusted according to the symptoms), in contrast to salmeterol-fluticasone, which is a fixed-dose treatment that, if taken regularly, may be used to control asthma symptoms. The proposed advantage of the variable-dose approach compared with the fixed-dose approach is the reduced need for ICS over time and better control. There is debate about the merits of both strategies.<sup>10,11</sup> In addition, the role of combination therapy in regaining and maintaining control after an exacerbation of asthma has been examined in only one published trial.<sup>12</sup>

## **1.2 Current Clinical Practice**

The goal of asthma management includes the alleviation of breathlessness, the improvement of airway functioning (and thus health status), the prevention and treatment of exacerbations, and the reduction of mortality. These aims can be achieved by some patients using ICS monotherapy. Guidelines on treatment and management recommend the addition of a LABA for asthma that cannot be optimally controlled using ICS alone.<sup>4</sup>

For clinicians, there are three treatment questions on the use of a LABA and ICS in managing asthma:

- 1. Should an adult with intermittent to mild asthma who is symptomatic on short-acting betaagonist therapy (steroid-naive) receive ICS monotherapy or LABA-ICS combination therapy as initial maintenance therapy?
- 2. Should an adult with chronic asthma who is symptomatic on ICS therapy receive an increased dose of ICS monotherapy or an addition of a LABA to existing therapy to achieve asthma control?
- 3. Should an adult with chronic asthma that is controlled on ICS therapy maintain ICS monotherapy or receive a reduction in ICS dose and the addition of a LABA to maintain asthma control?

Differences in the stability and severity of a patient's asthma distinguish which of these treatment questions are asked and how they are answered according to clinical guidelines (Figure 1).

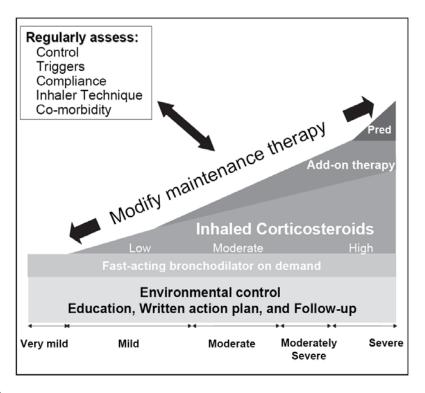


Figure 1: Continuum of Asthma Management\*

\*This information was originally published in the Canadian Respiratory Journal 2004;11(Supp A):9A-18A.

Pred = prednisone.

#### 1.2.1 Clinical practice guidelines

To obtain the answers to the treatment questions, clinicians can consult any of three clinical practice guidelines: the Canadian Consensus Guidelines,<sup>4</sup> which were developed by the Canadian Thoracic Society (CTS); the National Asthma Education and Prevention Program (NAEPP) guidelines,<sup>9</sup> which were developed with the National Heart, Lung, and Blood Institute (NHLBI) of the United States National Institutes of Health (NIH); and the Global Initiative for Asthma (GINA) guidelines<sup>8</sup> (Appendix 8).

In the guidelines, conventional evidence hierarchies are used to grade the strength of the evidence (based on study design and data) on which the recommendations are based. (The evidence grade does not reflect the clinical importance of the recommendation.) The highest grade of evidence is most often used to support recommendations. The guidelines vary in the frequency with which they link specific recommendations to the supporting evidence. All guidelines recommendation about the comparative efficacy of LABA-ICS combination products (for example, salmeterol-fluticasone and formoterol-budesonide) for maintenance therapy. No information in any of the guidelines can be applied to questions about the clinical benefit of switching from fixed-dose to variable-dose combination therapy.

For patients who are using ICS but who remain symptomatic, the CTS guidelines recommend that the addition of a LABA provides more clinical benefit than doubling the dose of ICS (highest level of supporting evidence). NAEPP and GINA link the recommendations for this indication to the highest level of evidence and provide similar direction. NAEPP recommends that LABAs be used with ICSs for long-term control and prevention of symptoms in moderate or severe persistent asthma. For patients 5 years of age or older with moderate persistent asthma or asthma that is inadequately controlled by low-dose ICS, increasing the ICS dose should be given equal weight to adding LABA. For patients 5 years of age or older with moderate persistent asthma or asthma that is inadequately controlled by ICS alone, the combination of ICS and LABA is preferred. GINA recommends combining a low-dose of ICS with inhaled LABA for adolescents and adults who need an increase in ICS dose and additional treatment. For those needing a further increase in ICS dose and additional treatment, the combination of a medium- or high-dose of ICS with a LABA is recommended.

The CTS and NAEPP guidelines do not provide a recommendation about the comparative efficacy of combination therapies. The CTS guidelines state that there is no supporting evidence of superior effect from using the combination formulation compared with the separate administration of the drugs. The GINA guidelines state that delivering ICS and LABA in a combination inhaler is as effective as giving each drug separately and that combination inhalers containing formoterol and budesonide may be used for rescue and maintenance (highest level of supporting evidence).

The CTS guidelines state that neither salmeterol nor formoterol when used with ICS has been shown to produce major adverse effects in patients with asthma (supporting evidence not graded). Based on the highest level of evidence, the NAEPP guidelines recommend that to reduce the potential of adverse effects, a LABA should be added to a low- or medium-dose of ICS instead of a higher dose of ICS (highest supporting evidence). The guidelines state that there is an increased risk of severe exacerbations associated with the daily use of LABAs for asthma that is poorly controlled using ICS alone, that the daily use of a LABA generally should not exceed 100 mcg salmeterol or 24 mcg formoterol, and that adding salmeterol to ICS may result in increased asthma-related deaths (no supporting evidence grade). The GINA guidelines do not address the comparative safety of ICS and LABA-ICS.

# **1.3 Overview of Technology**

#### 1.3.1 Interventions

Most of the drugs that are used to manage chronic asthma in adults are delivered through inhalation devices. The drugs include LABAs, ICSs, and fixed-dose combinations (Table 1).

#### 1.3.2 Patient group

Patients who qualify for treatment using ICSs include those with persistent asthma symptoms. Patients who remain symptomatic while on ICS maintenance therapy may qualify for additional treatment.

Table 1: Long-Acting Beta2-Agonists and Inhaled Corticosteroids Available for Management           of Chronic Asthma					
Drug	Supplied	Trade Name	Manufacturer		
Long-acting beta	2-agonists		·		
Formoterol	12 mcg/actuation (1 inhaler 6.9 g), 6 mcg/actuation (1 inhaler 10.2 g)	Oxeze	AstraZeneca		
Salmeterol	50 mcg	Serevent	GlaxoSmithKline		
Inhaled corticost	eroids	- <b>·</b>			
Budesonide	100 mcg, 200 mcg	Pulmicort	AstraZeneca		
Fluticasone	Diskus 50 mcg, 100 mcg, 250 mcg, 500 mcg; HFA 50 mcg, 125 mcg, 250 mcg	Flovent	GlaxoSmithKline		
Beclomethasone	50 mcg, 100 mcg	QVAR	Graceway Pharmaceuticals		
Ciclesonide	100 mcg, 200 mcg	Alvesco	Nycomed Canada		
Triamcinolone acetonide*	nolone 100 mcg		Sanofi-Aventis Canada		
Fixed-dose combinations					
Formoterol- budesonide	6 mcg/100 mcg, 6 mcg/200 mcg	Symbicort	AstraZeneca		
Salmeterol- fluticasone	25 mcg/125 mcg, 25 mcg/250 mcg, 50 mcg/100 mcg, 50 mcg/250 mcg, 50 mcg/500 mcg	Advair	GlaxoSmithKline		

\*Available in Canada only as a nasal inhaler.

#### 1.3.3 Variation in Canadian provincial policies

In the Atlantic provinces, patients meet specific criteria before they can be reimbursed for the cost of LABA-ICS combination products. Combination products have been a general formulary benefit to patients with asthma since 2000 in Alberta, with age restrictions on use.

- In Atlantic Canada and Quebec, LABA-ICS combination products are not general benefit drugs. Before patients can have access to LABA-ICS combination products, the use of ICS monotherapy must have failed a test based on asthma symptoms. There is interest in determining what ICS dose should be tried before a LABA is added to a patient's therapy.
- In Alberta, Advair has been a general benefit drug since April 2000. The use of Symbicort is restricted to patients older than 12 years of age because it is available in a Turbuhaler device, which is not approved for use by younger children.
- The Non-insured Health Benefits Program is interested in how LABAs should be used by patients with asthma in light of safety issues with LABA monotherapy. LABA-ICS fixed-dose combination products are listed as a limited use benefit in patients whose asthma symptoms are uncontrolled using ICS.

The safety of ICS monotherapy is a concern. The use of ICS may cause immune system effects and produce higher chances of infections, lower bone mineral density, and more eye problems (including glaucoma and cataracts). The clinical impact of possible dose-sparing effects with combination therapy is unclear. A systematic review has concluded that in adults with asthma using moderate- to high-maintenance doses of ICS, the addition of a LABA has an ICS-sparing effect.<sup>13</sup> The ICS dose may be reduced while the same degree of asthma control is achieved. The addition of a LABA permits more participants on maintenance ICS monotherapy to reduce the use of ICS. The magnitude of the ICS dose reduction needs to be determined.<sup>14</sup> There is uncertainty about the optimal stage to start LABA-ICS combination therapy considering the potential of long-term benefit, harm, and costs.

The safety concerns when LABA is used include headache, tremor, nervousness, and throat irritation. LABAs in combination with ICS may also cause increased blood pressure, fast and irregular heartbeat, and allergic reactions (for example, rash, hives, and swelling of the face, mouth, and tongue).<sup>15</sup>

# 2 THE ISSUE

LABA and ICS combination maintenance therapy for persistent asthma is an established clinical practice. Although provincial public drug plans fund combination therapy, there is variation between many drug plans in the criteria for reimbursement. This variation may stem from concerns about appropriate clinical care and the sustainability of drug funding given limited resources. Information on the effects of dose, timing, potential for harm, and target population on clinical and cost-effectiveness is needed to understand comparative effectiveness before deciding how combination therapy should be funded.

# **3 OBJECTIVES**

The objectives of this project were to conduct a systematic review and primary economic analysis to evaluate the clinical efficacy, safety, and cost-effectiveness of LABA-ICS combination therapy for adults (12 years of age or older) who are diagnosed with persistent asthma. To achieve these objectives, the following research questions were proposed:

- What is the clinical effectiveness of LABA plus ICS maintenance therapy (as fixed-dose or single ingredient products) compared with ICS monotherapy in steroid-naive patients with persistent asthma (ICS treatment-naive or not receiving ICS therapy for one month or more before the treatment period) aged 12 years or older?
  - How does this difference vary according to different disease stages at which LABA-ICS combination therapy is started?
  - How does this difference vary according to type of maintenance therapy (fixed-dose versus variable-dose)?
  - What is the effect of switching to a variable-dose approach from a fixed-dose combination therapy?
- What is the clinical effectiveness of LABA plus ICS maintenance therapy (as fixed-dose or single ingredient products) compared with ICS monotherapy in patients with persistent asthma aged 12 years or older who have been stabilized on ICS therapy?
  - How does this difference vary according to different doses of ICS monotherapy before adding a LABA?
  - How does this difference vary according to different disease stages at which LABA-ICS combination therapy is started?
  - How does this difference vary according to type of maintenance therapy (fixed-dose versus variable-dose)?
  - What is the effect of switching to a variable-dose approach from a fixed-dose combination therapy?
- What is the effectiveness of salmeterol-fluticasone compared with formoterol-budesonide maintenance therapy in patients with persistent asthma aged 12 years or older?
- Are there differences in adverse events (AEs) between combination LABA-ICS treatment (for example, inhaled salmeterol-fluticasone and formoterol-budesonide) and ICS monotherapy?
- Is there evidence that adding a LABA to ICS allows the ICS dose to be reduced (do LABAs have a steroid-sparing effect)?
- What is the cost-effectiveness of LABA plus ICS maintenance therapy compared with ICS monotherapy in patients with asthma aged 12 years or older who are steroid-naive, in patients aged 12 years or older with asthma that is uncontrolled on a low dose of ICS monotherapy, and in patients aged 12 years or older with asthma that is uncontrolled on a medium dose of ICS monotherapy?
- What are the recommendations regarding LABA plus ICS use in Canadian, North American, and international (GINA) guidelines for the management of asthma? What level of evidence and strength of recommendation grading was used?

# 4 CLINICAL REVIEW

## 4.1 Methods

A protocol for the systematic review was written a priori and followed throughout the process.

### 4.1.1 Literature searches

The research librarian, in collaboration with the Health Technology Assessment (HTA) team, developed and implemented search strategies that were designed to identify randomized controlled trials (RCTs) relevant to efficacy, effectiveness, and safety (Appendix 1.1).

Comprehensive searches of the following electronic databases were conducted: BIOSIS Previews, EMBASE, MEDLINE, CENTRAL, Web of Science, PubMed (last 180 days), Cochrane Database of Systematic Reviews, and the HTA Database. The search for all databases was limited to 2006 to 2008 except PubMed (as noted above) and the Cochrane Library (no year restrictions applied). It is likely that all primary studies on this topic up to 2006 were identified as the included studies of 15 literature reviews,<sup>5,13,14,16-27</sup> which were screened and evaluated for inclusion. The searches were not restricted by language or publication status.

To identify additional evidence about safety, Canada's Adverse Drug Reaction Database and European Medicines Agency (EMEA) were searched. Results from the literature searches were entered into Reference Manager for Windows bibliographic database version 11.0 (ISI ResearchSoft, 2005).

Original studies from the reviews that met the inclusion criteria for this review were retrieved. A forward search of the Web of Science from 2006 was conducted using published references from studies (for example, SMART<sup>28</sup> and GOAL<sup>29</sup>).

In addition to scanning the bibliographies of previous reviews, the literature search was supplemented by scanning the reference lists of asthma guidelines.<sup>4,8,9</sup> Government and professional associations and clinical trials registers were searched to identify unpublished studies and studies in progress.

Pharmaceutical manufacturers (AstraZeneca, GlaxoSmithKline, Graceway Pharmaceuticals, Novartis, and Nycomed Canada) were contacted by the Canadian Agency for Drugs and Technologies in Health (CADTH) for information about unpublished completed or ongoing studies that examined the efficacy or safety of LABA-ICS combination therapy compared with ICS monotherapy in the treatment of adult persistent asthma.

### 4.1.2 Selection criteria and method

#### a) Selection criteria

#### Screening criteria

A study was considered to be irrelevant if it met one of the following criteria:

• It was a letter, editorial, or lay press article

- 50% or more of the study participants were 12 years old or younger
- Participants were not using LABA-ICS combination therapy
- It did not evaluate interventions for the treatment of persistent asthma.

#### Inclusion and exclusion criteria

To be included, a study had to meet all the following criteria:

- It was a report of primary research (abstracts were excluded because they were often not detailed enough for an accurate assessment of study population parameters)
- The study design was an RCT
- The population was more than 50% adult patients (older than 12 years) with a diagnosis of mild to severe persistent asthma (patients with comorbid pulmonary diseases, for example, bronchitis, cystic fibrosis, chronic obstructive pulmonary disease, were excluded)
- The setting was non-acute care
- The intervention was combination therapy of LABA and ICS fixed- or variable-dose administered twice daily for a minimum of 60 days
- The comparator was ICS monotherapy of higher, equal, or lower dose to that used in combination therapy
- The co-interventions could be xanthines, anticholinergics, and non-steroidal antiinflammatory drugs, provided a consistent dose was used throughout the study
- The study provided numeric data on at least one clinical efficacy outcome of interest, including exacerbations that led to the use of oral steroids or admission to hospital, pulmonary function (forced expiratory volume in one second [FEV<sub>1</sub>], peak expiratory flow [PEF]), symptom score, percentage of symptom-free days (SFDs), night-time wakenings, rescue-free days, disease-specific quality of life (for example, Asthma Quality of Life Questionnaire [AQLQ]) scores, rescue medication use, and any treatment-related AE.

#### b) Selection method

In the first stage of literature selection, screening based on the titles, subtitles, abstracts, and keywords was conducted by two reviewers. The screening criteria were applied as broadly as possible to ensure that only irrelevant studies were excluded. The full texts of all potentially relevant articles and of articles designated as "unclear" were retrieved. The level of agreement between the two reviewers in the application of the screening criteria was assessed on a 10% random sample of the articles. This phase was repeated until a satisfactory agreement level was reached, and inter-rater variations were minimized. Additional reviewers were compared on inter-rater variation and agreement.

In the second stage of literature selection, two reviewers independently appraised the full text of all the studies that were "potentially relevant" and "unclear." They used a standard form with the inclusion and exclusion criteria for studies on efficacy and safety (Appendix 4). To be included, a study must meet all the predetermined eligibility criteria. Disagreements about inclusion or exclusion of studies were resolved through consensus between two reviewers. When consensus was not possible, a third reviewer acted as arbitrator. Data from unpublished studies were included if available. The decisions to include or exclude studies were documented, and the reasons for exclusion appear in Appendix 2.

#### 4.1.3 Data extraction strategy

In the first phase of data extraction, a pretested form was developed with the assistance of the clinical experts (BHR and CL). Data were extracted independently by two reviewers, entered into an Excel spreadsheet (Microsoft Corp. 2003), and cross-checked for accuracy and completeness. Details that were extracted included study design, inclusion and exclusion criteria, population, intervention, and results for various outcomes (Appendix 4).

In the second phase of data extraction, the biostatistician (BV) extracted data from the reviews and entered the data into Review Manager software (Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2007). The data were cross-checked for accuracy and completeness by two reviewers (KB, KO).

The ICS history of patients was based on the medication that was administered before randomization and treatment. During the run-in period, if previously ICS-naive participants were placed on a regimen of ICS, the participants were considered to be on maintenance ICS and no longer ICS-naive. If no ICS history was provided, participants were assumed to be on maintenance therapy before enrolment. When an element of the patient population thought to be important in treatment comparisons (for example, ICS use, duration of asthma, severity) was not reported in the baseline characteristics, it was estimated from inclusion and exclusion criteria if reported. For example, when duration of asthma or asthma severity was not reported in the baseline characteristics, these data were used to characterize the study population. The periods before randomized treatment periods were considered to be "run-in" periods regardless of the label that was applied by study authors. ICS dose was classified as "low," "medium," or "high" based on the GINA-estimated equipotent daily doses of inhaled glucocorticosteroids for adults.<sup>8</sup> For outcomes, only end-of-trial data were summarized.

Evidence tables were created to summarize the characteristics of the included studies. The tables included information on study characteristics (for example, source of the article, study design, setting, methodological quality) and study population characteristics (for example, treatment groups, sample size, reported outcomes).

#### 4.1.4 Quality assessment

The methodological quality of each study depends on internal and external validity. Internal validity is defined as the confidence that the design, conduct, and report of a trial prevent or reduce bias in the outcomes.<sup>30</sup>

The methodological quality of all trials was assessed using the Jadad scale<sup>31</sup> and the Schulz criteria for allocation concealment.<sup>30</sup> The former is a validated five-point scale<sup>31</sup> with three items that are rated as "yes" or "no" and that are related to internal validity (randomization, double-blinding, and description of withdrawals and dropouts). The Schulz tool is used to look at the evidence of a relationship between the potential for bias in the results and allocation concealment.<sup>32</sup> Information was collected on whether an intention-to-treat analysis was planned and performed, and on the source of funding. A trial was considered to be pharmaceutical company.<sup>33</sup>

Two reviewers independently assessed the methodological quality of studies. Disagreements were resolved by consensus between the reviewers or adjudicated by a third reviewer (BHR) when necessary. Inter-rater reliability ( $\kappa$  statistics) was used to identify inconsistencies in interpretation of the criteria to help standardize the assessment of study quality.

#### 4.1.5 Data synthesis and analysis

#### a) Efficacy

When there was homogeneity among studies in design, population, intervention, and outcomes, data on the efficacy, effectiveness, and safety of ICS and LABA were meta-analyzed using Review Manager software (Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2007) to support inferences about the magnitude and direction of the effect of the interventions. The summary statistics included risk ratios or rate ratios<sup>34</sup> with corresponding 95% confidence intervals (CIs) for dichotomous outcomes and weighted mean differences or standardized mean differences with 95% CIs for continuous outcomes. In keeping with recommendations for meta-analysis, random effects models were used in all analyses.<sup>35</sup> Studies that were clinically and methodologically similar were combined in a meta-analysis, and statistical heterogeneity was explored in a subgroup analysis (for example, by dose, duration, or disease severity). The definitions of exacerbations vary across studies. All indicate, however, a clinically important aspect of loss of asthma control. As a result, exacerbations were pooled regardless of the definition.

Several common sources of heterogeneity were explored. These were methodological (differences in study design) and clinical (differences in characteristics of the participants, exposures, or outcome measures). If there was evidence of substantial statistical heterogeneity among studies ( $I^2 > 70\%$ ),<sup>36</sup> potential sources of heterogeneity were explored qualitatively. Where possible, we used quantitative methods to assess whether the observed differences between studies were greater than chance alone using  $I^2$  and  $\chi^2$  statistics. Publication bias or the selective publication of research depending on the results was assessed. In a qualitative analysis, we considered this source of bias by examining who conducted, commissioned, and supported the studies. Our interpretations were made in light of the potential for bias. Where a quantitative analysis has been conducted, we explored publication bias by means of funnel plot analysis.

When at least two studies reported a comparison and outcome, a meta-analysis was conducted. We presented the results of the studies and provided a qualitative assessment based on study quality, size and direction of the effect observed, and statistical and clinical significance of the study findings.

The clinical importance of the results of meta-analysis was assessed using minimal clinically important differences (MCIDs) from the literature.<sup>37,38</sup> The following MCIDs were selected a priori: PEF 18.79 L/min, FEV<sub>1</sub> 0.23 L, per cent-predicted FEV<sub>1</sub> 10% to 12%, SABA use 0.81 puffs/day, and AQLQ score 0.5. For LABA-ICS compared with higher-dose ICS and LABA-ICS compared with a different LABA-ICS, potential equivalence in pulmonary function, symptom control, and quality of life was determined using the MCIDs. With any outcome for which the 95% CI fell within a positive and negative value of a predetermined MCID, the maintenance effects of the LABA-ICS combination therapy and ICS monotherapy were considered to be equivalent.

#### b) Safety

The studies that did not report data for a particular AE were excluded when data were pooled. It was not assumed that if an event was not reported, it did not occur. Studies reporting that no clinically significant AEs occurred were excluded from the pooled risk estimate because it was unclear what parameters were measured. When only percentages of AEs were reported, the number of events was calculated using the number of participants who were randomized to each arm.

## 4.2 Results

#### 4.2.1 Quantity of research available

A total of 114 reports were considered to be relevant (Figure 2). Six reports<sup>11,39-43</sup> were considered to be multiple publications of other published studies,<sup>29,44-47</sup> and one report<sup>48</sup> was a subanalysis of an unpublished industry trial,<sup>49</sup> yielding 107 unique trials. Nineteen trials addressed the use of LABA-ICS in steroid-naive patients, 37 addressed the use of LABA-ICS compared with a similar-dose ICS monotherapy, 31 addressed the use of LABA-ICS compared with a higher-dose ICS monotherapy, 12 addressed the comparative effectiveness of LABA-ICS therapies, 79 addressed the safety of LABA-ICS compared with ICS monotherapy, and 12 addressed the potential steroid-sparing effect of LABA-ICS therapy. Because of the variation in measurement and reporting of outcomes, a list of clinically important efficacy and safety outcomes (15 and 10 respectively) was created by the clinical experts (BHR, CL). Numeric data on these outcomes were then extracted by the review team.

#### a) Trials from previous reviews

A hand-search of the results of 15 literature reviews (five Cochrane systematic reviews, <sup>5,13,14,21,23</sup> one NHS HTA,<sup>25</sup> and nine literature reviews<sup>16-20,22,24,26,27</sup>) examining LABA-ICS therapy for adult persistent asthma identified 94 potentially relevant trials. After the full texts were examined against the inclusion criteria, 64 trials were included.

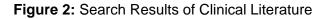
#### b) Results from bibliographic database search

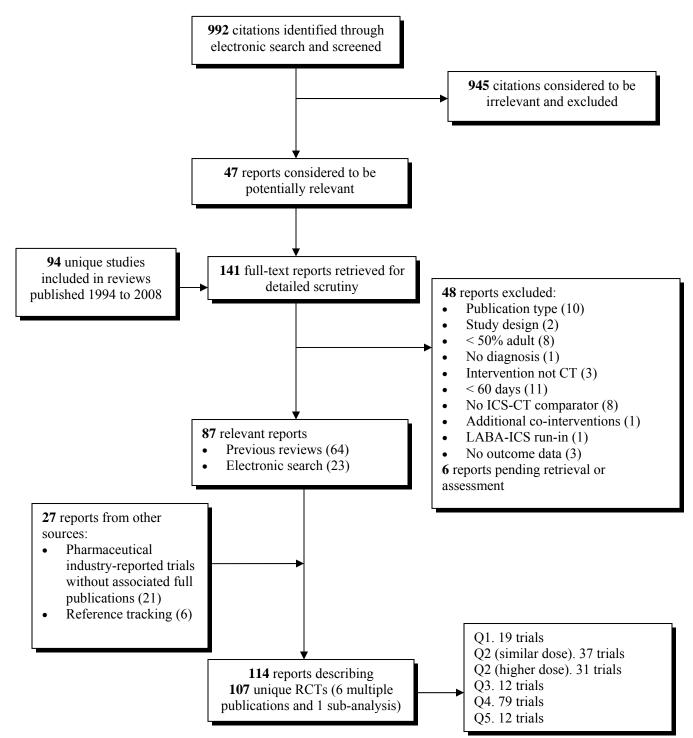
Searches of seven electronic bibliographic databases resulted in the identification of 992 records. Of these, 945 were excluded. The inter-rater agreement for the screening phase before consensus was strong ( $\kappa = 0.57$ , prevalence-and-bias-adjusted  $\kappa = 0.90$ , prevalence index = 0.87, bias index = 0.008).<sup>50,51</sup> The assessment of the full text of the remaining 47 potentially relevant reports using the defined set of inclusion criteria resulted in 23 trials being included. The level of agreement between reviewers during this phase before consensus was high ( $\kappa = 0.74$ ).

Of the 141 reports that were identified through the examination of previous reviews and a search of electronic databases, 87 were considered to be relevant.

#### c) Non-indexed literature and reference tracking

A search of a database of pharmaceutical industry-conducted trials (<u>www.clinicalstudyresults.org</u>) and reference tracking of included studies resulted in the inclusion of an additional 21 and six reported trials respectively.





CT = combination therapy; ICS = inhaled corticosteroid; LABA = long-acting beta<sub>2</sub>-agonist; RCTs = randomized controlled trials.

#### d) Industry contact

Of five pharmaceutical manufacturers (AstraZeneca, GlaxoSmithKline, Graceway Pharmaceuticals, Novartis, and Nycomed Canada) to which a letter was sent from CADTH requesting previous and ongoing research on the effectiveness or safety of LABA-ICS combination therapies and cost-effectiveness data, three did not respond. AstraZeneca provided a bibliography and full text for 26 references on Oxeze and Symbicort (formoterol-budesonide), all of which had been retrieved through our electronic searches and evaluated. GlaxoSmithKline provided a bibliography and full text for 37 references examining Flovent and Advair (salmeterol-fluticasone), one<sup>52</sup> of which had not been captured by our search, but which failed to satisfy the inclusion criteria.

#### 4.2.2 Study characteristics

The results of included trials were published or reported between 1994 and 2008 (median 2004; interquartile range [IQR] 2001 to 2006). Of the reports, 85 (79.4%) were published as journal articles. The remaining 22 industry-reported trial results (20.6%) were available online.

Among all trials, 104 (97.2%) reported funding, and 102 (93.7%) reported funding from the pharmaceutical industry or an affiliation with a pharmaceutical manufacturer of at least one author. Companies that were the sole source of funding were GlaxoSmithKline (61 trials), AstraZeneca (31 trials), Novartis (four trials), Chiesi Pharmaceuticals (two trials), and AstraDraco (one trial). One trial reported industry funding without specifying the company, one trial reported GlaxoSmithKline funding in addition to government and institutional funding, and one trial reported pharmaceutical industry funding that was not described in addition to government funding. Two trials reported receiving only institutional funding, and three trials did not declare the funding source.

All 107 studies (100%) were reported as parallel group randomized controlled clinical trials. The treatment period of the trials ranged from eight to 52 weeks (median 12 weeks; IQR 12 to 24) with most trials (75.7%) lasting less than 26 weeks. Of the 107 studies, 90 (84%) compared a combination therapy with ICS monotherapy. The remaining studies compared different combination therapies.

The median number of participants who were randomized in the 107 trials was 429 (IQR 199 to 582). The age of participants was 18 years or older in 39 (36.4%) studies. The remaining studies included patients ranging in age from 4 to 87 years. Severity ranged from intermittent to severe with most studies including a range of asthma severity. Most did not provide results based on this severity assessment. Most studies included non-smokers, past smokers, and current smokers. Four trials (3.7%) included only non-smokers. One trial<sup>53</sup> was designed to assess the efficacy of salmeterol-fluticasone in patients with asthma and a smoking history of 10 or more pack-years.

Compliance was assessed using patient-reported diaries, internal counters, and inhaler weight. Of the 40 trials that reported the method of compliance (37.4%), 38 (95%) reported using diaries. Of all studies, 41 (38.3%) did not report the assessment of compliance.

Pulmonary function measures were the most frequently reported primary outcome (63% of studies), followed by asthma control (37%). Secondary outcomes were most frequently measures

of asthma control (94% of studies). Pulmonary function measures were reported almost as frequently (92%). Quality-of-life measures were the least frequently reported primary and secondary outcomes (4% and 20% respectively). Descriptions of studies appear in Appendix 6.

#### 4.2.3 Quality of included trials

The overall methodological quality of the 107 included studies was high (median Jadad score 4; IQR 3 to 4). Allocation concealment was considered to be adequate in 16 (15%) studies and unclear in 91 (85%) (Table 2). The results of quality assessment appear in Appendix 5.

Table 2: Methodological Quality of Included Studies				
Quality Component	Number of Studies (%)			
Randomization	107 (100)			
Double-blinding	94 (87.9)			
Description of withdrawals and dropouts	103 (96.3)			
Appropriate method of randomization	37 (34.6)			
Appropriate method of double-blinding	60 (56.0)			
Inappropriate method of randomization	0 (0)			
Inappropriate method of double-blinding	0 (0)			
Adequate concealment of treatment allocation	16 (15.0)			
Inadequate concealment of treatment allocation	0 (0)			
Unclear concealment of treatment allocation	91 (85.0)			

*a) Effectiveness of LABA-ICS therapy for steroid-naive adults* Nineteen unique RCTs<sup>29,46,54-70</sup> assessed the effectiveness of LABA-ICS therapy compared with ICS monotherapy in steroid-naive participants (not receiving ICS therapy for one month or longer before the treatment period). Fifteen trials<sup>29,46,54-61,63,64,67,69,70</sup> examined similar ICS doses, and four<sup>62,65,66,68</sup> examined a double or greater ICS dose. The age of included participants was 18 years or older in five (26.3%) studies.<sup>46,59,63,66,70</sup> Three trials<sup>54,62,69</sup> included only participants with mild asthma, and two<sup>60,67</sup> included only participants with moderate asthma. The median treatment duration was 10 weeks (IQR 10 to 26).

#### Methodological quality

The overall methodological quality of the 19 included studies was high (median Jadad score 4; IQR 3 to 4). Allocation concealment was considered to be unclear in all trials (Table 3). Because of the high scores (Jadad score 3 or higher) of almost all studies, no sensitivity analyses were conducted based on methodological quality.

Table 3: Methodological Quality of Steroid-Naive Studies				
Quality Component	Number of Studies (%)			
Randomization	19 (100)			
Double-blinding	17 (89.5)			
Description of withdrawals and dropouts	17 (89.5)			
Appropriate method of randomization	5 (26.3)			
Appropriate method of double-blinding	6 (31.5)			
Inappropriate method of randomization	0 (0)			
Inappropriate method of double-blinding	0 (0)			
Adequate concealment of treatment allocation	0 (0)			
Inadequate concealment of treatment allocation	0 (0)			
Unclear concealment of treatment allocation	19 (100)			

All studies contributed at least one outcome for meta-analysis on the effectiveness of LABA-ICS compared with ICS for clinical outcomes. The following results focus on key outcomes in pulmonary function, symptom control, and quality of life. The pooled estimates of effect appear in Table 4. A description of the characteristics of the studies that were pooled for each outcome, subgroup analyses, potential sources of statistical heterogeneity, and forest plots appear in Appendix 7. It was considered inappropriate to conduct subgroup analyses based on asthma severity for any outcome measures, because a small proportion of studies (less than 20% of available studies for any one outcome) reported results for populations that were restricted to one asthma severity class. Further subgroup analyses would require individual patient meta-analysis.

#### **Pulmonary function measures**

The results of meta-analysis indicated a clinically important difference favouring LABA-ICS for morning PEF. The combined results for evening PEF and absolute and per cent-predicted FEV<sub>1</sub> indicated statistically significant differences favouring LABA-ICS. The difference between treatments for evening PEF was potentially clinically important. The difference in FEV<sub>1</sub> was not considered to be clinically important when compared with a priori selected MCIDs. Subgroup analyses based on dose of ICS failed to indicate clinically important differences in the magnitude or precision of the treatment effect.

#### Asthma symptom control measures

A meta-analysis indicated statistically significant differences favouring LABA-ICS for the reduction in the percentage of participants with one or more exacerbation, time to first exacerbation, SABA use, and an increase in SFDs. Results for the remaining symptom control measures did not indicate statistically significant differences between the two treatments. Subgroup analyses based on treatment duration of ICS did not indicate clinically important differences in the magnitude or precision of the treatment effect.

#### Asthma quality-of-life measures

A meta-analysis indicated a statistically significant difference in AQLQ score favouring LABA-ICS. The difference was not considered to be clinically important and was reported in only two trials. 
 Table 4: Effectiveness of Long-Acting Beta<sub>2</sub>-Agonists Used with Inhaled Corticosteroids

 Compared with Inhaled Corticosteroids in Steroid-Naive Adults (19 studies)

Compared with Inh	aled Corticos	teroids in Steroid-Naive Adults	s (19 sti	udies)
Outcome	No. of Studies (No. of patients)	Pooled Estimate (95% CI)	l <sup>2</sup> (%)	A Priori MCID
Pulmonary function				!
PEF a.m.	15 (7,056)	WMD 20.78 L/min (14.03 to 27.53)	91	18.79 L/min
Subgroup: similar-dose ICS comparison	11 (4,265)	WMD 20.47 L/min (18.00 to 22.93)	7	
Subgroup: higher-dose ICS comparison	4 (2,791)	WMD 18.54 L/min (-0.98 to 38.06)	95	
PEF p.m.	11 (3,224)	WMD 17.93 L/min (14.95 to 20.92)	0	18.79 L/min
FEV <sub>1</sub> (absolute)	11 (5,581)	WMD 0.11 L (0.06 to 0.15)	66	0.23 L
Subgroup: similar-dose ICS comparison	8 (2,907)	WMD 0.13 L (0.08 to 0.18)	46	
Subgroup: higher-dose ICS comparison	3 (2,674)	WMD 0.06 L (0.01 to 0.11)	48	
FEV <sub>1</sub> (% predicted)	4 (548)	WMD 1.68 (0.13 to 3.24)	0	10% to 12%
Asthma symptom control				
Total number of exacerbations	5 (4,159)	WMD -0.03 (-0.06 to 0.01)	84	Not available
Time to first exacerbation	1 (156)	Hazard ratio 0.44 (0.24 to 0.82)	NA	Not available
% participants with one or more exacerbations	1 (128)	RR 0.57 (0.35 to 0.91)	NA	Not available
Number of severe exacerbations	2 (609)	WMD 0.02 (-0.03 to 0.07)	56	Not available
SABA use (puffs/day)	9 (4,468)	WMD -0.23 (-0.40 to -0.06)	79	-0.81 puffs/day
Symptom-free days (median %)	9 (3,369)	WMD 6.66 (3.70 to 9.61)	36	Not available
Subgroup: treatment duration < 6 months	5 (1,185)	WMD 8.59 (3.98 to 13.20)	23	Not available
Subgroup: treatment duration 6 to 12 months	4 (2,184)	WMD 5.30 (1.44 to 9.16)	45	Not available
Days with optimal control	0	Not reported	NA	Not available
Proportion of symptom-free days	2 (1,370)	RR 1.06 (1.01 to 1.12)	0	Not available
Percentage of participants achieving optimal control	3 (2,525)	RR 1.14 (0.78 to 1.67)	90	Not available
Health-related quality of life				
AQLQ	2 (1,289)	WMD 0.17 (0.11 to 0.22)	7	0.5
<u> </u>			1	

AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; FEV<sub>1</sub> = forced expiratory volume in one second; ICS = inhaled corticosteroid; MCID = minimal clinically important difference; min = minute; NA = not available; PEF = peak expiratory flow; RR = relative risk; SABA = short-acting beta<sub>2</sub>-agonist; WMD = weighted mean difference.

#### Discussion

Nineteen studies involving a total of 12,309 participants evaluated the efficacy of LABA-ICS therapy compared with ICS monotherapy in steroid-naive adults. Meta-analyses indicated that LABA-ICS may have a clinically important benefit compared with ICS monotherapy in improving morning PEF and increasing the number of SFDs. Assuming a study control-group risk of exacerbation of 47.5% based on the percentage of participants experiencing one or more exacerbation, the number needed to treat to prevent one exacerbation is four (95% CI 3 to 24). This is based on one trial of 12 weeks' duration that enrolled patients with poorly controlled asthma. These patients were treated with a very low dose of ICS considering the baseline level of asthma control. This may explain the difference between the two arms in the number of asthma exacerbations, favouring the LABA-ICS combination in this short-term study.<sup>68</sup>

This systematic review identified seven more RCTs with steroid-naive adults than the previous systematic review and meta-analysis,<sup>5</sup> which included eight trials. Despite the differences in the number of included trials, the results of this review are congruent with those of the previous review, which reported statistically significant results favouring LABA-ICS for morning PEF and absolute FEV<sub>1</sub>, and SFDs. In addition, the review reported no difference between treatments with respect to SABA use or health-related quality of life.

The results of this and the previous review<sup>5</sup> highlight the discrepancy between the apparent benefits based on lung function measures compared with the more modest benefit based on symptom control and quality of life. The data remain inadequate to assess whether patient characteristics such as baseline severity affects the response to combination treatment. More large trials with longer treatment periods are needed to adequately assess the relative efficacy of treatment and responders.

*Generalizability:* The generalizability of these results is limited because the participants in most of these studies had been treated previously with ICS and so were not steroid-naive. One study<sup>58</sup> involved steroid-naive participants. Most asthma is managed in a primary care setting where self-management behaviours and optimal adherence to appropriate treatment are promoted. Although the patients in the trials would likely achieve a high degree of adherence, this measure was infrequently reported despite claims that the data were collected. None of the trials reported the use or recording of self-management behaviours. Based on these limitations, the minimal treatment benefits reported here may or may not translate into similar clinical responses in a primary care setting. Moreover, many countries were represented in the included studies, suggesting few limitations on the generalizability of the results across populations.

*Implications for practice:* In addition to the assessment of statistical significance, the MCID between treatments that have been reported in the literature are emphasized in this review.<sup>37,38</sup> These differences represent the minimal treatment effect perceptible by patients for an outcome. Furthermore, primary endpoints or outcomes in asthma drug trials should be important to patients, clinically relevant, and related to the goal of the trial.<sup>71</sup> It is debatable whether small lung function changes are clinically relevant in the management of asthma or important to the patient. Thus, the evidence suggests that the use of combination therapy as initial therapy is of limited or no additional benefit compared with ICS monotherapy for the management of persistent asthma in steroid-naive adults.

**b)** Effectiveness of LABA-ICS as maintenance therapy (versus similar-dose ICS) Thirty-seven unique RCTs<sup>29,45,47,58,72-104</sup> assessed the effectiveness of LABA-ICS combination therapy compared with a similar-dose ICS monotherapy in adults receiving ICS monotherapy for one month or longer before the treatment period. Fourteen trials<sup>45,47,58,72,74,77,79,81,86,91,98,100,102,103</sup> compared LABA-ICS with low-dose ICS, 15 trials<sup>29,78,82-85,87-90,92,94-96,99</sup> with medium-dose ICS, and eight trials<sup>73,75,76,80,93,97,101,104</sup> with high-dose ICS. The age of included participants was 18 years or older in nine (24.3%) studies.<sup>45,73,78,84-86,88-90</sup> Participants had mild asthma only (three trials),<sup>72,79,91</sup> moderate asthma only (five trials),<sup>83,85,87,93,95</sup> severe asthma only (one trial),<sup>73</sup> intermittent to mild asthma (two trials),<sup>58,74</sup> intermittent to moderate asthma (two trials),<sup>81,103</sup> intermittent to severe asthma (six trials),<sup>29,75,76,82,94,97</sup> mild to moderate asthma (nine trials),<sup>45,47,77,78,84,86,88,90,98</sup> mild to severe asthma (five trials),<sup>89,99,100,102,104</sup> and moderate to severe asthma (four trials).<sup>80,92,96,101</sup> The median treatment duration was 12 weeks (IQR 12 to 28).

#### Methodological quality

The methodological quality of 37 studies with similar-dose maintenance ICS comparison groups was high (median Jadad score 4, IQR 4 to 4.5) (Table 5). Allocation concealment was considered to be adequate in seven (18.9%) studies and unclear in 30 (81.1%). Because of the high scores (Jadad score 3 or more) of almost all studies, no sensitivity analyses were conducted based on methodological quality.

Corticosteroid versus Similar-Dose Inhaled Corticosteroid Studies				
Quality Component	Number of Studies (%)			
Randomization	37 (100)			
Double-blinding	35 (94.6)			
Description of withdrawals and dropouts	37 (100)			
Appropriate method of randomization	14 (37.8)			
Appropriate method of double-blinding	30 (81.1)			
Inappropriate method of randomization	0 (0)			
Inappropriate method of double-blinding	0 (0)			
Adequate concealment of treatment allocation	7 (18.9)			
Inadequate concealment of treatment allocation	0 (0)			
Unclear concealment of treatment allocation	30 (81.1)			

 Table 5: Methodological Quality of 37 Long-Acting Beta<sub>2</sub>-Agonist Used with Inhaled

 Corticosteroid versus Similar-Dose Inhaled Corticosteroid Studies

Participants in 32 trials experienced a run-in phase with ICS monotherapy. All these studies provided at least one clinical outcome for meta-analysis. Participants in five trials<sup>74,79,84,99,101</sup> were run-in on low-, medium-, or high-dose ICS regimens or LABA-ICS combination therapy, and the results were reported in aggregate. The results from the mixed-treatment studies are reported separately. The following results focus on the key outcomes in pulmonary function, symptom control, and quality of life. The pooled estimates of effect appear in Table 6. A description of the characteristics of the studies that are pooled for each outcome, subgroup analyses, potential sources of statistical heterogeneity, and forest plots appear in Appendix 7. It was considered inappropriate to conduct subgroup analyses based on asthma severity for any outcome measures, because a small proportion of studies (less than 20% of available studies for any one outcome) reported results for populations restricted to one asthma severity class.

#### **Pulmonary function measures**

The results of meta-analysis indicated a clinically important difference favouring LABA-ICS for morning and evening PEF. Statistically significant differences favouring LABA-ICS were found for absolute and per cent-predicted FEV<sub>1</sub>. The differences were not considered to be clinically important when compared with the MCID that was chosen a priori.

#### Asthma control measures

A meta-analysis indicated statistically significant differences favouring LABA-ICS for reducing the number of patients experiencing one or more exacerbations, increasing the number of SFDs, and potentially increasing the number of days with optimal control. Subgroup analysis based on dose of ICS indicated a greater effect with the medium-dose comparison than with the low-dose comparison for reduction in SABA use, and with the medium- and high-dose comparisons than with the low-dose comparisons for increase in SFDs and optimal control days. No clinically important differences in the other outcomes were identified.

#### Asthma quality-of-life measures

A meta-analysis indicated a statistically significant difference favouring LABA-ICS as measured using the AQLQ score. The difference was not considered to be clinically important. A subgroup analysis based on comparison ICS dose indicated little change in the magnitude and precision of the treatment effect.

Table 6: Comparative Efficacy of Long-Acting Beta <sub>2</sub> -Agonists Used with Inhaled           Corticosteroids versus Similar-Dose Inhaled Corticosteroids (37 studies)				
Outcome	No. of Studies (No. of patients)	Pooled Estimate (95% CI)	l <sup>2</sup> (%)	A priori MCID
Pulmonary function				
PEF a.m.	30 (12,565)	WMD 24.45 L/min (21.98 to 26.92)	45	18.79 L/min
Mixed overall	4 (1,363)	WMD 24.88 L/min (13.09 to 36.66)	67	
Low-dose ICS	10 (4,135)	WMD 20.98 L/min (17.51 to 24.46)	41	
Low-dose ICS (mixed)	1 (181)	WMD 30.60 L/min (15.91 to 45.29)	NA	
Medium-dose ICS	13 (5,854)	WMD 27.70 L/min (24.15 to 31.26)	14	
Medium-dose ICS (mixed)	2 (609)	WMD 14.66 L/min (3.24 to 26.08)	0	
High-dose ICS	7 (2,572)	WMD 24.78 L/min (21.05 to 28.52)	11	
High-dose ICS (mixed)	1 (573)	WMD 34.70 L/min (27.54 to 41.86)	NA	
PEF p.m.	25 (8,279)	WMD 21.31 L/min (18.77 to 23.86)	39	18.79 L/min
Low-dose ICS	7 (2,710)	WMD 18.31 L/min (15.39 to 21.24)	0	
Low-dose ICS (mixed)	1 (181)	WMD 27.60 L/min (14.40 to 40.80)	NA	
Medium-dose ICS	11 (3,274)	WMD 25.82 L/min (21.11 to 30.52)	38	
High-dose ICS	7 (2,294)	WMD 19.36 L/min (15.06 to 23.66)	29	
FEV <sub>1</sub> (absolute)	24 (9,718)	WMD 0.14 L (0.12 to 0.17)	39	0.23 L
Mixed overall	4 (1,349)	WMD 0.10 L (0.06 to 0.14)	10	
Low-dose ICS	7 (2,364)	WMD 0.14 L (0.09 to 0.18)	36	
Low-dose ICS (mixed)	1 (181)	WMD 0.22 L (0.08 to 0.36)	NA	

**Table 6:** Comparative Efficacy of Long-Acting Beta<sub>2</sub>-Agonists Used with Inhaled

 Corticosteroids versus Similar-Dose Inhaled Corticosteroids (37 studies)

Corticosteroids versus Similar-Dose Inhaled Corticosteroids (37 studies)				
Outcome	No. of Studies (No. of patients)	Pooled Estimate (95% CI)	l <sup>2</sup> (%)	A priori MCID
Medium-dose ICS	11 (5,376)	WMD 0.18 L (0.13 to 0.22)	46	
Medium-dose ICS	2 (600)	WMD 0.08 L (0.00 to 0.15)	0	
(mixed)				
High-dose ICS	6 (1,978)	WMD 0.10 L (0.05 to 0.14)	0	
High-dose ICS (mixed)	1 (568)	WMD 0.10 L (0.06 to 0.14)	NA	
FEV <sub>1</sub> (% predicted)	7 (2,556)	WMD 3.36 (2.02 to 4.70)	43	10% to 12%
Low-dose ICS	3 (1,158)	WMD 3.86 (1.18 to 6.54)	74	
Medium-dose ICS	1 (54)	WMD 2.70 (-0.23 to 5.63)	NA	
High-dose ICS	3 (1,344)	WMD 3.05 (1.01 to 5.10)	15	
Asthma symptom cont				J
Total number of exacerbations	4 (3,303)	Rate ratio 0.89 (0.80 to 0.99)	35	Not available
High-dose (mixed)	1 (576)	WMD -0.14 (-0.23 to -0.05)	NA	
Number of participants with one or more exacerbations	13 (4,402)	RR 0.80 (0.70 to 0.90)	23	Not available
	2(7(2))	DD 0 42 (0 20 to 0 02)	5.4	-
Mixed overall Low-dose ICS	2 (763)	RR 0.42 (0.20 to 0.92)	54 53	-
	3 (1,036)	RR 0.80 (0.63 to 1.01)		-
Medium-dose ICS	6 (1,530)	RR 0.83 (0.65 to 1.06)	0	-
Medium-dose ICS (mixed)	1 (187)	RR 0.24 (0.08 to 0.70)	NA	-
High-dose ICS	3 (1020)	RR 0.73 (0.53 to 1.01)	52	_
High-dose ICS (mixed)	1 (576)	RR 0.55 (0.39 to 0.78)	NA	
Number of participants with one or more mild exacerbations	5 (2,009)	RR 0.81 (0.74 to 0.90)	0	Not available
Low-dose ICS	2 (864)	RR 0.88 (0.76 to 1.01)	0	
High-dose ICS	3 (1,145)	RR 0.75 (0.64 to 0.87)	0	
Number of mild exacerbations	2 (612)	Rate ratio 0.83 (0.56 to 1.23)	82	Not available
Low-dose ICS	1 (341)	Rate ratio 0.69 (0.56 to 0.85)	NA	-
Medium-dose ICS	1 (271)	Rate ratio 1.02 (0.79 to 1.32)	NA	-
Asthma symptom cont			1	
Number of participants with one or more	6 (1,820)	RR 0.96 (0.76 to 1.21)	0	Not available
severe exacerbations				
Low-dose ICS	3 (892)	RR 0.74 (0.48 to 1.13)	0	
Medium-dose ICS	1 (65)	RR 0.94 (0.62 to 1.42)	NA	
High-dose ICS	2 (689)	RR 1.17 (0.82 to 1.67)	0	

Long-Acting Beta<sub>2</sub>-Agonist and Inhaled Corticosteroid Combination Therapy for Adult Persistent Asthma: Systematic Review of Clinical Outcomes and Economic Evaluation **Table 6:** Comparative Efficacy of Long-Acting Beta<sub>2</sub>-Agonists Used with Inhaled Corticosteroids versus Similar-Dose Inhaled Corticosteroids (37 studies)

Corticosteroids versus Similar-Dose Inhaled Corticosteroids (37 studies)				
Outcome	No. of Studies (No. of patients)	Pooled Estimate (95% CI)	l <sup>2</sup> (%)	A priori MCID
Number of severe	2 (612)	Rate ratio 0.82 (0.54 to 1.25)	84	Not available
exacerbations				-
Low-dose ICS	1 (341)	Rate ratio 0.67 (0.54 to 0.82)	NA	_
Medium-dose ICS	1 (271)	Rate ratio 1.02 (0.79 to 1.32)	NA	
SABA use (puffs/day)	19 (6,006)	WMD -0.75 (-0.96 to -0.54)	78	-0.81 puffs/day
Mixed overall	2 (985)	WMD -0.60 (-0.85 to -0.36)	NA	
Low-dose ICS	6 (2,229)	WMD -0.39 (-0.64 to -0.14)	67	
Medium-dose ICS	10 (3,164)	WMD -0.78 (-1.02 to -0.55)	54	
Medium-dose ICS (mixed)	1 (417)	WMD -0.30 (-0.95 to 0.35)	NA	
High-dose ICS	3 (613)	WMD -1.60 (-2.80 to -0.41)	87	-
High-dose ICS (mixed)	1 (568)	WMD -0.65 (-0.91 to -0.39)	NA	
Symptom-free days (median %)	26 (11,796)	WMD 12.51 (8.43 to 15.87)	87	Not available
Mixed overall	3 (1,179)	WMD 7.30 (-2.14 to 16.73)	54	
Low-dose ICS	9 (4,094)	WMD 6.87 (3.41 to 10.34)	61	-
Medium-dose ICS	10 (5,188)	WMD 15.20 (9.52 to 20.87)	80	
Medium-dose ICS (mixed)	2 (606)	WMD 1.06 (-9.43 to 11.55)	0	
High-dose ICS	7 (2,514)	WMD 14.20 (9.83 to 18.57)	49	-
High-dose ICS (mixed)	1 (573)	WMD 13.07 (8.10 to 18.04)	NA	
Days with optimal control	6 (3,262)	WMD 10.10 (6.77 to 13.42)	53	Not available
Mixed overall	2 (749)	WMD 21.58 (6.58 to 36.57)	82	
Low-dose ICS	3 (1,765)	WMD 6.92 (4.11 to 9.73)	0	
Low-dose ICS (mixed)	1 (181)	WMD 30.20 (18.55 to 41.85)	NA	
Medium-dose ICS	2 (1,041)	WMD 12.97 (8.32 to 17.61)	0	1
High-dose ICS	1 (456)	WMD 16.05 (10.08 to 22.02)	NA	
High-dose ICS (mixed)	1 (568)	WMD 14.79 (9.55 to 20.03)	NA	
Health-related quality of	of life			
AQLQ	5 (2,999)	WMD 0.29 (0.18 to 0.39)	43	0.5
Medium-dose ICS	2 (665)	WMD 0.21 (0.07 to 0.35)	0	1
High-dose ICS	3 (2,334)	WMD 0.32 (0.17 to 0.46)	61	1

 $AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; FEV_1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; MCID = minimal clinically important difference; min = minute; NA = not available; PEF = peak expiratory flow; RR = relative risk; SABA = short-acting beta_2-agonist; WMD = weighted mean difference.$ 

#### Discussion

Thirty-seven studies involving a total of 18,430 participants evaluated the efficacy of LABA-ICS therapy compared with similar-dose ICS monotherapy. A meta-analysis indicated that LABA-ICS has a clinically important benefit compared with ICS monotherapy in improving morning and evening PEF, reducing the total number of exacerbations and proportion of participants experiencing one or more exacerbation, reducing the use of SABA inhalers, and increasing the number of SFDs and days with optimal control. Assuming a study control-group risk of exacerbation of 27% based on the number of participants experiencing one or more exacerbation, the number needed to treat to prevent one exacerbation is 19 (95% CI 13 to 38) (studies lasted from eight weeks to 40 weeks).

This systematic review identified 11 more trials for similar-dose comparisons than did a previous systematic review and meta-analysis.<sup>23</sup> The previous review reported statistically significant results favouring LABA-ICS for morning PEF, absolute FEV<sub>1</sub>, and per cent predicted FEV<sub>1</sub>. The results of the previous review indicated a benefit favouring LABA-ICS for reducing the number of exacerbations requiring oral corticosteroids or admission to hospital, percentage of SFDs, and SABA use. Though the results of this review indicate a statistically significant reduction in the number of patients experiencing one or more exacerbations, the apparent benefit disappears when the results are grouped by dose.

LABA-ICS was favoured for health-related quality of life (AQLQ) in the previous review. The estimated benefits for absolute  $FEV_1$  and health-related quality of life that were reported, though statistically significant, do not meet the a priori criteria for clinical importance that are used in this review (0.23 L and change in score of 0.5 respectively).

*Generalizability:* Most asthma is managed in a primary care setting, and most guidelines recommend starting treatment with low- to moderate-dose ICS. Many clinicians, especially those in the developed world, need to decide whether to start therapy with a LABA-ICS combination. Many countries were represented in the included studies, suggesting few limitations on the generalizability of the results across populations. The high adherence that is likely to be achieved in these trials may limit the generalizability of the results.

*Implications for practice:* In addition to the assessment of statistical significance, the MCID between treatments that have been reported in the literature is emphasized. For many outcomes, the MCID was not reached. Furthermore, primary endpoints or outcomes in asthma drug trials should be important to the patient, clinically relevant, and related to the goal of the trial. For example, it is debatable whether small lung function changes are clinically relevant in the management of asthma or important to the patient. The studies did not identify quality-of-life benefits, and there were small reductions in exacerbations. This suggests that cost-effectiveness analyses will be valuable in decision-making.

c) Effectiveness of LABA-ICS as maintenance therapy (versus higher-dose ICS) Thirty-one unique  $RCTs^{53,58,65,66,76,79,101,103-126}$  assessed the effectiveness of LABA-ICS

Thirty-one unique RCTs<sup>53,58,65,66,76,79,101,103-126</sup> assessed the effectiveness of LABA-ICS combination therapy compared with ICS monotherapy in patients on maintenance ICS (receiving ICS therapy before the treatment period). All trials compared LABA-ICS with a double or greater dose of ICS. The age of included participants was 18 years or older in 12 (38.7%) studies.<sup>53,66,106,108,111,113-115,117,118,120,121</sup> The studies covered mild asthma only (three trials),<sup>79,121,123</sup>

moderate asthma only (four trials),<sup>106,108,114,124</sup> intermittent to mild asthma (one trial),<sup>58</sup> intermittent to moderate asthma (two trials),<sup>103,113</sup> intermittent to severe asthma (five trials),<sup>76,105,111,115,125</sup> mild to moderate asthma (five trials),<sup>65,112,120,122,126</sup> mild to severe asthma (four trials),<sup>53,66,104,107</sup> and moderate to severe asthma (seven trials).<sup>101,109,110,116-119</sup> The median duration of treatment was 16 weeks (IQR 12 to 24).

#### Methodological quality

The methodological quality of 31 higher-dose maintenance ICS studies was high (median Jadad score 4; IQR 3 to 4.5) (Table 7). Allocation concealment was considered to be adequate in four (12.9%) studies and unclear in 27 (87.1%). Because of the high scores (Jadad score 3 or higher) of almost all studies, no sensitivity analyses were conducted based on quality.

<b>Table 7:</b> Methodological Quality of Maintenance Inhaled Corticosteroid Studies: Higher Dose (31 studies)				
Quality Component	Number of Studies (%)			
Randomization	31 (100)			
Double-blinding	30 (96.8)			
Description of withdrawals and dropouts	31 (100)			
Appropriate method of randomization	23 (38.7)			
Appropriate method of double-blinding	17 (54.8)			
Inappropriate method of randomization	0 (0)			
Inappropriate method of double-blinding	0 (0)			
Adequate concealment of treatment allocation	4 (12.9)			
Inadequate concealment of treatment allocation	0 (0)			
Unclear concealment of treatment allocation	27 (87.1)			

Participants in 30 trials were run-in on ICS monotherapy. All these studies provided data about at least one clinical outcome for meta-analysis. Participants in three trials <sup>79,101,124</sup> were run-in on low-, medium-, and high-dose ICS regimens or LABA-ICS combination therapy. The results were reported in aggregate. The results from this mixed-treatment study are reported separately. The following results focus on the key outcomes in pulmonary function, symptom control, and quality of life. The pooled estimates of effect appear in Table 8. A description of the characteristics of the studies that were pooled for each outcome, subgroup analyses, potential sources of statistical heterogeneity, and forest plots appear in Appendix 7. It was considered inappropriate to conduct subgroup analyses based on asthma severity for any outcome measures, because a small proportion of studies (less than 20% of available studies for any one outcome) reported results for populations restricted to one asthma severity class.

#### **Pulmonary function measures**

The results of meta-analysis indicated that statistically significant results favouring LABA-ICS were found for morning and evening PEF and absolute and per cent-predicted FEV<sub>1</sub>. The difference between treatments for morning PEF was potentially clinically important based on the a priori MCID. The 95% CIs for evening PEF and absolute and per cent-predicted FEV<sub>1</sub> suggested clinical equivalence. The results from subgroup analyses based on comparison ICS dose indicated a potentially clinically important difference favouring LABA-ICS high-dose comparisons for increasing morning and evening PEF.

#### Asthma control measures

A meta-analysis indicated statistically significant differences favouring LABA-ICS for reducing the number of participants experiencing one or more exacerbations, the number of participants with severe exacerbations, the number of severe exacerbations, SABA use, and increasing SFDs and days with optimal control. The range of the 95% CI suggested potential clinical equivalence between the treatments for reduction in SABA use.

#### Asthma quality-of life-measures

The precision of the 95% CI resulting from meta-analysis suggests that the two treatments are clinically equivalent for change in AQLQ score.

Table 8: Comparative Efficacy of Long-Acting Beta2-Agonists Used with Inhaled           Corticosteroids versus Higher-Dose Inhaled Corticosteroids (31 studies)				
Outcome	No. of Studies (No. of patients)	Pooled Estimate (95% CI)	l <sup>2</sup> (%)	A Priori MCID
Pulmonary function				
PEF a.m.	25 (13,389)	WMD 18.24 L/min (15.72 to 20.76)	49	18.79 L/min
Mixed dose (overall)	3 (710)	WMD 17.85 L/min (2.09 to 33.61)	71	
Low-dose ICS	5 (2,342)	WMD 15.77 L/min (8.13 to 23.41)	83	
Low-dose ICS (mixed)	1 (148)	WMD 3.90 L/min (-12.18 to 19.98)	NA	
Medium-dose ICS	14 (8,510)	WMD 17.93 L/min (14.87 to 20.99)	42	
Medium-dose ICS (mixed)	1 (300)	WMD 18.60 L/min (-2.33 to 39.53)	NA	
High-dose ICS	7 (2,537)	WMD 21.78 L/min (17.10 to 26.46)	0	
High-dose ICS (mixed)	1 (262)	WMD 28.00 L/min (19.45 to 36.55)	NA	
PEF p.m.	23 (12,510)	WMD 15.24 L/min (13.19 to 17.30)	31	18.79 L/min
Mixed dose (overall)	1 (300)	WMD 24.60 L/min (3.40 to 48.80)	NA	
Low-dose ICS	3 (1,707)	WMD 13.15 L/min (7.23 to 19.07)	68	
Medium-dose ICS	14 (8,508)	WMD 13.72 L/min (11.84 to 15.60)	0	
High-dose ICS	6 (2,295)	WMD 21.48 L/min (17.05 to 25.90)	0	
FEV <sub>1</sub> (absolute)	17 (8,297)	WMD 0.09 L/min (0.07 to 0.11)	16	0.23 L
Mixed dose (overall)	3 (709)	WMD 0.04 L/min (-0.04 to 0.12)	71	
Low-dose ICS	2 (1,240)	WMD 0.11 L/min (0.03 to 0.18)	43	
Low-dose ICS (mixed)	1 (148)	WMD -0.02 L/min (-0.07 to 0.03)	NA	
Medium-dose ICS	11 (6,121)	WMD 0.07 L/min (0.05 to 0.09)	0	
Medium-dose ICS (mixed)	1 (300)	WMD 0.07 L/min (-0.11 to 0.25)	NA	

Long-Acting Beta<sub>2</sub>-Agonist and Inhaled Corticosteroid Combination Therapy for Adult Persistent Asthma: Systematic Review of Clinical Outcomes and Economic Evaluation

**Table 8:** Comparative Efficacy of Long-Acting Beta<sub>2</sub>-Agonists Used with Inhaled

 Corticosteroids versus Higher-Dose Inhaled Corticosteroids (31 studies)

	``````````````````````````````````````	pher-Dose Inhaled Corticosteroids		,
Outcome	No. of Studies (No. of patients)	Pooled Estimate (95% CI)	l <sup>2</sup> (%)	A Priori MCID
High-dose ICS	4 (936)	WMD 0.14 L/min (0.04 to 0.23)	27	_
High-dose ICS (mixed)	1 (261)	WMD 0.08 L/min (0.03 to 0.13)	NA	
FEV <sub>1</sub> (% predicted)	5 (2,503)	WMD 2.14 (0.95 to 3.34)	31	10% to 12%
Mixed dose (overall)	1 (300)	WMD 2.40 (-0.76 to 5.56)	NA	
Low-dose ICS	2 (964)	WMD 1.35 (0.19 to 2.51)	0	
Medium-dose ICS	1 (454)	WMD 2.70 (0.06 to 5.34)	NA	
High-dose ICS	2 (1,085)	WMD 3.76 (1.81 to 5.71)	0	
Asthma symptom contr	ol			
Total number of exacerbations	6 (4,645)	Rate ratio 0.72 (0.56 to 0.94)	95	Not available
Mixed dose (overall)	1 (265)	WMD -0.13 (-0.23 to -0.03)	NA	
Low-dose ICS	2 (1,332)	Rate ratio 0.51 (0.38 to 0.67)	85	
Medium-dose ICS	4 (3,314)	Rate ratio 0.87 (0.63 to 1.19)	94	]
Number of participants with one or more exacerbations	20 (10,726)	RR 0.82 (0.73 to 0.91)	40	Not available
Mixed dose (overall)	2 (565)	RR 0.87 (0.55 to 1.36)	51	
Low-dose ICS	3 (1,494)	RR 0.79 (0.57 to 1.09)	79	
Medium-dose ICS	11 (6,917)	RR 0.83 (0.71 to 0.97)	41	
Medium-dose ICS (mixed)	1 (300)	RR 1.05 (0.73 to 1.53)	NA	
High-dose ICS	6 (2,315)	RR 0.81(0.69 to 0.96)	0	
High-dose ICS (mixed)	1 (265)	RR 0.66 (0.39 to 1.12)	NA	
Patients with severe exacerbations	7 (5,889)	RR 0.65 (0.57 to 0.75)	0	Not available
Low-dose ICS	1 (697)	RR 0.49 (0.32 to 0.75)	0	
Medium-dose ICS	4 (4,495)	RR 0.68 (0.58 to 0.80)	0	
High-dose ICS	2 (697)	RR 0.64 (0.47 to 0.88)	0	1
Number of severe exacerbations	1 (2,760)	Rate ratio 0.60 (0.55 to 0.66)	NA	Not available
Patients with mild exacerbations	4 (1,467)	RR 0.84 (0.64 to 1.11)	51	Not available
Medium-dose ICS	2 (770)	RR 0.87 (0.55 to 1.37)	73	1
High-dose ICS	2 (697)	RR 0.80 (0.51 to 1.25)	48	1
Number of mild exacerbations	1 (426)	WMD 0.06 (-0.22 to 0.35)	NA	Not available
Exacerbations requiring hospitalization	6 (2,469)	RR 0.80 (0.51 to 1.24)	0	Not available
Medium-dose ICS	4 (1,772)	RR 0.95 (0.58 to 1.56)	0	
High-dose ICS	1 (496)	RR 0.43 (0.17 to 1.12)	NA	1

Long-Acting Beta<sub>2</sub>-Agonist and Inhaled Corticosteroid Combination Therapy for Adult Persistent Asthma: Systematic Review of Clinical Outcomes and Economic Evaluation **Table 8:** Comparative Efficacy of Long-Acting Beta<sub>2</sub>-Agonists Used with Inhaled Corticosteroids versus Higher-Dose Inhaled Corticosteroids (31 studies)

Corticosteroids versus Higher-Dose Inhaled Corticosteroids (31 studies)						
Outcome	No. of Studies (No. of patients)	Pooled Estimate (95% CI)	l <sup>2</sup> (%)	A Priori MCID		
Exacerbations requiring ICS	7 (2,906)	RR 0.85 (0.72 to 1.00)	0	Not available		
Medium-dose ICS	5 (2,209)	RR 0.87 (0.70 to 1.07)	0			
High-dose ICS	2 (697)	RR 0.83 (0.63 to 1.08)	0			
SABA use (puffs/day)	17 (10,823)	WMD -0.43 (-0.55 to -0.30)	79	-0.81		
Mixed dose (overall)	3 (708)	WMD -0.27 (-0.72 to 0.19)	NA	puffs/day		
Low-dose ICS	4 (2,342)	WMD -0.19 (-0.33 to -0.05)	51			
Low-dose ICS (mixed)	1 (148)	WMD -0.30 (-1.11 to 0.51)	NA			
Medium-dose ICS	10 (7,505)	WMD -0.46 (-0.64 to -0.29)	79	]		
Medium-dose ICS (mixed)	1 (300)	WMD 0.00 (-0.11 to 0.11)	NA	]		
High-dose ICS	3 (976)	WMD -0.95 (-1.37 to -0.52)	52			
High-dose ICS (mixed)	1 (260)	WMD -0.59 (-0.72 to 0.19)	NA			
Symptom-free days (median %)	16 (10,702)	WMD 8.37 (4.68 to 12.06)	87	Not available		
Mixed dose (overall)	2 (562)	WMD 15.66 (11.85 to 19.48)	0			
Low-dose ICS	4 (2,124)	WMD 3.12 (-0.79 to 7.02)	66			
Medium-dose ICS	9 (7,068)	WMD 6.44 (3.17 to 9.70)	71			
Medium-dose ICS (mixed)	1 (300)	WMD 14.90 (10.37 to 19.43)	NA			
High-dose ICS	3 (1,510)	WMD 26.20 (9.22 to 43.17)	91			
High-dose ICS (mixed)	1 (262)	WMD 17.53 (10.46 to 24.60)	NA			
Days with optimal control	3 (5,347)	WMD 8.12 (6.02 to 10.22)	0	Not available		
Low-dose ICS	1 (697)	WMD 7.60 (2.95 to 12.25)	NA			
Medium-dose ICS	2 (4,650)	WMD 8.25 (5.90 to 10.61)	0			
Mean ICS dose	1 (1,890)	SMD -0.20 (-0.30 to -0.11)	NA	Not available		
Change in ICS dose	1 (2,760)	RR 0.53 (0.43 to 0.64)	NA	Not available		
Health-related quality of						
AQLQ	2 (270)	WMD 0.01 (-0.23 to 0.25)	0	0.5		
Mixed dose (overall)	1 (148)	WMD 0.08 (-0.06 to 0.22)	NA			
Low-dose ICS	1 (255)	WMD 0.00 (-0.25 to 0.25)	NA	]		
Medium-dose ICS	1 (15)	WMD 0.18 (-0.82 to 1.18)	NA			

 $AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; FEV_1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; MCID = minimal clinically important difference; min = minute; NA = not available; PEF = peak expiratory flow; RR = relative risk; SABA = short-acting beta_2-agonist; SMD = standardized mean difference; WMD = weighted mean difference.$ 

#### Discussion

Thirty-one RCTs involving a total of 17,222 participants evaluated the efficacy of LABA-ICS therapy compared with higher-dose ICS monotherapy. Meta-analyses indicated that LABA-ICS may have a clinically important benefit compared with ICS monotherapy in reducing the risk of an exacerbation and increasing the number of SFDs and days with optimal control. Assuming a study control-group risk of exacerbation of 28% based on the number of participants experiencing one or more exacerbations, the number needed to treat to prevent one exacerbation is 23 (95% CI 16 to 52) (based on studies ranging from 12 weeks to 24 weeks in duration).

The results of this systematic review are similar to those of another systematic review and metaanalysis,<sup>14</sup> which included 30 RCTs. The review reported statistically significant results favouring LABA-ICS for morning and evening PEF, absolute FEV<sub>1</sub>, and per cent-predicted FEV<sub>1</sub>. The differences between treatments for morning and evening PEF were clinically important. The estimated benefits for absolute FEV<sub>1</sub> and per cent-predicted FEV<sub>1</sub> as reported by the review authors, though statistically significant, failed to meet the a priori criteria for clinical importance that were used in this review (0.23 L and 12% respectively). The results of the previous review indicated a statistically significant difference favouring LABA-ICS in reduction of SABA use and SFDs, with the reduction in SABA use being clinically important. The results failed to indicate a difference between the treatments in reduction of exacerbations requiring oral corticosteroids or admission to hospital. Health-related quality of life (AQLQ) was not statistically significantly different between the two treatments.

*Generalizability:* Most asthma is managed in a primary care setting. Most guidelines recommend starting treatment with low- to moderate-dose ICS. The mixed-dose comparisons for SFDs suggest large treatment differences of 16% overall and 15% and 17.5% for medium and high doses respectively. The small number of studies and mixture of patient treatment history make these results difficult to interpret. Many clinicians, especially those in the developed world, have to decide whether to double the ICS dose or use LABA-ICS combination agents. Many countries were represented in the included studies, suggesting few limitations on the generalizability of the results across populations. Finally, the high adherence likely to be achieved in these trials may limit the generalizability of the results.

*Implications for practice:* In addition to the assessment of statistical significance, the MCIDs between treatments that have been reported previously in the literature are emphasized in this review. For many of the outcomes with defined MCIDs, no differences were clinically important. Furthermore, primary endpoints or outcomes in asthma drug trials should be important to the patient, clinically relevant, and related to the goal of the trial. For example, it is debatable whether small lung function changes are clinically relevant for the management of asthma or important to the patient. The failure of the studies to identify clinically important quality-of-life benefits and the estimated exacerbation reductions suggests that the results of cost-effectiveness analyses will be valuable in decision-making.

*d)* Effectiveness of LABA-ICS therapy versus a different LABA-ICS therapy in adults Twelve RCTs<sup>10,11,127-136</sup> assessed the efficacy of LABA-ICS combination therapies for adult persistent asthma against one another. Nine trials<sup>10,11,127-131,133,136</sup> compared formoterol-budesonide with salmeterol-fluticasone, two compared formoterol-beclomethasone with salmeterol-fluticasone, <sup>134,135</sup> and one compared formoterol-budesonide with formoterol-

beclomethasone.<sup>133</sup> Eight trials<sup>10,11,127-136,128-132,134-136</sup> compared different fixed-dose regimens. Three trials<sup>10,11,127,129,130,132,133</sup> compared variable dose with fixed dose. One trial<sup>130</sup> compared variable dose with variable dose. The comparison of LABA-ICS with a similar dose of LABA-ICS was examined in eight trials.<sup>11,127-129,131,133,134,136</sup> The remaining four trials<sup>10,130,132,135</sup> assessed LABA-ICS with a double or greater dose of LABA-ICS. The age of included participants was 18 years or older in four (33.3%) studies.<sup>11,128,132,135</sup> The median treatment duration was 18 weeks (IQR 12 to 26).

Three<sup>10,129,131</sup> studies compared SMART therapy (formoterol-budesonide maintenance therapy plus formoterol-budesonide as needed for reliever therapy) with salmeterol-fluticasone maintenance therapy plus SABA for reliever therapy.

#### Methodological quality

The methodological quality of the 12 trials was high (median Jadad score 5; IQR 4 to 5). Allocation concealment was considered to be adequate in five (41.7%) trials and unclear in seven (58.3%) (Table 9). Because of the high scores (Jadad score 3 or higher) of almost all studies, no sensitivity analyses based on quality were conducted.

Table 9: Methodological Quality of 12 Combination Head-to-Head Studies of Long-ActingBeta2-Agonists Used with Inhaled Corticosteroids					
Quality Component	Number of Studies (%)				
Randomization	12 (100)				
Double-blinding	10 (83.3)				
Description of withdrawals and dropouts	12 (100)				
Appropriate method of randomization	9 (75.0)				
Appropriate method of double-blinding	10 (83.3)				
Inappropriate method of randomization	0 (0)				
Inappropriate method of double-blinding	0 (0)				
Adequate concealment of treatment allocation	5 (41.7)				
Inadequate concealment of treatment allocation	0 (0)				
Unclear concealment of treatment allocation	7 (58.3)				

All potential indirect comparison studies were RCTs. Two (28.6%) described the randomization method and were judged to have used adequate randomization procedures. Double-blinding was reported in one (14.3%) trial, which described the methods by which the investigator and participants were blinded. Withdrawals or dropouts, if any occurred, and the accounting of all participants were reported in all seven trials. The allocation concealment was unclear in all studies (Table 10).

Table 10: Methodological Quality of Seven Potential Indirect Comparison Studies					
Quality Component	Number of Studies (%)				
Randomization	7 (100)				
Double-blinding	1 (14.3)				
Description of withdrawals and dropouts	7 (100)				
Appropriate method of randomization	2 (28.6)				
Appropriate method of double-blinding	0				
Inappropriate method of randomization	0				
Inappropriate method of double-blinding	0				
Adequate concealment of treatment allocation	0				
Inadequate concealment of treatment allocation	0				
Unclear concealment of treatment allocation	7 (100)				

All 12 head-to-head studies contributed at least one outcome for meta-analysis of the effectiveness of different LABA-ICS combinations on clinical outcomes. The following results focus on the key outcomes from pulmonary function, symptom control, and quality of life. The pooled estimates of effect appear in Tables 11 to 13. A description of the characteristics of the studies that were pooled for each outcome, subgroup analyses, potential sources of statistical heterogeneity, and forest plots appear in Appendix 7. It was considered inappropriate to conduct subgroup analyses based on asthma severity for any outcome measures, because a small proportion of studies (less than 20% of available studies for any one outcome) reported results for populations restricted to one asthma severity class.

#### **Pulmonary function measures**

The results of meta-analysis indicated that there was a statistically significant difference favouring salmeterol-fluticasone compared with formoterol-budesonide for morning PEF. This difference was not considered to be clinically important. No statistically significant differences were indicated for the remaining pulmonary function measures.

#### Asthma symptom control measures

Meta-analytic results indicated a statistically significant difference favouring salmeterolfluticasone compared with formoterol-budesonide for an increase in SFDs. There was a statistically significant difference favouring formoterol-budesonide compared with salmeterolfluticasone for time to first exacerbation. There were no statistically significant differences between LABA-ICS combinations for the remaining symptom control measures.

Table 11: Efficacy of Formoterol-Budesonide Compared with Salmeterol-Fluticasone           (nine studies)					
Outcome	No. of Studies (No. of patients)	b. of Pooled Estimate (95% CI) dies b. of		A Priori MCID	
Pulmonary function	•		·)	•	
PEF a.m.	8 (9,115)	WMD -1.89 L/min (-3.74 to -0.04)	0	18.79 L/min	
PEF p.m.	4 (5,531)	WMD -0.29 L/min (-2.51 to 1.93)	0	18.79 L/min	
FEV <sub>1</sub> (absolute)	8 (11,119)	WMD 0.01 L (-0.01 to 0.02)	22	0.23 L	
FEV <sub>1</sub> (% predicted)	0			10% to 12%	
Asthma symptom control				•	
Total number of exacerbations during study	6 (6,682)	WMD 0.06 (-0.02 to 0.15)	95	Not available	
Time to first exacerbation	4 (7,470)	Hazard ratio 0.82 (0.72 to 0.93)	0	Not available	
% participants with 1 or more exacerbations	3 (2,979)	Risk ratio 1.03 (0.95 to 1.11)	0	Not available	
Number of severe exacerbations	3 (5,762)	Rate ratio 0.99 (0.69 to 1.42)	84	Not available	
Number of mild exacerbations	2 (2,656)	Risk ratio 1.32 (0.85 to 2.07)	97	Not available	
SABA use (puffs/day)	6 (9,210)	WMD -0.03 (-0.12 to 0.07)	77	-0.81 puffs/day	
Symptom-free days (median %)	6 (9,210)	WMD -1.60 (-3.03 to -0.17)	0	Not available	
Days with optimal control	2 (3,496)	WMD -0.03 (-3.12 to 3.05)	39	Not available	
% participants stepping down their dose	1 (2,143)	Risk ratio 1.22 (1.09 to 1.37)	NA	Not available	
Proportion of symptom- free days	1 (658)	Risk ratio 1.00 (0.87 to 1.15)	NA	Not available	
Health-related quality of life	9	·	•	·	
AQLQ	2 (4,371)	WMD 0.02 (-0.04 to 0.09)	0	0.5	

 $AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; FEV_1 = forced expiratory volume in one second; MCID = minimal clinically important difference; min = minute; PEF = peak expiratory flow; SABA = short-acting beta<sub>2</sub>-agonist; WMD = weighted mean difference.$ 

Table 12: Efficacy of Formoterol-Beclomethasone Compared with Salmeterol-Fluticasone           (two studies)						
Outcome	No. of Studies (No. of patients)	Pooled Estimate (95% CI)	l <sup>2</sup> (%)	A Priori MCID		
<b>Pulmonary function</b>						
PEF a.m.	2 (469)	WMD -8.11 L/min (-20.24 to -4.02)	0	18.79 L/min		
PEF p.m.	2 (469)	WMD -6.01 L/min (-19.89 to 7.87)	21	18.79 L/min		
FEV <sub>1</sub> (% predicted)	1 (241)	WMD -3.10 (-6.89 to 0.69)	NA	10% to 12%		
FEV <sub>1</sub> (absolute)	2 (469)	WMD 0.01 L (-0.18 to 0.15)	75	0.23 L		
Asthma symptom cont	rol					
Time to first exacerbation	1 (228)	Hazard ratio 0.67 (0.28 to 1.58)	NA			
% participants with 1 or more exacerbations	1 (228)	Risk ratio 0.66 (0.28 to 1.54)	NA			
SABA use (puffs/day)	1 (228)	WMD -0.19 (-0.04 to 0.42)	NA	-0.81 puffs/day		
Symptom-free days (median %)	2 (469)	WMD -1.07 (-6.22 to 8.35)	0			

 $CI = confidence interval; FEV_1 = forced expiratory volume in one second; MCID = minimal clinically important difference; min = minute; NA = not available; PEF = peak expiratory flow; SABA = short-acting beta<sub>2</sub>-agonist; WMD = weighted mean difference.$ 

#### Asthma quality of life measures

Meta-analysis failed to identify a statistically significant difference between LABA-ICS combinations for change in AQLQ score.

Twelve studies involving a total of 13,266 participants evaluated the relative efficacy of LABA-ICS therapies for adult persistent asthma against one another. Meta-analyses indicated that there was no clinically important benefit of one LABA-ICS combination compared with another in improving pulmonary function measures, asthma symptom control, or health-related quality of life. This systematic review identified four more RCTs on salmeterol-fluticasone compared with formoterol-budesonide combination therapy than a previous systematic review and metaanalysis,<sup>21</sup> which included five trials. Despite the difference in the number of trials, the results of this review are congruent with those of the previous review, which reported no statistically significant differences between treatments.

Table 13: Efficacy of Formoterol-Budesonide Compared with Formoterol-Beclomethasone           (one study)						
Outcome	No. of Studies (No. of patients)	Pooled Estimate (95% CI)	l <sup>2</sup> (%)	A Priori MCID		
<b>Pulmonary function</b>						
PEF a.m.	1 (216)	WMD -0.80L/min (-13.70 to 12.10)	NA	18.79 L/min		
PEF p.m.	1 (216)	WMD -0.07 L/min (-12.59 to 12.45)	NA	18.79 L/min		
FEV <sub>1</sub> (absolute)	1 (216)	WMD 0.05 L (-0.07 to 0.17)	NA	0.23 L		
Asthma symptom cont	rol					
Time to first exacerbation	1 (216)	Hazard ratio 0.83 (0.56 to 0.1.23)	NA			
% participants with 1 or more exacerbations	1 (216)	Risk ratio 0.69 (0.35 to 1.38)	NA			
Number of mild exacerbations	1 (216)	Risk ratio 0.65 (0.31 to 1.39)	NA			
SABA use (puffs/day)	1 (216)	WMD -0.01 (-0.33 to 0.31)	NA	-0.81 puffs/day		
Symptom-free days (median %)	1 (216)	WMD -4.00 (-21.60 to 13.60)	NA			

CI = confidence interval; FEV<sub>1</sub> = forced expiratory volume in one second; MCID = minimal clinically important difference; min = minute; NA = not available; PEF = peak expiratory flow; SABA = short-acting beta2-agonist; WMD = weighted mean difference.

**SMART therapy** Three studies<sup>10,129,131</sup> compared SMART (formoterol-budesonide adjustable maintenance therapy plus formoterol-budesonide as needed for reliever therapy) with salmeterol-fluticasone maintenance therapy plus a SABA for reliever therapy. All three studies included participants who had at least moderate to severe asthma. One study<sup>131</sup> compared formoterol-budesonide to a similar dose of salmeterol-fluticasone. Two studies<sup>10,129</sup> compared formoterol-budesonide to double-dose salmeterol-fluticasone. Two studies<sup>129,131</sup> showed improvements in lung function and asthma symptoms in the SMART group. The other study showed no difference in these outcomes between treatment groups. SMART therapy prolonged the time to first exacerbation in two studies.<sup>10,129</sup> The rate of severe exacerbations was statistically significantly lower with SMART therapy compared with fluticasone-salmeterol in all three studies. The use of SMART resulted in a lower mean dose of ICS in two studies.<sup>10,129</sup> No separate subgroup analysis was conducted. The results suggest improvement favouring SMART therapy.

Generalizability: Most asthma is managed in a primary care setting. Most guidelines recommend adding LABA-ICS combination agents when asthma is uncontrolled with moderate doses of ICS monotherapy. Many clinicians, especially those in the developed world, have to decide which agent to select and whether to use fixed or variable dosing. Many countries were represented in the included studies, suggesting few limitations on the generalizability of the results. The high adherence likely to be achieved in these trials may limit the generalizability of the results.

*Implications for practice:* In addition to the assessment of statistical significance, the MCID between treatments that have been reported in the literature are emphasized. Where they were defined, the MCIDs were not reached for any of the outcomes. Furthermore, primary endpoints or outcomes in asthma drug trials should be important to the patient, clinically relevant, and related to the goal of the trial. For example, it is debatable whether small lung function changes are clinically relevant for the management of asthma or important to the patient. The failure of these studies to identify clinically important quality-of-life benefits or exacerbation reductions suggests a lack of difference between the treatments. The wide confidence intervals, especially for clinically important outcomes such as severe exacerbations, prevent a conclusion of equivalence.

#### e) Potential steroid-sparing effect of LABA-ICS maintenance therapy

Twelve unique RCTs<sup>49,137-147</sup> compared the potential steroid-sparing effects of LABA-ICS combination therapy with ICS monotherapy. Seven trials<sup>49,137,138,140,141,144,147</sup> used an abrupt dose-reduction design in which asymptomatic patients receiving ICS monotherapy were randomized to receive the run-in dose of ICS monotherapy or half the run-in dose and the addition of a LABA. One trial<sup>142</sup> used the abrupt dose-reduction design in which asymptomatic on ICS monotherapy. Four trials<sup>139,143,145,147</sup> used a dose-tapering design in which asymptomatic patients receiving ICS monotherapy were randomized to receive ICS alone or the same dose of ICS and the addition of a LABA. Participants in both groups who achieved control of asthma were given the next dose down. This process was repeated until treatment failure or until no drug was administered. These designs were classified as Design 1 (for example, abrupt reduction) and Design 2 (for example, step down reduction).

Six trials<sup>49,137,142,144-146</sup> compared salmeterol-fluticasone with fluticasone alone, three<sup>138,140,141</sup> compared formoterol-budesonide with budesonide alone, one<sup>147</sup> compared salmeterol-budesonide with budesonide alone, and one<sup>143</sup> compared salmeterol-ICS with ICS (unidentified) alone. A fixed dose of LABA-ICS was compared with a fixed dose of ICS in all trials. The age of included participants was 18 years or older in eight (66.7%) studies.<sup>138-141,143,145-147</sup> Three trials<sup>49,137,146</sup> included only participants with moderate asthma, and one<sup>145</sup> included only participants with severe asthma. The remaining trials examined participants with asthma that was intermittent to mild (one trial),<sup>147</sup> intermittent to severe (three trials),<sup>138,140,141</sup> mild to moderate (one trial),<sup>139</sup> mild to severe (one trial),<sup>144</sup> and moderate to severe (one trial).<sup>143</sup> One trial<sup>142</sup> did not report the baseline severity of the participants. The median treatment duration was 24 weeks (IQR 16 to 37).

#### Methodological quality

The methodological quality of the 12 steroid-sparing studies was high (median Jadad score 3; IQR 3 to 3.5) (Table 14). Allocation concealment was considered adequate in one (8.3%) study and unclear in 11 (91.7%). Because of the high scores (Jadad score 3 or higher) of almost all studies, no sensitivity analyses were conducted.

Table 14: Methodological Quality of 12 Steroid-Sparing Studies					
Quality Component Number of Studies (%)					
Randomization	12 (100)				
Double-blinding	12 (100)				
Description of withdrawals and dropouts	10 (83.3)				
Appropriate method of randomization	2 (16.7)				
Appropriate method of double-blinding	3 (25.0)				
Inappropriate method of randomization	0 (0)				
Inappropriate method of double-blinding	0 (0)				
Adequate concealment of treatment allocation	1 (8.3)				
Inadequate concealment of treatment allocation	0 (0)				
Unclear concealment of treatment allocation	11 (91.7)				

All 12 steroid-sparing studies contributed at least one outcome for meta-analysis of the effectiveness of different LABA-ICS combinations on clinical outcomes. The following results focus on the key outcomes on pulmonary function, symptom control, and quality of life. The pooled estimates of effect appear in Table 15. A description of the characteristics of the studies that were pooled for each outcome, subgroup analyses, potential sources of statistical heterogeneity, and forest plots appear in Appendix 7. It was considered inappropriate to conduct subgroup analyses based on asthma severity for any outcome measures, because a small proportion of studies (less than 20% of available studies for any one outcome) reported results for populations restricted to one asthma severity class.

#### **Pulmonary function measures**

The results of meta-analysis indicated a statistically significant difference favouring LABA-ICS for morning and evening PEF and for absolute and per cent-predicted  $FEV_1$ . Because none of the differences was clinically important when compared with a priori selected MCIDs, the precision of the 95% CIs indicated clinical equivalence between treatments for absolute and per cent-predicted  $FEV_1$ .

#### Asthma control measures

A meta-analysis indicated a statistically significant difference favouring LABA-ICS for an increase in SFDs and a reduction in mean ICS dose. The precision of the 95% CI for SABA use suggested potential clinical equivalence between the two treatments. A subgroup analysis indicated a clinically important difference favouring LABA-ICS for reducing SABA use in Design 2. There were no clinically important differences between treatments for the remaining measures.

#### Asthma quality-of-life measures

The pooled results did not indicate a statistically significant difference between the two treatments in AQLQ score.

Outcome	No. of	on Therapy (12 studies) Pooled Estimate (95% CI)	l <sup>2</sup> (%)	A Priori MCID
outcome	Studies (No. of patients)	1 Obeu Estimate (33 / 61)	1 (70)	
Pulmonary function	_ <b> </b> ,			
PEF a.m.	10	WMD 18.20 (14.24 to	0	18.79 L/min
	(2,660)	22.16)		
Design 1	7 (2,408)	WMD 17.58 (13.25 to	0	
	2 (252)	21.90)		
Design 2	3 (252)	WMD 21.44 (11.60 to	0	
PEF p.m.	7 (1,323)	31.28) WMD 16.12 (11.71 to	0	18.79 L/min
гег р.ш.	/(1,525)	20.53)	0	16./9 L/IIIII
Design 1	4 (1,071)	WMD 15.70 (10.80 to	0	
Dough	. (1,071)	20.59)	Ū	
Design 2	3 (252)	WMD 17.94 (7.78 to 28.09)	0	
FEV <sub>1</sub> (absolute)	7 (1,171)	WMD 0.09 (0.06 to 0.12)	0	0.23 L
Design 1	4 (919)	WMD 0.09 (0.05 to 0.12)	0	
Design 2	3 (252)	WMD 0.15 (-0.02 to 0.31)	0	
FEV <sub>1</sub> (% predicted)	5 (1,241)	WMD 4.75 (2.38 to 7.11)	41	10% to 12%
Design 1	4 (1,217)	WMD 4.25 (2.03 to 6.47)	35	
Design 2	1 (24)	WMD 9.70 (2.77 to 16.63)	NA	
Asthma symptom control				
Total number of exacerbations	0			Not available
Time to first exacerbation	0	NA	NA	Not available
% participants with 1 or more exacerbations	2 (494)	RR 1.23 (0.59 to 2.56)	0	Not available
Design 1	1 (308)	RR 1.65 (0.40 to 6.76)	NA	
Design 2	1 (186)	RR 1.11 (0.47 to 2.61)	NA	
Number of severe exacerbations	2 (912)	WMD -0.18 (-0.40 to 0.04)	0	Not available
Number of mild exacerbations	2 (912)	WMD 22.98 (-12.84 to 58.79)	94	Not available
SABA use (puffs/day)	6 (2,146)	WMD -0.17 (-0.38 to 0.04)	92	-0.81 puffs/day
Design 1	5 (2,112)	WMD -0.15 (-0.35 to 0.05)	93	_ •
Design 2	1 (34)	WMD -2.56 (-4.82 to -0.30)	NA	
Symptom-free days (median %)	6 (2,194)	WMD 5.24 (1.26 to 9.21)	52	
Design 1	5 (2,034)	WMD 5.57 (1.45 to 9.70)	59	
Design 2	1 (160)	WMD -4.40 (-25.5 to 16.70)	NA	
Days with optimal control	0	NA	NA	Not available

Table 15: Steroid-Sparing Effect of Long-Acting Beta2-Agonist and Inhaled Corticosteroid           Combination Therapy (12 studies)					
Outcome	No. of Studies (No. of patients)	Pooled Estimate (95% CI)	l <sup>2</sup> (%)	A Priori MCID	
Mean ICS dose	2 (150)	SMD -0.38 (-0.70 to -0.06)	0	Not available	
Design 1	1 (126)	SMD -0.40 (-0.75 to -0.04)	NA		
Design 2	1 (24)	SMD -0.28 (-1.09 to 0.52)	NA		
Health-related quality of life					
AQLQ	2 (161)	WMD 0.54 (-0.19 to 1.27)	76	0.5	
Design 1	1 (137)	WMD 0.24 (0.04 to 0.44)			
Design 2	1 (24)	WMD 1.00 (0.29 to 1.71)			

 $AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; FEV_1 = forced expiratory volume in one second; ICS = inhaled corticosteroid; MCID = minimal clinically important difference; min = minute; NA = not available; PEF = peak expiratory flow; RR = relative risk; SABA = short-acting beta_2-agonist; SMD = standardized mean difference; WMD = weighted mean difference.$ 

#### Discussion

Twelve studies involving a total of 3,352 participants evaluated the potential steroid-sparing effects of LABA-ICS combination therapy versus ICS monotherapy. Meta-analyses failed to indicate clinically important differences between LABA-ICS and ICS for any pulmonary function measures. There were statistically significant differences favouring LABA-ICS for increase in SFDs and reduction of mean ICS dose. Subgroup analyses indicated a statistically significant reduction in SABA use favouring LABA-ICS for step-down reduction of ICS (Design 2).

This systematic review identified two more RCTs for LABA-ICS combination therapy compared with ICS monotherapy than a previous systematic review and meta-analysis,<sup>13</sup> which included 19 publications describing 10 trials. Despite the difference in the number of trials, the results of this review are congruent with those of the previous review, which reported that LABA-ICS combination therapy has an ICS-sparing effect. This review found that LABA-ICS combination therapy also reduces SABA use when compared with ICS monotherapy.

*Generalizability:* Most asthma is managed in a primary care setting. Most guidelines recommend adding LABA-ICS combination agents when asthma is uncontrolled with moderate doses of ICS monotherapy. Clinicians have to select the dose of ICS agent, taking into account the potential for dose-related side effects (especially the development of cataracts). Therefore, clinicians, especially those in the developed world, need evidence that supports dose reduction while control is maintained or improved. Many countries were represented in the included studies, suggesting few limitations on the generalizability of the results. The high adherence likely to be achieved in these trials may limit the generalizability of the results.

*Implications for practice:* In addition to the assessment of statistical significance, the MCID between treatments that have been reported in the literature was emphasized. For most of the outcomes in this comparative effectiveness review, the MCID was not reached. The range of difference as indicated by the 95% CIs for three outcomes suggested a clinical equivalence

between LABA-ICS combination and ICS monotherapy. Furthermore, primary endpoints or outcomes in asthma drug trials should be important to the patient, clinically relevant, and related to the goal of the trial. For example, it is debatable whether small lung function changes are clinically relevant for the management of asthma or important to the patient. The failure of this systematic review to identify clinically important differences in quality-of-life benefits or exacerbation reductions suggests a lack of difference between the treatments. The wide confidence intervals, limited number of studies, and small number of patients studied prevent a conclusion of equivalence.

*f)* **Comparative safety of LABA-ICS therapies for adults with persistent asthma** Twenty-four low-dose trials, <sup>45-47,56,57,59,61-65,68,69,72,74,81,91,98,100,102,103,113,122,123</sup> 37 medium-dose trials, <sup>29,49,53,60,66,67,70,82-85,87-90,92,94-96,99,105-107,109,110,112,114,117,119,121,124-126,137,140,144,147</sup> and 18 highdose trials <sup>73,75,76,80,93,97,101,104,108,115,116,118,120,141-143,145,146</sup> reported data on the safety of LABA-ICS combination therapy compared with ICS monotherapy based on 10 events that were clinically relevant: number of participants reporting one or more AEs (61 trials), total serious adverse events (53 trials), headache (51 trials), withdrawals due to AE (49 trials), upper respiratory tract infections (39 trials), candidiasis (29 trials), treatment-related AEs (28 trials), worsening asthma (27 trials), deaths (fatal serious adverse events [26 trials] and all-cause mortality [four trials]), and hoarseness (19 trials).

The pooled estimate for worsening asthma indicated a statistically significant difference favouring LABA-ICS. Pooled estimates for the remaining nine of the 10 events did not indicate a statistically significant difference between the two treatments (Table 16). Subgroup analyses based on comparison ICS dose indicated no clinically important differences from the overall pooled results for nine of the 10 outcomes.

#### Discussion

The safety of LABA-ICS combination therapy compared with ICS monotherapy was evaluated based on data from 79 RCTs involving a total of more than 30,000 participants reporting data on 10 key safety measures. There were no differences between the treatments for nine of the 10 measures. The worsening of asthma was reduced by 22% (95% CI 34% to 10%) when using LABA-ICS therapy.

The results of this study are comparable with two examinations of the safety of LABA-ICS combination therapy compared with ICS monotherapy. Jaeschke et al.<sup>20</sup> examined 62 RCTs and found no differences between LABA-ICS combination therapy and ICS monotherapy for risk of asthma-related hospitalizations, non-fatal serious adverse events, and all-cause mortality. Bateman et al.<sup>16</sup> examined 66 RCTs comparing salmeterol-ICS with ICS monotherapy and found a decrease in risk of severe exacerbations (requiring oral corticosteroids) favouring salmeterol-ICS and no difference between treatments for asthma-related hospitalizations. Our results are similar to those of the authors of both reviews, who concluded that a paucity of data precluded any conclusions about the effect of LABA-ICS on asthma-related deaths and intubations.

Table 16: Safety of Long-Acting Beta2-Agonists Used with Inhaled Corticosteroids Compared with Inhaled Corticosteroid Monotherapy (79 studies)							
Outcome		No. of Studies Reporting Outcome Data (No. of events / No. of participants)	No. of Studies Contributing to Pooled Estimate* (No. of events / No. of participants)	Pooled Estimate (95% CI)	l <sup>2</sup> %		
Number participa experier more A	ants noing 1 or	61 (16,647/29,506)	59 (16,647/29,311)	RR 0.99 (0.97 to 1.01)	5		
Total SA	AEs	53 (843/28,781)	All studies	RR 1.03 (0.90 to 1.19)	0		
Headacl	ne	51 (2,167/26,323)	All studies	RR 0.95 (0.88 to 1.03)	0		
Withdra AE	wal due to	49 (643/24,800)	48 (643/24,638)	RR 0.98 (0.83 to 1.15)	0		
Upper re tract inf	espiratory ection	39 (2,468/20,553)	All studies	RR 1.01 (0.94 to 1.09)	0		
Candidi	asis	29 (339/16,196)	All studies	RR 0.85 (0.64 to 1.14)	18		
Treatme AEs	ent-related	28 (611/14,550)	19 (611/11,792)	RR 1.10 (0.93 to 1.29) RD -0.00 (-0.00 to 0.00)	0		
Worsen	ing asthma	27 (723/11,504)	All studies	RR 0.78 (0.66 to 0.90)	5		
Death	Fatal SAE	26 (7/10,621)	6 (7/4,449)	RR 0.89 (0.24 to 3.24) RD -0.00 (-0.00 to 0.00)	0		
	All-cause mortality	4 (4/2,944)	2 (4/2,040)	RR 0.42 (0.06 to 2.84)	0		
Hoarser	iess	19 (276/9,872)	All studies	RR 1.18 (0.93 to 1.50)	0		

AE = adverse event; CI = confidence interval; RD = risk difference; RR = risk ratio; SAE = serious adverse event. \*Risk ratios could not be calculated for studies that reported no events for intervention and control arms.

One key issue for clinicians and patients is the side effects (especially fatalities) that are associated with LABA-ICS combination therapy. Therefore, evidence of safety while asthma control is maintained or improved is clinically important. The combined studies are based on many populations in many countries and cover intermittent to severe asthma in patients ranging in age from 12 years to 80 years with varied baseline characteristics (for example, ICS use, asthma history, and smoking history). The high adherence that is likely to be achieved in these trials may limit the generalizability of the results.

*Implications for practice:* This review emphasized the 10 key side effects commonly reported in the literature. For most of the outcomes in this comparative effectiveness review, there was no strong evidence of increased risks associated with the addition of LABA to ICS therapy. The failure of this systematic review to identify clinically important side effect differences, the narrow confidence intervals, and the large number of studies and patients included suggest a conclusion of equivalence for all but the rarest side effects (such as death). Moreover, there is evidence that asthma control is improved with LABA-ICS combination therapy.

# 5 ECONOMIC ANALYSIS

### 5.1 Review of Economic Studies

A review of economic evaluations compared LABA-ICS combination therapy with ICS monotherapy for asthma in patients 12 years of age or older. Studies that examined the comparative efficacy of different LABAs and those examining fixed versus variable dosing of the LABA formoterol were reviewed. The results appear in Appendix 11.

#### 5.1.1 Methods

#### a) Literature search strategy

A systematic literature review focused on studies that reported the costs and outcomes of LABA-ICS therapy and head-to-head comparisons of LABA in the treatment of asthma. No language restrictions or limitations to searches were imposed.

The search strategy was similar to that of the clinical review with additional economic terms (Appendix 1.2). References that were provided by pharmaceutical manufacturers and the reference lists of all included studies and review articles were scanned to identify additional potentially relevant studies.

#### b) Selection criteria

Studies that compared the costs and outcomes of LABA-ICS therapy compared with ICS monotherapy were included. Studies were included even if they did not relate cost to outcome data in a cost-effectiveness or cost-utility analysis. Two reviewers (DC, KC) assessed all abstracts for relevance, and full texts were obtained for those judged to be potentially relevant.

#### c) Selection method

Using the literature search strategy, 992 studies were initially identified. The abstracts and titles of these studies were reviewed. Additional studies were identified by manufacturers or through reviewing the reference lists of potentially relevant studies. In total, 54 studies were identified as potentially relevant. Full papers and reports were examined by both reviewers (DC, KC). Studies were included if both reviewers agreed on relevance. Disagreements were resolved by consensus. Of the 54 reports examined, 17 met the inclusion criteria.

#### d) Data extraction strategy

Data were extracted by one reviewer (DC, KC) and verified by the other reviewer. Data were extracted on publication information, population characteristics, treatment, form of analysis, health care resources, perspective, time horizon, and results (Appendix 12 Tables 1-4).

#### e) Strategy for assessing validity of included studies

It is necessary to assess the quality of economic studies of the use of LABAs for asthma to determine the suitability of studies in aiding decision-making about the cost-effectiveness of treatments. A 10-point checklist as suggested by Drummond et al.<sup>148</sup> for assessing the quality of economic evaluations was adopted (Appendix 9). Two reviewers (DC, KC) assessed each included study for quality. Disagreements were resolved through consensus.

#### f) Data analysis methods

Data from all included studies were appraised to identify common results, variations, and weaknesses.

#### 5.1.2 Results

#### a) Studies identified

A total of 54 articles were selected, and 17 met the inclusion criteria.<sup>130,149-164</sup> An additional study was identified by industry. Reasons for exclusion included the following: comparators did not include LABA (22 studies), abstract only (four studies), cost and outcomes not reported (four studies), device study (two studies), review articles (two studies), children only (one study), and LABA not in combination with ICS (two studies). Of the 18 included studies, three examined a fixed compared with variable dosing regimen for formoterol, <sup>158,159,165</sup> and four were head-to-head comparisons of two LABAs.<sup>160-163</sup> Descriptions of these studies appear in Appendices 10 and 11.

Of the remaining 11 studies, six focused on the cost and efficacy of LABA-ICS therapy in patients with mild to moderate asthma that was not controlled on ICS monotherapy,<sup>5,149-153</sup> and five studies examined LABA-ICS therapy in patients with moderate to severe asthma that was not controlled on ICS monotherapy.<sup>130,154-157</sup>

# b) Studies comparing LABA-ICS combination therapy with ICS monotherapy for mild to moderate asthma

Six studies compared LABA-ICS combination therapy with ICS monotherapy in patients with mild to moderate asthma (Appendix 12 Tables 1 and 2). Four of these studies examined salmeterol-fluticasone, <sup>151-153,164</sup> and two examined formoterol-budesonide.<sup>149,150</sup> The doses included budesonide 200 mcg/day to 800 mcg/day, formoterol 9 mcg/day to 24 mcg/day, fluticasone 200 mcg/day to 1,000 mcg/day, and salmeterol 100 mcg/day. In all studies, the addition of the LABA was compared with the same dose of ICS. In one study, a higher dose of ICS was compared with a combination that included a lower dose of ICS.<sup>149</sup> Two studies were conducted from a Swedish context;<sup>149,161</sup> two from a UK context;<sup>151,158</sup> one from a Swedish, UK, and Spanish context;<sup>150</sup> and one from a US context.<sup>164</sup>

Five studies were cost-effectiveness analyses.<sup>149,150,158,161,164</sup> Four studies measured effectiveness by SFDs,<sup>149,150,152,164</sup> two by successfully controlled weeks,<sup>152,153</sup> and one by rescue-free days.<sup>164</sup> One study included a cost-utility analysis that used a mapping algorithm to convert asthma quality-of-life scores to quality-adjusted life-years (QALYs).<sup>151</sup> For all studies the effectiveness data were derived from an RCT of one year's<sup>149-151,164</sup> or 12 weeks' duration.<sup>152,153</sup> All studies included analysis from a health care perspective. Two studies also conducted analysis from a societal perspective.

In all studies, asthma medication and health care resource use data were collected from the RCTs. For the two studies examining a societal perspective, data on days of work loss were also derived from the RCT.

Most studies found that LABA-ICS was more costly and more effective than a similar dose of ICS. In one study, LABA-ICS was dominant (less costly and more effective). This result only applied in certain settings.<sup>150</sup>

In all but one study,<sup>151</sup> the results of cost-effectiveness analyses were reported as a cost per SFD, successfully treated week, or rescue-free days. The use of these endpoints instead of QALYs precludes comparisons with other diseases, and recommendations are difficult to make. In the cost-utility analysis,<sup>151</sup> the cost was £13,700 per QALY at a low dose, £11,000 at a moderate dose, and £7,600 at a high dose for salmeterol-fluticasone compared with fluticasone alone.

All studies were funded by the pharmaceutical industry: AstraZeneca (two trials) and GlaxoSmithKline (four trials).

#### c) Studies comparing LABA-ICS to ICS alone for moderate to severe asthma

Details of the four studies that compared LABA-ICS with ICS alone in patients with moderate to severe asthma appear in Appendix 12 Tables 3 and 4. Two studies<sup>155,156</sup> compared salmeterol-fluticasone with a similar dose of fluticasone alone, and two studies compared formoterol-budesonide with a higher dose of fluticasone<sup>157</sup> and salmeterol-fluticasone with a higher dose of budesonide.<sup>154</sup> Three studies were conducted from a Swedish context,<sup>154-156</sup> and one was conducted from the context of Germany and the Netherlands.<sup>157</sup>

All four studies were cost-effectiveness analyses, and all reported the cost per episode-free day. Three studies also reported the cost per successfully controlled week and SFD.<sup>154-156</sup> In all cases, the effectiveness data were derived from RCTs that lasted 12 weeks, except in one study, which lasted 24 weeks.<sup>154</sup> The health care system perspective was used in all studies. One study included a secondary analysis from a societal perspective.<sup>157</sup>

Resource use (asthma medication, health care resource, and productivity costs) was collected from the RCTs.

In one study, LABA-ICS was dominant (less costly and more effective).<sup>157</sup> In the other three studies, LABA-ICS was more costly and more effective.<sup>154-156</sup> In these studies, outcomes are expressed as costs per SFD, episode-free day, or successfully treated week. Because these outcomes cannot be compared with those of other diseases, the results cannot be easily interpreted.

All studies were funded by the pharmaceutical industry: AstraZeneca (one) and GlaxoSmithKline (three).

#### d) Methodological quality

Details about the quality assessment of studies appear in Appendix 13.

Based on the 10-point checklist, every study was of sufficient quality for most of the checklist items (six to nine items where the studies were of sufficient quality).

The checklist item that was least likely to be of sufficient quality was the valuation of resource use (16 of 18 studies and 10 of the 10 studies), because most studies collected resource use from many countries and applied unit costs from one country.

All studies were of sufficient quality in establishing the effectiveness of treatment programs, the measurement of resource use, and the adjustment of differential timing (because of the limited time horizon of all studies).

#### 5.1.3 Summary and discussion

Based on the Drummond 10-point checklist, the 10 studies examining the cost-effectiveness of LABA-ICS compared with ICS alone were reasonably high quality.

One study was a formal cost-utility analysis. This limited the applicability of the studies to decision-making. In all 10 studies, unit costs were derived for a different country than at least a proportion of the resource use data. All studies were funded by the pharmaceutical industry. Seven of the 10 studies compared LABA-ICS combinations with similar-dose ICS monotherapy instead of higher-dose ICS monotherapy. No studies were Canadian. Given these weaknesses among the studies, the completion of a full economic analysis from a Canadian context was appropriate.

### 5.2 Economic Evaluation

#### 5.2.1 Objective

The objective of the primary economic evaluation was to assess the cost-effectiveness of LABA-ICS maintenance therapy compared with ICS monotherapy for ICS-naive patients and those with asthma that is uncontrolled on low- or medium-dose ICS monotherapy.

#### 5.2.2 Methods

#### a) Type of economic evaluation

The primary analysis was a cost-utility analysis, and the secondary analysis was a cost-effectiveness analysis. All analyses followed the CADTH guidelines for economic evaluations.<sup>166</sup>

#### b) Target population

The cost-effectiveness of LABA-ICS therapy was assessed in three groups:

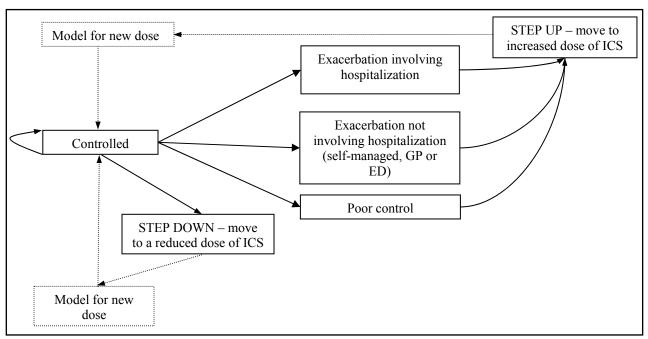
- patients with asthma who are aged 12 years or older and who are steroid-naive
- patients who are aged 12 years or older with asthma that is uncontrolled on a low dose of ICS monotherapy
- patients who are aged 12 years or older with asthma that is uncontrolled on a medium dose of ICS monotherapy.

#### c) Comparators

The analysis was a comparison of four strategies that were based on the optimum time to introduce a LABA-ICS:

- Strategy A: after asthma is uncontrolled on high-dose ICS monotherapy
- Strategy B: after asthma is uncontrolled on medium-dose ICS monotherapy
- Strategy C: after asthma is uncontrolled on low-dose ICS monotherapy
- Strategy D: at the onset of ICS therapy for ICS-naive patients (Appendix 14 Figure 1).





ED = emergency department; GP = general practitioner; ICS = inhaled corticosteroid.

The dose of ICS was based on Canadian guidelines for the management of asthma<sup>4</sup> (Appendix 14 Table 1). It was assumed that steroid-naive patients start on the same dose of ICS whether they begin on LABA-ICS therapy or ICS monotherapy. It was also assumed that patients with uncontrolled asthma would have a LABA added to the dose of ICS, or the dose of ICS would be increased during monotherapy.

Given the paucity of data and lack of differences between LABA-ICSs, the analysis was conducted for LABA-ICSs as a group instead of comparing each type of combination therapy with ICS monotherapy.

#### d) Perspective

The analysis was conducted from the perspective of a provincial ministry of health.

#### e) Effectiveness

In the primary analysis, effectiveness was assessed in QALYs. In the secondary analysis, the following outcomes of effectiveness were assessed: exacerbations avoided and successfully controlled weeks.

#### f) Time horizon

The primary analysis was conducted for a 12-week time horizon, and the secondary analysis for one year.

#### g) Modelling

A Markov cohort model was developed using Microsoft Excel to predict the outcomes of the four pharmaceutical management strategies.<sup>167</sup> A cycle length of one week was used. The patient

cohort (Figure 3) transitions each week in prescribed drug therapy (same dose, reduced dose [step down], and increased dose [step up]) and incidence of exacerbations (self-managed, general practitioner- [GP-] managed, emergency department visits, and hospitalizations). For each new dose, the model structure is replicated, and new transition probabilities and drug costs will apply.

#### h) Transition probabilities

For each treatment option, the following probabilities are required:

- step up in therapy
- step down in therapy
- exacerbation
- self-managed exacerbation
- medically managed exacerbation (managed solely by a GP)
- discharge without hospitalization of a patient reporting to the emergency department with an exacerbation.

The probability of a step up in monotherapy and in combination therapy was taken from the RCTs in the clinical review and was based on the withdrawal rates that were used in previous models.<sup>25</sup> First, the withdrawal rates of the ICS monotherapy arms were transformed to weekly rates, and then they were combined as a weighted sum to obtain a baseline weekly rate. Next, the relative risk of withdrawal on combination therapy compared with monotherapy was obtained by conducting a meta-analysis of the weekly withdrawal rates. The weekly withdrawal rate in combination therapy was the product of the rate for monotherapy and the relative risk.

The probability of step down in therapy was unavailable from the RCTs. Thus, we used the same rate as was used in a National Health Service HTA<sup>25</sup> where the rate was assumed to be constant for all treatment options. For patients on a low dose of ICS, we assumed no probability of step down.

The probability of an exacerbation during monotherapy and combination therapy was taken from the RCTs in the clinical review. First, exacerbations during ICS monotherapy were transformed to weekly exacerbation rates, and then they were combined as a weighted sum to get a baseline weekly rate. Next, the relative risk of exacerbation on combination therapy compared with monotherapy was obtained by conducting a meta-analysis of the weekly rates. The weekly exacerbation rate during combination therapy was the product of the rate during monotherapy and the relative risk.

The definition of exacerbation differed among studies. Therefore, data on all severities of exacerbation were used. To determine the distribution of the severity of exacerbations, probabilities of the management of exacerbation were derived from Canadian studies.<sup>168,169</sup> Because insufficient data were available from the published studies, we assumed that therapy affects the rate of exacerbation, not the type of exacerbations. The direction of bias resulting from this assumption is unknown, but the impact was tested by sensitivity analysis.

In the baseline analysis, we assumed that no exacerbations are self-managed. This can be an assumption that is biased in favour of the more active therapies and was subjected to sensitivity analysis. The probability that a medically managed exacerbation is managed solely by a GP was derived from a study of urgent care costs. This study provided the number of exacerbations that

were managed medically and the number that required only visits to the GP.<sup>169</sup> For all other medically managed exacerbations, we assumed that patients went to an emergency department. The probability that a patient reporting to the emergency department with an exacerbation is discharged without hospitalization was derived from a study in Alberta with data from 2004 to 2005.<sup>168</sup>

#### *i)* Resource use and costs

The analysis required estimates of the weekly costs of drug therapy and the costs that were associated with the management of exacerbations. All costs were estimated in 2008 Canadian dollars. The weekly costs of drug therapy were estimated as the weighted average of combination therapies and ICS monotherapy with low, medium, and high doses of ICS (Appendix 14). We calculated the prescription costs of each drug therapy based on data from the Ontario Drug formulary and included an 8% pharmacist's mark up and a \$7 dispensing fee.<sup>170</sup> A weekly cost was estimated to be the total cost of a prescription divided by the number of weeks of therapy per prescription based on the assumed fixed daily dosage.

The costs of exacerbations were obtained from Canadian sources. The costs of a GP-managed exacerbation were derived from the Ontario Schedule of Fees and Benefits.<sup>171</sup> The cost of an emergency department-managed exacerbation was obtained from a Canadian study and then updated to 2008 Canadian dollars based on the Bank of Canada inflation calculator.<sup>169,172</sup> The costs of hospitalizations were derived from the Ontario Case Costing Initiative data.<sup>173</sup>

#### j) Discount rate

Given the limited time horizon of the primary and secondary analyses, no discounting was applied.

#### k) Valuing outcomes

Weekly utility values were derived from a UK National Institute for Health Research HTA report.<sup>25</sup> Utility values were obtained for asthma without exacerbations, exacerbation without hospitalization, and exacerbation with hospitalization. Alternative estimates of utility values were used in a sensitivity analysis.<sup>151,153</sup>

#### I) Base analysis

Base analysis was conducted through a deterministic analysis in which point estimates for each parameter were entered into the model. This provides an estimate of the costs, QALYs, and effectiveness for each alternative, and allows estimation of incremental cost-effectiveness ratios.

#### m) Analysis of uncertainty

Univariate sensitivity analysis was conducted to assess the robustness of the study's results to changing assumptions in the model.<sup>174</sup> Specific analyses were:

- analysis for 52 weeks instead of 12 weeks
- assumptions that different rates of exacerbations were managed through self care (25%, 50%, 75%, base case 0%)
- assumptions that LABA-ICS reduces the proportion of exacerbations requiring medical management (25%, 50%, 75%, base case 100%)
- alternative estimates of utility values<sup>151,153</sup>
- halving and doubling the costs of exacerbations

- highest and lowest relative risks for step up from an RCT in the meta-analysis
- highest and lowest relative risks for exacerbations from an RCT in the meta-analysis
- assumptions that there was no step down on ICS monotherapy.

In addition, three threshold analyses were conducted. For each set of parameters, the analysis focused on identifying the values required for incremental cost-utility ratios to be lower than \$50,000. Analysis was conducted on the additional SABA use by patients on ICS monotherapy, a percentage increase in the disutilities that were associated with exacerbations, and a percentage increase in the costs that were associated with exacerbations.

Probabilistic analysis was conducted using a Monte Carlo simulation using the relative risk reductions that were associated with treatment.<sup>175</sup> The probability distributions of transition probabilities, relative risks, cost, and utilities were incorporated into the analysis. Estimates of incremental costs and QALYs were obtained by rerunning the model using values from the related probability distributions. In this study, 3,000 replications were conducted (a set of 3,000 outcome estimates was obtained). Cost-effectiveness acceptability curves present the probability that each therapy is optimal given different values of willingness to pay for an additional QALY.<sup>176</sup>

#### 5.2.3 Results

#### a) Parameter values

Parameter estimates and probability distributions for all variables in the analysis appear in Appendix 14 Tables 2 to 4.

#### b) Base analysis

The results of the cost-utility analysis appear in Table 17. The incremental QALY gain is small for all strategies at 12 weeks and one year. Total costs are higher the earlier that LABA is introduced. The incremental cost per QALY gained is similar at 12 weeks and at one year.

The incremental cost per QALY gained for LABA is lower the later it is introduced into therapy although differences in QALY are small. With steroid-naive patients, the incremental cost per QALY gained from treatment with LABA-ICS combination therapy instead of ICS monotherapy is \$3.3 million. For patients with asthma that is uncontrolled on low-dose ICS, the incremental cost per QALY gained from treatment with LABA plus low-dose ICS instead of medium-dose ICS monotherapy is \$1.6 million. For patients with asthma that is uncontrolled on medium-dose ICS, the incremental cost per QALY gained from treatment with LABA plus low-dose ICS instead of medium-dose ICS, the incremental cost per QALY gained from treatment with LABA plus medium-dose ICS, the incremental cost per QALY gained from treatment with LABA plus medium-dose ICS instead of high-dose ICS monotherapy is \$190,000.

Table 17: Base Results of Cost-Utility Analysis						
	Total Cost (\$)	Total QALYs	Incremental Cost per QALY Gained (\$)			
12-week time horizon						
Strategy A: Introduce LABA after asthma is uncontrolled on high-dose ICS monotherapy	74.84	0.1798231				
Strategy B: Introduce LABA after asthma is uncontrolled on medium-dose ICS monotherapy	74.86	0.1798232	193,793.88 <sup>1</sup>			
Strategy C: Introduce LABA after asthma is uncontrolled on low-dose ICS monotherapy	78.78	0.1798256	1,627,739.53 <sup>2</sup>			
Strategy D: Introduce LABA to ICS-naive patients	183.19	0.1798572	3,297,180.25 <sup>3</sup>			
One-year time horizon						
Strategy A	353.70	0.7790921				
Strategy B	355.12	0.7790998	184,224.85*			
Strategy C	426.56	0.7791411	1,726,992.86 <sup>†</sup>			
Strategy D	842.75	0.7792474	3,915,346.07 <sup>‡</sup>			

ICS = inhaled corticosteroid; LABA = long-acting beta<sub>2</sub>-agonist; QALYs = quality-adjusted life-years.

\*Versus Strategy A.

†Versus Strategy B. ‡Versus Strategy C.

The results of the secondary cost-effectiveness analysis (Table 18) are similar to the findings of the cost-utility analysis on the decline in the incremental cost-effectiveness ratio the later that LABA is introduced into therapy. The incremental cost per successfully controlled week ranged from \$57 after the addition of LABA when asthma is uncontrolled on medium-dose ICS to \$1,375 when treatment-naive patients start on LABA-ICS therapy. The incremental cost per exacerbation avoided ranged from \$787 for the addition of LABA when asthma is uncontrolled on medium-dose ICS to \$13,385 when treatment-naive patients start on LABA-ICS therapy.

Table 18: Results of Cost-Effectiveness Analysis					
	Cost (\$)	Number of Exacerbations	Controlled Weeks	Incremental Cost per Exacerbation Avoided (\$)	Incremental Cost per Additional Controlled Weeks (\$)
12-week time horizon					
Strategy A	74.84	0.04358	10.8393		
Strategy B	74.86	0.04356	10.8396	786.69*	56.85*
Strategy C	78.79	0.04296	10.8478	6607.69 <sup>†</sup>	476.29 <sup>†</sup>
Strategy D	183.19	0.03516	10.9238	13,384.66 <sup>‡</sup>	1374.56 <sup>‡</sup>
One-year time horizon					
Strategy A	353.70	0.22366	27.8431		
Strategy B	355.12	0.22176	27.9595	747.85*	12.19*
Strategy C	426.56	0.21157	28.5845	7010.60 <sup>†</sup>	114.31 <sup>†</sup>
Strategy D	842.75	0.18538	29.6783	15,894.06 <sup>‡</sup>	380.51 <sup>‡</sup>

\*Versus Strategy A.

†Versus Strategy B.

‡Versus Strategy C.

#### c) Sensitivity analysis

The results of the univariate sensitivity analysis (Appendix 15) seemed to be insensitive to changes in assumptions (the incremental cost-utility ratios do not differ from the base-case analysis).

A threshold analysis focused on the required incremental weekly SABA use during ICS monotherapy that would lead to an incremental cost per QALY gained of \$50,000 based on a 12-week time horizon. Among steroid-naive patients, the incremental use of SABA during ICS monotherapy would be 231 additional puffs per week. For patients with asthma that is uncontrolled using low-dose ICS monotherapy, the incremental use of SABA would be 324 additional puffs per week. For patients with asthma that is uncontrolled using medium-dose ICS monotherapy, the incremental use of SABA would be 62 additional puffs per week.

A threshold analysis of exacerbations focused on the required percentage increase in disutility that would lead to an incremental cost per QALY gained of \$50,000 based on a 12-week time horizon. Among steroid-naive patients, the increase would be 3,180% (equivalent to utility values of -13.1 for non-hospitalizations and -28 for hospitalizations). Among patients with asthma that is uncontrolled using low-dose ICS, the increase would be 1,550% (equivalent to utility values of -6.1 for non-hospitalizations and -10.1 for hospitalizations). Among patients with asthma that is uncontrolled using medium-dose ICS, the increase would be 140% (equivalent to utility values of -0.04 for non-hospitalizations and -0.61 for hospitalizations).

A threshold analysis of the costs of exacerbations focused on the required incremental percentage increase in costs that would lead to an incremental cost per QALY gained of \$50,000 based on a 12-week time horizon. Among steroid-naive patients, the increase in costs would be 15,710% (equivalent to the costs of a GP-managed exacerbation of \$8,900 and a hospital-managed exacerbation of \$560,000). Among patients with asthma that is uncontrolled using low-dose ICS, the increase in costs would be 7,300% (equivalent to the costs of a GP-managed exacerbation of \$274,000). Among patients with asthma that is uncontrolled on medium-dose ICS, the increase in costs would be 700% (equivalent to costs of a GP-managed exacerbation of \$274,000). Among patients with asthma that is uncontrolled on medium-dose ICS, the increase in costs would be 700% (equivalent to costs of a GP-managed exacerbation of \$450 and a hospital-managed exacerbation of \$28,000).

#### d) Probabilistic analysis

The incremental cost per QALY gained from introducing LABA was higher in the probabilistic analysis compared with the deterministic analysis (Appendix 15 Table 2). When ICS plus low-dose LABA was compared with low-dose ICS alone for treatment-naive patients, ICS monotherapy dominated (less costly and more effective). The difference in the results from the deterministic analysis arises because of the uncertainty about the estimates of relative risks. The base value of the relative risk that is used in the deterministic analysis is the median value that is reported in the meta-analysis. It is not the expected value of the relative risk (as defined by the lognormal distribution), which is higher than the median value. Thus, the higher incremental cost per QALY gained that was determined in the probabilistic analysis may be a truer estimate of the incremental cost-utility ratio.

The probabilities that each of the four treatment strategies is the optimum based on alternative threshold values of a QALY appear in Figure 4. For all threshold values, the probability that Strategy A or Strategy B is the optimum is 0%. The probability that strategy C is the optimum increases the higher the threshold value of a QALY, but it is not greater than 25%.

#### 5.2.4 Summary and Discussion

Ten economic evaluations comparing LABA-ICS with ICS alone were identified during a systematic review. The weaknesses of the studies included the form of analysis, funding, and comparators. Therefore, a full economic analysis from the Canadian context was conducted.

The economic analysis found that the later LABA was introduced into therapy the more costeffective the treatment strategy became. For all analyses, the introduction of LABA was associated with an incremental cost-utility ratio of greater than \$190,000. This suggests that the comparisons do not meet conventional definitions of cost-effectiveness. Thus, the optimum of the four strategies was introducing LABA to patients with asthma that was uncontrolled at high doses of ICS. The introduction of LABA before patients have tried high-dose ICS monotherapy does not seem to be justified based on the criteria of cost-effectiveness.

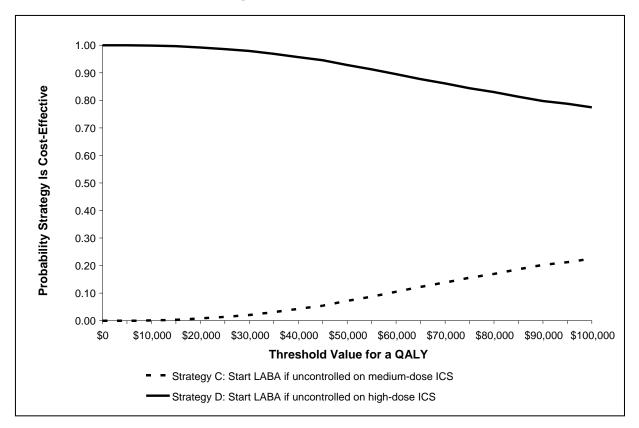


Figure 4: Cost-Effectiveness

 $ICS = inhaled \ corticosteroid; \ LABA = long-acting \ beta_2-agonist; \ QALY = quality-adjusted \ life-year.$ 

# 6 HEALTH SERVICES IMPACT

### 6.1 Population Impact

Because asthma commonly occurs among children and adults, many Canadians could be exposed to the benefits and risks of using LABA-ICS. This review suggests that the side effects of these drugs are no worse than those of accepted standard care with ICS monotherapy. Although uncertainty exists about the relative clinical effectiveness of LABA-ICS combinations, there is limited uncertainty relating to cost-effectiveness. Treatment using any LABA-ICS could be started only after a trial of ICS has been unsuccessful. In the health care environment, the impact of this decision could be huge. Reducing the cost of care, maintaining asthma control, and reducing hospitalization all have positive patient and societal impacts. As more non-specialist physicians learn more about LABA-ICS, it is likely that more patients will be using LABA-ICS.

### 6.2 Budget Impact

The objective of the budget impact analysis is to forecast expenditure on LABAs and ICSs that are used to treat asthma during 2008-2009, 2009-2010, and 2010-2011 based on different assumptions about changes in prescribing patterns. British Columbia data were used as a sample because these data included the required information on dose (Appendix 16).

The base-case analysis was the projected increase in expenditure during 2008-2009, 2009-2010, and 2010-2011 (Appendix 17 Table 1). If prescribing trends continue as they did during the past five years, the expenditure on asthma medications increases yearly. The impact of implementing each of the three scenarios at 25%, 50%, 75%, and 100% appears in Appendix 17 Tables 1 to 4.

If only those patients receiving a low-dose LABA-ICS are switched to receiving a higher-dose ICS, the cost savings by 2010-2011 are approximately \$11,000 (0.1%) per year for a 25% switch and approximately \$44,000 (0.4%) per year for a 100% switch.

Switching all patients receiving a low- and medium-dose LABA-ICS to receiving a higher-dose ICS provides savings ranging from more than \$125,000 (1.1%) per year for a 25% switch to approximately \$500,000 (4.6%) per year for a 100% switch.

If those on a low- and medium-dose LABA-ICS are switched to a higher-dose ICS, and those on single-inhaler LABA are given an increased dose of ICS, the cost savings range from approximately \$270,000 (2.5%) per year for a 25% switch to approximately \$1.1 million (10%) per year for a 100% switch.

In all scenarios, the forecasted expenditure on LABA-ICSs for patients with asthma will increase during the next three years even with switches from a low- and medium-dose LABA-ICS to higher doses of ICS monotherapy. Benefits will arise through reductions in the costs of therapy from switching to ICS monotherapy with the highest forecasted savings being approximately 10% of the associated budget. For these savings to come about, the introduction of LABAs has to be delayed until asthma is uncontrolled on high-dose ICS monotherapy.

The budget impact analysis estimates the impact on only the drug formulary budget (not on other health care resources). This reflects current practice. Changes in drug management may affect the overall health care budget through changes in the costs of general practice visits and of the management of exacerbations.

### 6.3 Ethical, Equity, and Psychosocial Issues

Benevolence and non-maleficence imply that any asthma therapy is efficacious and carries no incremental risk.<sup>177</sup> The results of this review imply that the best balance between these two principles will occur when the guidelines for asthma management are followed (adding LABA only after a trial of ICS monotherapy fails to control asthma symptoms). In addition, the high cost per QALY in various scenarios suggests that the widespread adoption of LABA-ICS therapy cannot be justified.

Starting LABA-ICS therapy without a trial of ICS monotherapy may affect patient autonomy by making pharmacologic treatment the cornerstone of management instead of other less costly, more patient-centred approaches. Despite the factors that influence asthma control and the potential for better adherence with complex regimens,<sup>178</sup> patients should be given the information and opportunity to maximize self-management and treatment adherence. A better understanding of the variables influencing non-adherence and the regular identification of patients' reasons for poor control might individualize approaches to improve adherence instead of using a "one-size-fits-all" pharmacological approach.<sup>178</sup> The high adherence likely achieved in the included trials may only be possible in a trial, reinforcing the need for adequate patient education about self-management.

Pharmaceutical industry-sponsored research has been shown to be biased toward the reporting of positive results for clinical topics.<sup>179-181</sup> Therefore, the frequent involvement of industry in studies of the effectiveness, safety, and cost-effectiveness of LABA-ICS therapies raise concern, especially given the evidence of industry bias in pulmonary and respiratory research.<sup>33</sup> It is unlikely that these studies could have occurred without such support given the cost of multicentre trials and the need to match dummy inhalers with proprietary devices. Detailed reporting of industry involvement in such trials would allow more assessments of potential industry bias.

# 7 DISCUSSION

### 7.1 Summary of Results

#### 7.1.1 Clinical review

In total, 107 unique RCTs assessed the clinical effectiveness and safety of LABA-ICS therapy compared with ICS monotherapy or another LABA-ICS. The methodological quality of the studies was moderate to high. Almost all were funded by the pharmaceutical industry. The results of meta-analyses indicated that LABA-ICS may have a clinically important benefit compared with ICS monotherapy in improving morning PEF, reducing SABA use and the risk of

an exacerbation, and increasing the number of SFDs for steroid-naive adults. Adding a LABA to the existing dose of ICS may have a clinically important benefit compared with ICS monotherapy in increasing morning and evening PEF, the number of SFDs, and the number of days with optimal control for adults with asthma that is uncontrolled on ICS monotherapy, and in reducing the number of exacerbations. Adding a LABA to the existing dose of ICS may have a clinically important benefit compared with doubling or quadrupling the dose of ICS monotherapy in reducing the risk of an exacerbation, and increasing the number of SFDs and days with optimal control for adults with asthma that is uncontrolled on ICS monotherapy. There are unlikely to be clinically important benefits of using one LABA-ICS compared with another in improving pulmonary function, asthma symptom control, or health-related quality of life. LABA-ICS seems to have a steroid-sparing effect for those with asthma that is controlled on ICS monotherapy. The similarity in the safety profile of the two treatments makes the clinical significance of this effect unclear. There were few, if any, statistically significant differences between the treatments for several clinically important AE measures, although LABA-ICS therapy may reduce the risk of worsening asthma when compared with ICS monotherapy.

#### 7.1.2 Economic analysis

Limitations in applying the results of economic evaluations to the Canadian context supported the need for a primary analysis. The incremental QALY gain from introducing LABA earlier is small for all comparisons at 12 weeks and one year. Total costs are higher the earlier that LABA is introduced in the four strategies. Among steroid-naive patients, the incremental cost per QALY gained from treatment with LABA-ICS combination therapy instead of ICS monotherapy is \$3.3 million. Among patients with asthma that is uncontrolled on low-dose ICS, the incremental cost per QALY gained from treatment with LABA plus low-dose ICS instead of medium-dose ICS monotherapy is \$1.6 million. For patients with asthma that is uncontrolled on medium-dose ICS instead of high-dose ICS monotherapy is \$190,000. The results were insensitive to changes in relevant parameters.

### 7.2 Strengths and Limitations of This Assessment

### 7.2.1 Clinical review

The clinical and economic reviews followed transparent and accepted methods for conducting systematic reviews and health technology assessments. A protocol outlining the scope and methods was accepted before the start of the review. Experts in the clinical management of asthma provided advice throughout the review. Conflicts of interests among the research team have been declared and would be considered minimal.

The project team and advisors believed that an examination of the potential benefit of LABA-ICS as initial maintenance therapy was of clinical importance. This is not recommended in asthma guidelines; but in clinical practice, many patients have received a LABA-ICS as initial maintenance therapy, sometimes without an objective diagnosis of asthma. Canadian asthma experts<sup>182</sup> noted that the intent of pharmaceutical marketing may have been to start patients on LABA-ICS therapy instead of ICS monotherapy despite a lack of convincing evidence on the efficacy of LABA-ICS therapy for this purpose. The evidence that is reviewed here reveals a lack of justification for such a practice.

The quality of the evidence synthesis and the incorporation of MCID values<sup>37,38</sup> are strengths of this assessment. For large reviews with many included patients, the use of MCID allows a clearer application of the results to practice. It is likely, however, that the thresholds for some outcomes are unrealistically low, and they are yet to be developed for others. For example, the MCID for change in morning and evening PEF of 18.23 L/min is too low given an MCID of 10% to 12% for change in predicted PEF.

An understanding of the MCIDs is crucial in the interpretation of the results of this review. With a large sample size, many clinically unimportant differences may become statistically significant. In practice, however, a tiny difference is unlikely to be relevant to patients or to clinicians. Furthermore, although the respiratory function tests are reproducible, a variation can be noticed from one test to another. Ignoring this may lead to an invalid interpretation of the clinical findings. Although the literature does not provide a value for clinically significant results in all cases, this remains central to the interpretation of the meta-analysis. In the studies that are used to estimate MCIDs, participants were asked if they saw an improvement of asthma overall after treatment, and the authors looked at the average improvement in lung function. The determination of improvement was subjective, and the amount of improvement varied depending on whether the participants were in the placebo or the active treatment group. Therefore, the strength of the association that was observed by the study authors between change in PEF and participants reporting feeling better is unclear.

This review has addressed gaps in clinical practice guidelines for the delivery of LABA-ICS therapy to steroid-naive patients and the comparative effectiveness of LABA-ICS products (for example, salmeterol-fluticasone and formoterol-budesonide) for maintenance therapy. This review has provided a balanced assessment of pulmonary function, symptom control, and quality-of-life data. Measures of airflow obstruction reflect one component of asthma. Composite outcomes such as those in the Asthma Control Questionnaire are more likely to be relevant because they reflect the symptoms and the changes in airway calibre. Other tools such as the ACSS (asthma control scoring system) score also include airway inflammation. Ultimately, the occurrence of exacerbations is likely to be one of the most clinically relevant outcomes because it has the greatest impact on the patient and on the cost for society.

Because of the lack of standardized reporting on symptom control and health-related quality of life, the evidence base of these outcomes is weaker than that of pulmonary function. For example, the definitions of mild and severe exacerbations varied from study to study in terms of change in pulmonary function, use of rescue medication, asthma symptoms, or combinations of these measures. In some studies, the definitions of exacerbations were not reported. The lack of clinically important differences between treatments reflects differences in discrete measures thought to be clinically important in the management of asthma. These measures, however, do not sum to an assessment of overall "asthma control," a term that refers to a global assessment of symptoms, reliever use, lung function, and the frequency and severity of exacerbations. Although the combination of the reported differences between discrete measures suggests differences between treatments based on asthma outcomes, more valid estimates of the relative efficacy of

the LABA-ICS and ICS strategies would be provided by studies that assess the full complement of measures that constitute asthma control for individual patients.

This review has limitations. First, it was not possible to report every outcome measure from each trial. The key measures of pulmonary function, symptom control, and health-related quality of life were selected based on expert opinion and reporting frequency. Because there are many ways of reporting asthma outcomes, the selection of key measures meant that the proportion of included studies contributing to effect estimates varied. Thus, the benefit of LABA-ICS therapy may be overestimated for those measures where few studies contribute data.<sup>183</sup>

Second, most studies included patients from more than one asthma severity class. This resulted in an inability to assess differences in the effectiveness of adding a LABA according to disease severity (defined by GINA classification based on authors' description of study population baseline characteristics). Insofar as treatment dose accurately reflects or can be a proxy for disease severity, the results show that effectiveness and safety change little across severity. Future studies that aim to assess this aspect of combination therapy could use more restrictive asthma severity criteria at enrolment.

Third, though almost all studies reported treatment-related AEs, no study was of long enough duration to adequately assess the safety of long-term high-dose ICS use.

Fourth, there was no assessment of the effect of inhaler devices (for example, a metered dose inhaler with or without a spacer device, Turbuhaler, Diskus), and no distinction was made based on the use of separate compared with single inhalers or propellant type. Despite this, our results are similar to those in reviews that have made these distinctions.

Fifth, industry sponsorship is of concern in research, and this body of research is mainly industry-funded. It is unlikely that these studies could have been produced without such support. The fact that so many trials are unpublished and report non-clinically important measures as primary outcomes remains a concern.<sup>33,184</sup>

Sixth, publication and selection bias are potential limitations of any systematic review. The search and identification of unpublished research reduce the risk of publication bias. In addition, the rigorous methods that are used reduce the risk of selection bias.

#### 7.2.2 Economic analysis

The potential limitations of the economic analysis were addressed through sensitivity analysis. The sensitivity of results to changes in the following parameters was explored: effectiveness of adding LABA, costs of exacerbations, and quality-of-life effects of exacerbations. For all sensitivity analyses, the same conclusions could be drawn as from the base analysis. One weakness of this study was the failure to include SABA use in the base analysis. The clinical data on the effectiveness of LABA use in reducing SABA use were limited. Thus, a threshold analysis was conducted to identify how frequent SABA use would have to be for the introduction of LABA to be cost-effective. The frequency of SABA use was higher than expected among patients with asthma. Therefore, this limitation does not affect the study conclusions. Further threshold analyses were conducted on the costs and utilities of exacerbations. An analysis

showed that these values would have to be extreme for the interpretation of the analysis to change.

With the large number of outcomes that were used in RCTs of LABA, the modelling of asthma to include possible benefits is problematic. The modelling framework includes the benefits of therapy in maintaining good control and reducing exacerbations. Other outcomes may be excluded, but the limited quality of available data and the heterogeneity in reporting exclude this from consideration.

## 7.3 Generalizability of Findings

The outcomes of the studies largely depend on the population that is included in the study. The enrolment of patients with well-controlled mild asthma in a trial comparing LABA-ICS to ICS may result in similar improvement in both groups, whereas the enrolment of a group with poorly controlled severe asthma may favour the LABA-ICS group. It is difficult to take into account the effect of the severity of the disease among the patients who are enrolled in the trials. The number of exacerbations that occurred before patients entered the trials was seldom reported. To show a difference among treatments, the authors often enrolled patients who were likely to have frequent asthma exacerbations. The conclusions of those trials apply to this group of patients with asthma and may not apply to the population with asthma in general.

More than a third of the studies that were examined in this review involved the addition of a LABA to the same daily dose of ICS as was used during the ICS monotherapy with which it is compared. The results may be of limited clinical relevance in guideline-defined asthma management because the more realistic clinical choice for a patient with poorly controlled asthma who is already taking ICS is between increasing the ICS dose or adding a LABA (probably to the current ICS dose). The findings of this HTA, however, could apply to Canada and other developed countries. The studies included patients from many centres around the world. In addition, the clinical scenarios are relevant to practice, and the economic analysis is robust.

### 7.4 Knowledge Gaps

Because there is no reporting of relevant outcomes, there is a lack of knowledge about the clinical benefit of switching from fixed-dose to variable-dose combination therapy. The three RCTs that compared SMART to salmeterol-fluticasone disagreed in their findings, so clinically important differences may exist in the patient population and outcomes for which true benefits may be realized. In addition, the effect of using single inhalers compared with separate inhalers was outside the scope of this assessment.

There is a perception among patients and health care providers that the avoidance of environmental, dietary, and other triggers of asthma will improve control. Evidence on the effectiveness of non-pharmacological management is lacking.<sup>185</sup> No studies that were examined incorporated information about non-pharmacological management into the assessment.

The differences in treatment outcomes that are perceived by patients require more study because most knowledge about this comes from a few small studies. In addition, little is known about these differences based on symptom control and the most clinically relevant measures.

The results of this technology assessment can be used to guide decision-making about the use of LABA-ICS therapies if there is knowledge about the settings where they might be used. The evaluation of clinical practice guidelines (Appendix 8) found that there is consensus about the addition of LABA-ICS in clinical practice. The earlier addition of a LABA or starting LABA as a first-line agent in Canada seems unwarranted. More comparative research that provides evidence on potential clinical benefits after using fixed compared with variable dosing seems warranted. More studies on the potential differences between treatments based on serious AEs (for example, death) do not seem warranted because of the rarity of these events.

# 8 CONCLUSIONS

This review questions whether LABA-ICS should be prescribed for most patients with asthma. Although LABA-ICS brings benefit to the management of persistent adult asthma, this benefit is limited in the range of symptoms for which control is improved and in the clinical meaningfulness of those improvements. Moreover, the role of asthma education, action plans, and regular review in the included studies, which are all interventions that improve outcomes in chronic asthma, were poorly described. It is unknown how many patients have poorly controlled asthma and need LABA-ICS after a trial of ICS monotherapy when these non-pharmacological interventions are part of the management plan.

The effectiveness and safety results suggest that there are often statistically important but not clinically meaningful benefits from switching to combination therapy for the management of most asthma that is not controlled on ICS. For patients with asthma that is controlled on ICS, the addition of a LABA may help reduce the amount of daily ICS used and may thereby reduce the risk that is associated with prolonged use of daily high- and moderate-dose ICS. In addition, the number and severity of exacerbations can be reduced with this management strategy. There are no clinically important differences between the two main fixed-dose LABA-ICS therapies. No clinically important differences in safety were noted (although lower rates of worsening asthma were observed with the use of LABA-ICS).

The cost-effectiveness analysis suggests that the introduction of a LABA before patients have tried high-dose ICS monotherapy may not be justified. The later that a LABA is introduced into therapy, the more cost-effective the treatment strategy becomes. Introducing the use of a LABA to patients with asthma that is uncontrolled at high doses of ICS was the optimum of the four strategies that were considered. A sensitivity analysis revealed that these results were insensitive to changes in relevant parameters.

## 9 **REFERENCES**

- Statistics Canada. *Persons with asthma, by sex, by province and territory* [summary tables]. Ottawa: Statistics Canada; 2005. Available: <u>http://www40.statcan.ca/l01/cst01/health50a.htm</u> (accessed 2008 Aug 6).
- 2. Chen Y, Johansen H, Thillaiampalam S, Sambell C. Asthma. Health Rep 2005;16(2):43-6.
- 3. Haughney J, Price D, Kaplan A, Chrystyn H, Horne R, May N, et al. Achieving asthma control in practice: understanding the reasons for poor control. *Respir Med* 2008;102(12):1681-93.
- 4. Lemière C, Bai T, Balter M, Bayliff C, Becker A, Boulet LP, et al. Adult asthma consensus guidelines update 2003. *Can Respir J* 2004;11(Suppl A):9A-18A.
- Ni Chroinin M, Greenstone IR, Ducharme FM. Addition of inhaled long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults (review). *Cochrane Database of Syst Rev* 2004;(4):CD005307. Available: <u>http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD005307/frame.html</u> (accessed 2009 Sep 18).
- 6. Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: effect of long-acting β-agonists on severe asthma exacerbations and asthma-related deaths. *Ann Intern Med* 2006;144(12):904-12.
- 7. Knox AJ, Zhu YM, Pang L. Do long-acting beta2-andrenoceptor agonstists enhance the anti-inflammatory effect of glucocorticoids in asthma? *Eur Respir J* 2001;17:1059-61.
- The Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention The Global Initiative for Asthma; 2007. Available: http://www.ginasthma.com/Guidelineitem.asp?l1=2&l2=1&intId=1389 (accessed 2008 May 1).
- 9. National Heart Lung and Blood Institute (NHLBI). *Expert Panel Report 3 (EPR3): guidelines for the diagnosis and management of asthma*. Bethesda (MD): National Heart Lung and Blood Institute; 2007. Available: <u>http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm</u> (accessed 2009 Apr 30).
- 10. Bousquet J, Boulet LP, Peters MJ, Magnussen H, Quiralte J, Martinez-Aguilar NE, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med* 2007;101(12):2437-46.
- 11. Fitzgerald JM, Boulet LP, Follows RM. The CONCEPT trial: a 1-year, multicenter, randomized, doubleblind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. *Clin Ther* 2005;27(4):393-406.
- 12. Rowe BH, Wong E, Blitz S, Diner B, Mackey D, Ross S, et al. Adding long-acting beta-agonists to inhaled corticosteroids after discharge from the emergency department for acute asthma: a randomized controlled trial. *Acad Emerg Med* 2007;14(10):833-40.
- Gibson PG, Powell H, Ducharme F. Long-acting beta2-agonists as an inhaled corticosteroid-sparing agent for chronic asthma in adults and children. *Cochrane Database of Syst Rev* 2005;(4):CD005076. Available: <u>http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD005076/frame.html</u> (accessed 2009 Sep 18).
- Greenstone IR, Ni Chroinin MN, Masse V, Danish A, Magdalinos H, Zhang X, et al. Combination of inhaled long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma (review). *Cochrane Database of Syst Rev* 2005;(4):CD005533. Available: <u>http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD005533/frame.html</u> (accessed 2009 Sep 18).
- 15. U.S.Food and Drug Administration. +. Rockville (MD): FDA; 2009 Jul 21. Available: <u>http://www.fda.gov/cder/drug/infopage/LABA/default.htm</u> (accessed 2009 Sep 28).

- 16. Bateman E, Nelson H, Bousquet J, Kral K, Sutton L, Ortega H, et al. Meta-analysis: effects of adding salmeterol to inhaled corticosteroids on serious asthma-related events. *Ann Intern Med* 2008;149:33-42.
- 17. Edwards SJ, Gruffydd-Jones K, Ryan DP. Systematic review and meta-analysis of budesonide/formoterol in a single inhaler. *Curr Med Res Opin* 2007;23(8):1809-20.
- 18. Fabbri LM, Nicolini G, Olivieri D, Papi A. Inhaled beclometasone diproprionate/formoterol extra-fine fixed combination in the treatment of asthma: evidence and future perspectives. *Expert Opin Pharmacother* 2008;9(3):479-90.
- 19. Kankaanranta H, Lahdensuo A, Moilanen E, Barnes PJ. Add-on therapy options in asthma not adequately controlled by inhaled corticosteroids: a comprehensive review. *Respir Res* 2004;5(17).
- 20. Jaeschke R, O'Byrne PM, Mejza F, Parameswaran N, Lesniak W, Brozek J, et al. The safety of long-acting beta2-agonists among patients with asthma using inhaled corticosteroids. *Am J Resp Crit Care Med* 2008;178:1009-16.
- Lasserson TJ, Cates CJ, Ferrera G, Casali L. Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children. *Cochrane Database of Syst Rev* 2008;(1):CD004106. Available: <a href="http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004106/frame.html">http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004106/frame.html</a> (accessed 2009 Sep 18).
- 22. Levenson M. *Long-acting beta-agonists and adverse asthma events meta-analysis* [statistical briefing package]. Rockville (MD): U. S. Food and Drug Administration; 2008 Dec 12. Available: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-01-FDA.pdf (accessed 2009 May 5).
- 23. Ni Chroinin M, Greenstone IR, Danish A, Magdolinos H, Masse V, Zhang X, et al. Long-acting beta2agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma (review). *Cochrane Database of Syst Rev* 2005;(4):CD005535.
- 24. Reynolds NA, Lyseng-Williams KA, Wiseman LR. Inhaled salmeterol/fluticasone proprionate: a review of its use in asthma. *Drugs* 2005;65(12):1715-34.
- 25. Shepherd J, Rogers G, Anderson R, Main C, Thompson-Coon J, Hartwell D, et al. Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2-agonists for the treatment of chronic asthma in adults and children aged 12 years and over. *Health Technol Assess* 2008;12(19):1-360.
- 26. Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). *BMJ: British Medical Journal* 2000;320:1368-72.
- 27. Sin DD, Man J, Sharpe H, Gan WQ, Paul Man SF. Pharmacological management to reduce exacerbations in adults with asthma: a systematic review and meta-analysis. *Jama* 2004;292(3):367-76.
- 28. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;129(1):15-26.
- 29. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. *Am J Respir Crit Care Med* 2004;170(8):836-44.
- 30. Schultz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. *Lancet* 2002;359(9306):614-18.
- 31. Jadad AR, Moore A, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12.
- 32. Shultz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Jama* 1995;273:408-12.
- 33. Liss H. Publication bias in the pulmonary/allergy literature: effect of pharmaceutical company sponsorship. *Isr Med Assoc J* 2006;8:451-4.

- 34. Deeks JJ, Higgins JPT, Altman DG. Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions*. Version 5.0.1 [updated September 2008]: The Cochrane Collaboration; 2008. p.243-96. Available: www.cochrane-handbook.org.
- 35. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Fixed-effects versus random-effects models. In: *Introduction to meta-analysis*. London: John Wiley and Sons; 2009. p.78-86.
- 36. Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions*. Version 5.0.1 [updated September 2008]. Oxford: The Cochrane Collaboration; 2008. Available: <u>http://www.cochrane-handbook.org</u> (accessed 2009 May 1).
- 37. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. *J Clin Epidemiol* 1994;47:81-7.
- 38. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Resp J* 1999;14:23-7.
- 39. Woodcock AA, Bagdonas A, Boonsawat W, Gibbs MR, Bousquet J, Bateman ED, et al. Improvement in asthma endpoints when aiming for total control: salmeterol/fluticasone propionate versus fluticasone propionate alone. *Prim Care Respir J* 2007;16(3):155-61.
- 40. Bateman ED, Bousquet J, Keech ML, Busse WW, Clark TJ, Pedersen SE. The correlation between asthma control and health status: the GOAL study. *Eur Respir J* 2007;29(1):56-62.
- 41. Juniper EF, Jenkins C, Price MJ, James MH. Impact of inhaled salmeterol/fluticasone propionate combination product versus budesonide on the health-related quality of life of patients with asthma. *Am J Respir Med* 2002;1(6):435-40.
- 42. Chuchalin AG, Svensson K, Stahl E, Ovcharenko SI, Goriachkina LA, Sidorenko IV, et al. A health-related quality-of-life comparison of formoterol (oxis) turbuhaler plus budesonide (pulmicort) turbuhaler with budesonide turbuhaler alone and noncorticosteroid treatment in asthma: a randomized clinical study in Russia. *Respiration* 2002;69(5):427-33.
- 43. Murphy K, Nelson H, Parasuraman B, Boggs R, Miller C, O'Dowd L. The effect of budesonide and formoterol in one pressurized metered-dose inhaler on patient-reported outcomes in adults with mild-to-moderate persistent asthma. *Curr Med Res Opin* 2008;24(3):879-94.
- 44. Price DB, Williams AE, Yoxall S. Salmeterol/fluticasone stable-dose treatment compared with formoterol/budesonide adjustable maintenance dosing: impact on health-related quality of life. *Respir Res* 2007;8(46).
- 45. Kuna P, Creemers JP, Vondra V, Black PN, Lindqvist A, Nihlen U, et al. Once-daily dosing with budesonide/formoterol compared with twice-daily budesonide/formoterol and once-daily budesonide in adults with mild to moderate asthma. *Respir Med* 2006;100(12):2151-9.
- 46. Chuchalin AG, Ovcharenko SI, Goriachkina LA, Sidorenko IV, Tsof AN. The safety and efficacy of formoterol (oxis) turbuhaler plus budesonide (pulmicort) turbuhaler in mild to moderate asthma: a comparison with budesonide turbuhaler alone and current non-corticosteroid therapy in Russia. *Int J Clin Prac* 2002;56:15-20.
- 47. Corren J, Korenblat PE, Miller CJ, O'Brien CD, Mezzanotte WS. Twelve-week, randomized, placebocontrolled, multicenter study of the efficacy and tolerability of budesonide and formoterol in one metereddose inhaler compared with budesonide alone and formoterol alone in adolescents and adults with asthma. *Clin Ther* 2007;29(5):823-43.
- 48. Jarjour NN, Wilson SJ, Koenig SM, Laviolette M, Moore WC, Davis WB, et al. Control of airway inflammation maintained at a lower steroid dose with 100/50 microg of fluticasone propionate/salmeterol. *J Allergy Clin Immunol* 2006;118(1):44-52.

- 49. GlaxoSmithKline. A randomized, double-blind, parallel group, comparative trial of fluticasone propionate/salmeterol combination product 100/50mcg Diskus† inhaler bid versus fluticasone propionate 250mcg Diskus inhaler bid in adolescents and adults with moderate persistent asthma. *GlaxoSmithKline (GSK) Clinical Study Register* 2006. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/3393.pdf</u> (accessed 2009 Sep 18).
- 50. Byrt T, Bishop J, Carlin JB. Bias, prevalence and kappa. J Clin Epidemiol 1993;46(5):423-9.
- 51. Sim J, Wright CC. The kappa statistic in reliability studies: use, interpretation, and sample size requirements. *Phys Ther* 2005;85(3):257-68.
- 52. Godard P, Greillier P, Pigearias B, Nachbaur G, Desfougeres JL, Attali V. Maintaining asthma control in persistent asthma: comparison of three strategies in a 6-month double-blind randomised study. *Respir Med* 2008;102:1124-31.
- 53. GlaxoSmithKline. A phase IV, multi-centre, double-blind, parallel group, randomised study comparing Seretide (50/100mcg bd) via the Evohaler (MDI-HFA) with Flixotide (250mcg bd) via the Evohaler (MDI-HFA) in asthmatics with significant smoking history. GlaxoSmithKline (GSK) Clinical Study Register 2005. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/23651.pdf</u> (accessed 2009 Sep 18).
- 54. DiFranco A, Giannini D, Bacci E, Dente FL, Vagaggini B, Paggiaro PL. Comparison of different long-term asthma treatments in subjects with mild-to-moderate asthma. *Monaldi Arch Chest Dis* 1999;54(5):390-3.
- 55. Creticos PS, Freidhoff LR, Bernstein DI, Chu T, Khattignavong AP, Pasatiempo AM, et al. Comparison of an inhaled corticosteroid (triamcinolone acetonide) to a long-acting bronchodilator (salmeterol), the combination, and placebo in mild-moderate adult asthmatic patients. *Int Arch Allergy Immunol* 1999;118(2-4):345-6.
- 56. Boonsawat W, Goryachkina L, Jacques L, Frith L. Combined salmeterol/fluticasone propionate versus fluticasone propionate alone in mild asthma : a placebo-controlled comparison. *Clin Drug Invest* 2008;28(2):101-11.
- 57. Nelson HS, Wolfe JD, Gross G, Greos LS, Baitinger L, Scott C, et al. Efficacy and safety of fluticasone propionate 44 microg/salmeterol 21 microg administered in a hydrofluoroalkane metered-dose inhaler as an initial asthma maintenance treatment. *Ann Allergy Asthma Immunol* 2003;91(3):263-9.
- 58. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001;164(8 Pt 1):1392-7.
- 59. Grutters JC, Brinkman L, Aslander MM, van den Bosch JMM, Koenderman L, Lammers JW. Asthma therapy modulates priming-associated blood eosinophil responsiveness in allergic asthmatics. *Eur Respir J* 1999;14(4):915-22.
- 60. Rojas RA, Paluga I, Goldfrad CH, Duggan MT, Barnes N. Initiation of maintenance therapy with salmeterol/fluticasone propionate combination therapy in moderate asthma: a comparison with fluticasone propionate. *J Asthma* 2007;44(6):437-41.
- 61. Kerwin EM, Nathan RA, Meltzer EO, Ortega HG, Yancey SW, Schoaf L, et al. Efficacy and safety of fluticasone propionate/salmeterol 250/50 mcg Diskus administered once daily. *Respir Med* 2008;102(4):495-504.
- 62. Chuchalin A, Jacques L, Frith L. Salmeterol/fluticasone propionate via Diskus once daily versus fluticasone propionate twice daily in patients with mild asthma not previously receiving maintenance corticosteroids. *Clin Drug Invest* 2008;28(3):169-81.
- 63. Strand AM, Luckow A, Danish Initiative for Asthma treatment. Initiation of maintenance treatment of persistent asthma: salmeterol/fluticasone propionate combination treatment is more effective than inhaled steroid alone. *Respir Med* 2004;98:1008-15.
- 64. Murray J, Rosenthal R, Somerville L, Blake K, House K, Baitinger L, et al. Fluticasone proprionate and salmeterol administered via Diskus compared with salmeterol or fluticasone propionate alone in patients suboptimally controlled with short-acting beta2-agonists. *Ann Allergy Asthma Immunol* 2004;93:351-9.

- 65. GlaxoSmithKline. A 12-week multicentre, randomised, double-blind, double-dummy, parallel group study to compare the efficacy and tolerability of once daily (QD) salmeterol/fluticasone propionate combination (salm/FP) 50/100mcg at night via the Diskus/Accuhaler with QD budesonide (BUD) 400mcg at night via a breath-actuated dry powder inhaler (BADPI) as initial maintenance therapy in mild-to-moderate asthmatic subjects. *GlaxoSmithKline (GSK) Clinical Study Register* 2004. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/3346.pdf</u> (accessed 2009 Sep 18).
- 66. GlaxoSmithKline. A randomised, double blind, double-dummy, parallel-group, twelve week comparison of salmeterol/fluticasone propionate (FP) Diskus/Accuhaler 50/100mcg bd. with budesonide 200mcg bd. plus formoterol 4.5mcg bd. (both via breath-actuated dry powder inhaler [BADPI]) in adult and adolescent asthmatics. *GlaxoSmithKline (GSK) Clinical Study Register* 2004. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/3345.pdf</u> (accessed 2009 Sep 18).
- 67. GlaxoSmithKline. A 12-week, multi-centre, randomised, double-blind, parallel-group study to compare the efficacy and tolerability of salmeterol/fluticasone propionate combination (*Seretide*<sup>TM</sup>/*Viani*<sup>TM</sup>/*Advair*<sup>TM</sup>) 50/250ig twice-daily with fluticasone propionate 250ig twice-daily, all via the *Diskus*@/*Accuhaler*® as initial maintenance therapy in moderate persistent asthma. *GlaxoSmithKline* (*GSK*) *Clinical Study Register* 2005. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/3358.pdf</u> (accessed 2009 Sep 18).
- 68. GlaxoSmithKline. A phase IIIB, multi-centre, double-blind, parallel group, randomised study to compare the efficacy of the salmeterol/fluticasone propionate combination (25/50 mcg strength), 2 inhalations bd via HFA-MDI with beclomethasone dipropionate (BDP) 200mcg bd via metered dose inhaler (MDI) in adolescents and adults with asthma. *GlaxoSmithKline (GSK) Clinical Study Register* 2004. Available: <a href="http://www.gsk-clinicalstudyregister.com/files/pdf/3354.pdf">http://www.gsk-clinicalstudyregister.com/files/pdf/3354.pdf</a> (accessed 2009 Sep 18).
- 69. GlaxoSmithKline. A multicenter, randomized, double-blind, double-dummy, parallel group, 16-week comparison of asthma control in adolescents and adults receiving either fluticasone propionate/salmeterol Diskus<sup>™</sup> combination product 100/50mcg bid, fluticasone propionate Diskus<sup>™</sup> 100mcg bid, salmeterol xinafoate Diskus<sup>™</sup> 50mcg bid, or oral Montelukast 10mg QD. *GlaxoSmithKline (GSK) Clinical Study Register* 2005. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/23662.pdf</u> (accessed 2009 Sep 18).
- 70. Overbeek SE, Mulder PG, Baelemans SM, Hoogsteden HC, Prins JB. Formoterol added to low-dose budesonide has no additional antiinflammatory effect in asthmatic patients. *Chest* 2005;128:1121-7.
- 71. Anonymous. Endpoints in asthma drug trials what do they mean? Drug Ther Bull 2006;44:21-4.
- 72. Buhl R, Creemers JP, Vondra V, Martelli NA, Naya IP, Ekstrom T. Once-daily budesonide/formoterol in a single inhaler in adults with moderate persistent asthma. *Respir Med* 2003;97(4):323-30.
- 73. Boyd G. Salmeterol xinafoate in asthmatic patients under consideration for maintenance oral corticosteroid therapy. UK Study Group. *Eur Respir J* 1995;8(9):1494-8.
- 74. Pearlman DS, Peden D, Condemi JJ, Weinstein S, White M, Baitinger L, et al. Efficacy and safety of fluticasone propionate/salmeterol HFA 134A MDI in patients with mild-to-moderate persistent asthma. *J Asthma* 2004;41(8):797-806.
- 75. Aubier M, Pieters WR, Schlosser NJ, Steinmetz KO. Salmeterol/fluticasone propionate (50/500 microg) in combination in a Diskus inhaler (Seretide) is effective and safe in the treatment of steroid-dependent asthma. *Respir Med* 1999;93(12):876-84.
- 76. Ind PW, Dal NR, Colman NC, Fletcher CP, Browning D, James MH. Addition of salmeterol to fluticasone propionate treatment in moderate-to-severe asthma. *Respir Med* 2003;97(5):555-62.
- Fowler SJ, Currie GP, Lipworth BJ. Step-down therapy with low-dose fluticasone-salmeterol combination or medium-dose hydrofluoroalkane 134a-beclomethasone alone. *J Allergy Clin Immunol* 2002;109(6):929-35.
- 78. Koopmans JG, Lutter R, Jansen HM, van der Zee JS. Adding salmeterol to an inhaled corticosteroid: long term effects on bronchial inflammation in asthma. *Thorax* 2006;61(4):306-12.

- 79. Lemanske RF, Jr., Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, et al. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. *Jama* 2001;285(20):2594-603.
- 80. Jenkins C, Woolcock AJ, Saarelainen P, Lundback B, James MH. Salmeterol/fluticasone propionate combination therapy 50/250 microg twice daily is more effective than budesonide 800 microg twice daily in treating moderate to severe asthma. *Respir Med* 2000;94(7):715-23.
- 81. Kavuru M, Melamed J, Gross G, Laforce C, House K, Prillaman B, et al. Salmeterol and fluticasone propionate combined in a new powder inhalation device for the treatment of asthma: a randomized, doubleblind, placebo-controlled trial. *J Allergy Clin Immunol* 2000;105(6 Pt 1):1108-16.
- Kemp JP, Cook DA, Incaudo GA, Corren J, Kalberg C, Emmett A, et al. Salmeterol improves quality of life in patients with asthma requiring inhaled corticosteroids. Salmeterol Quality of Life Study Group. J Allergy Clin Immunol 1998;101(2 Pt 1):188-95.
- 83. Langton Hewer S., Hobbs J, French D, Lenney W. Pilgrim's progress: the effect of salmeterol in older children with chronic severe asthma. *Respir Med* 1995;89(6):435-40.
- 84. Lundbäck B, Ronmark E, Lindberg A, Jonsson AC, Larsson LG, Petavy F, et al. Control of mild to moderate asthma over 1-year with the combination of salmeterol and fluticasone propionate. *Respir Med* 2006;100(1):2-10.
- 85. Molimard M, Bourcereau J, Le Gros V, Bourdeix I, Leynadier F, Duroux P, et al. Comparison between formoterol 12 microg b.i.d. and on-demand salbutamol in moderate persistent asthma. *Respir Med* 2001;95(1):64-70.
- 86. Li X, Ward C, Thien F, Bish R, Bamford T, Bao X, et al. An antiinflammatory effect of salmeterol, a longacting beta(2) agonist, assessed in airway biopsies and bronchoalveolar lavage in asthma. *Am J Respir Crit Care Med* 1999;160(5 Pt 1):1493-9.
- 87. Shapiro G, Lumry W, Wolfe J, Given J, White MV, Woodring A, et al. Combined salmeterol 50 microg and fluticasone propionate 250 microg in the Diskus device for the treatment of asthma. *Am J Respir Crit Care Med* 2000;161(2 Pt 1):527-34.
- van der Molen T, Postma DS, Turner MO, Jong BM, Malo JL, Chapman K, et al. Effects of the long acting beta agonist formoterol on asthma control in asthmatic patients using inhaled corticosteroids. The Netherlands and Canadian Formoterol Study Investigators. *Thorax* 1997;52(6):535-9.
- Zetterstrom O, Buhl R, Mellem H, Perpina M, Hedman J, O'Neill S, et al. Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone. *Eur Respir J* 2001;18(2):262-8.
- 90. Fitzgerald JM. Sustained bronchoprotection, bronchodilatation, and symptom control during regular formoterol use in asthma of moderate or greater severity. *J Allergy Clin Immunol* 1999;103(3pt 1):427-35.
- 91. Price D, Dutchman D, Mawson A, Bodalia B, Duggan S, Todd P. Early asthma control and maintenance with eformoterol following reduction of inhaled corticosteroid dose. *Thorax* 2002;57(9):791-8.
- 92. Noonan M, Rosenwasser LJ, Martin P, O'Brien CD, O'Dowd L. Efficacy and safety of budesonide and formoterol in one pressurised metered-dose inhaler in adults and adolescents with moderate to severe asthma: a randomised clinical trial. *Drugs* 2006;66(17):2235-54.
- 93. Jenkins C, Kolarikova R, Kuna P, Caillaud D, Sanchis J, Popp W, et al. Efficacy and safety of high-dose budesonide/formoterol (Symbicort) compared with budesonide administered either concomitantly with formoterol or alone in patients with persistent symptomatic asthma. *Respirology* 2006;11(3):276-86.
- 94. Nathan RA, Rooklin A, Schoaf L, Scott C, Ellsworth A, House K, et al. Efficacy and tolerability of fluticasone propionate/salmeterol administered twice daily via hydrofluoroalkane 134a metered-dose inhaler in adolescent and adult patients with persistent asthma: a randomized, double-blind, placebo-controlled, 12-week study. *Clin Ther* 2006;28(1):73-85.

- 95. Koenig SM, Murray JJ, Wolfe J, Andersen L, Yancey S, Prillaman B, et al. Does measuring BHR add to guideline derived clinical measures in determining treatment for patients with persistent asthma? *Respir Med* 2008;102(5):665-73.
- 96. Morice AH, Peterson S, Beckman O, Osmanliev D. Therapeutic comparison of a new budesonide/formoterol pMDI with budesonide pMDI and budesonide/formoterol DPI in asthma. *Int J Clin Pract* 2007;61(11):1874-83.
- 97. van Noord JA, Lill H, Carrillo Diaz T, Greefhorst AP, Davies P. Clinical equivalence of a salmeterol/fluticasone propionate combination product (50/500ug) delivered via a chlorofluorocarbon-free metered-dose inhaler with the Diskus<sup>™</sup> in patients with moderate to severe asthma. *Clin Drug Invest* 2001;21(4):243-55.
- 98. Bateman ED, Silins V, Bogolubov M. Clinical equivalence of salmeterol/fluticasone propionate in combination (50/100ug twice daily) when administered via a chlorofluorocarbon-free metered dose inhaler or dry powder inhaler to patients with mild-to-moderate asthma. *Respir Med* 2001;95:136-46.
- 99. GlaxoSmithKline. A multicenter, randomized, double-blind, parallel group, 40-week comparison of asthma control using bronchial hyperresponsiveness as an additional guide to long-term treatment in adolescents and adults receiving either fluticasone propionate/salmeterol Diskus<sup>TM</sup> bid or fluticasone propionate Diskus<sup>TM</sup> bid (or placebo bid if asymptomatic). *GlaxoSmithKline (GSK) Clinical Study Register* 2007. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/23645.pdf</u> (accessed 2009 Sep 18).
- 100. GlaxoSmithKline. A multicenter, randomized, double-blind, parallel group, 52-week comparison of asthma control and measures of airway inflammation in subjects of African descent receiving fluticasone propionate/salmeterol 100/50mcg Diskus<sup>™</sup> bid or fluticasone propionate 100mcg Diskus<sup>™</sup> bid alone. *GlaxoSmithKline (GSK) Clinical Study Register* 2007. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/21094.pdf</u> (accessed 2009 Sep 18).
- Peters SP, Prenner BM, Mezzanotte WS, Martin P, O'Brien CD. Long-term safety and asthma control with budesonide/formoterol versus budesonide pressurized metered-dose inhaler in asthma patients. *Allergy Asthma Proc* 2008;29:499-516.
- 102. GlaxoSmithKline. A multicenter, randomized, double-blind, double-dummy, parallel group, 16-week comparison of asthma control in adolescents and adults receiving either fluticasone propionate/salmeterol Diskus combination product 100/50mcg bid, fluticasone propionate Diskus 100mcg bid, salmeterol xinafoate Diskus 50mcg bid, or oral Montelukast 10mg QD. *GlaxoSmithKline (GSK) Clinical Study Register* 2005. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/1074.pdf</u> (accessed 2009 Sep 18).
- 103. GlaxoSmithKline. (Inhaled fluticasone propionate and salmeterol in sputum induced study in asthma) salmeterol plus low-dose fluticasone propionate (FP) versus high-dose fluticasone propionate (FP) in naive patients with mild to moderate asthma: effects on pulmonary function, and inflammatory markers of induced sputum. *GlaxoSmithKline (GSK) Clinical Study Register* 2005. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/1205.pdf</u> (accessed 2009 Sep 18).
- 104. GlaxoSmithKline. A multi-centre double-blind, parallel group study to evaluate the relative clinical benefits of three treatment interventions: i) salmeterol xinafoate 50 mcg bd plus fluticasone propionate 250 mcg bd; ii) fluticasone propionate 500 mcg bd; iii) fluticasone propionate 250 mcg bd, in adult asthmatic subjects poorly controlled on current inhaled corticosteroids. *GlaxoSmithKline (GSK) Clinical Study Register* 2005. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/2838.pdf</u> (accessed 2009 Sep 18).
- 105. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;171(2):129-36.
- 106. Bateman ED, Bantje TA, Joao GM, Toumbis MG, Huber RM, Naya I, et al. Combination therapy with single inhaler budesonide/formoterol compared with high dose of fluticasone propionate alone in patients with moderate persistent asthma. *Am J Respir Med* 2003;2(3):275-81.

- Bouros D, Bachlitzanakis N, Kottakis J, Pfister P, Polychronopoulos V, Papadakis E, et al. Formoterol and beclomethasone versus higher dose beclomethasone as maintenance therapy in adult asthma. *Eur Respir J* 1999;14(3):627-32.
- Bergmann KC, Lindemann L, Braun R, Steinkamp G. Salmeterol/fluticasone propionate (50/250 microg) combination is superior to double dose fluticasone (500 microg) for the treatment of symptomatic moderate asthma. Swiss Med Wkly 2004;134(3-4):50-8.
- 109. Baraniuk J, Murray JJ, Nathan RA, Berger WE, Johnson M, Edwards LD, et al. Fluticasone alone or in combination with salmeterol vs triamcinolone in asthma. *Chest* 1999;116(3):625-32.
- 110. Condemi JJ, Goldstein S, Kalberg C, Yancey S, Emmett A, Rickard K. The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma. Salmeterol Study Group. *Ann Allergy Asthma Immunol* 1999;82(4):383-9.
- 111. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen & Hanburys Limited UK Study Group. *Lancet* 1994;344(8917):219-24.
- 112. Johansson G, McIvor RA, D'Ambrosio FP, Gratziou C, James MH. Comparison of salmeterol/fluticasone propionate combination with budesonide in patients with mild-to-moderate asthma. *Clin Drug Invest* 2001;21(9):633-42.
- 113. Lalloo UG, Malolepszy J, Kozma D, Krofta K, Ankerst J, Johansen B, et al. Budesonide and formoterol in a single inhaler improves asthma control compared with increasing the dose of corticosteroid in adults with mild-to-moderate asthma. *Chest* 2003;123(5):1480-7.
- 114. Kelsen SG, Church NL, Gillman SA, Lanier BQ, Emmett AH, Rickard KA, et al. Salmeterol added to inhaled corticosteroid therapy is superior to doubling the dose of inhaled corticosteroids: a randomized clinical trial. *J Asthma* 1999;36(8):703-15.
- 115. Mitchell C, Jenkins C, Scicchitano R, Rubinfeld A, Kottakis J. Formoterol (Foradil) and medium-high doses of inhaled corticosteroids are more effective than high doses of corticosteroids in moderate-to-severe asthma. *Pulm Pharmacol Ther* 2003;16(5):299-306.
- 116. Wallin A, Sue-Chu M, Bjermer L, Ward J, Sandstrom T, Lindberg A, et al. Effect of inhaled fluticasone with and without salmeterol on airway inflammation in asthma. *J Allergy Clin Immunol* 2003;112(1):72-8.
- 117. Murray JJ, Church NL, Anderson WH, Bernstein DI, Wenzel SE, Emmett A, et al. Concurrent use of salmeterol with inhaled corticosteroids is more effective than inhaled corticosteroid dose increases. *Allergy Asthma Proc* 1999;20(3):173-80.
- 118. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. *Am J Respir Crit Care Med* 1996;153(5):1481-8.
- 119. Scicchitano R, Aalbers R, Ukena D, Manjra A, Fouquert L, Centanni S, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. *Curr Med Res Opin* 2004;20(9):1403-18.
- 120. van Noord JA, Schreurs AJ, Mol SJ, Mulder PG. Addition of salmeterol versus doubling the dose of fluticasone propionate in patients with mild to moderate asthma. *Thorax* 1999;54(3):207-12.
- Vermetten FA, Boermans AJ, Luiten WD, Mulder PG, Vermue NA. Comparison of salmeterol with beclomethasone in adult patients with mild persistent asthma who are already on low-dose inhaled steroids. *J Asthma* 1999;36(1):97-106.
- 122. Rabe KF, Pizzichini E, Stallberg B, Romero S, Balanzat AM, Atienza T, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. *Chest* 2006;129(2):246-56.
- 123. Peters SP, Anthonisen N, Castro M, Holbrook JT, Irvin CG, Smith LJ, et al. Randomized comparison of strategies for reducing treatment in mild persistent asthma. *N Engl J Med* 2007;356(20):2027-39.

- 124. GlaxoSmithKline. A randomised, multi-centre, double blind, double-dummy, parallel-group comparison of Seretide RPID (50/100mg strength) bd with budesonide BADPI 400mg bd in steroid experienced adolescents and adults with reversible airways obstruction. *GlaxoSmithKline (GSK) Clinical Study Register* 2008. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/24440.pdf</u> (accessed 2009 Sep 18).
- 125. GlaxoSmithKline. A randomized, double-blind clinical trial comparing the efficacy and safety of salmeterol xinafoate 42mcg b.i.d.\* plus fluticasone propionate 88mcg b.i.d.\* versus fluticasone propionate 220mcg b.i.d.\* alone in subjects with asthma not well controlled on fluticasone propionate 88mcg b.i.d. *GlaxoSmithKline (GSK) Clinical Study Register* 2005. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/1012.pdf</u> (accessed 2009 Sep 18).
- 126. GlaxoSmithKline. A 12 week, randomized, double-blind, parallel group study to compare the efficacy and safety of salmeterol/fluticasone propionate/GR106642X (25/50 ig x 2 inhalations) bid with fluticasone propionate (125 ig x 2 inhalations) bid in adolescent and adult patients with mild to moderate asthma. *GlaxoSmithKline (GSK) Clinical Study Register* 2005. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/987.pdf</u> (accessed 2009 Sep 18).
- 127. Aalbers R, Backer V, Kava TT, Omenaas ER, Sandstrom T, Jorup C, et al. Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. *Curr Med Res Opin* 2004;20(2):225-40.
- 128. Dahl R, Chuchalin A, Gor D, Yoxall S, Sharma R. EXCEL: A randomised trial comparing salmeterol/fluticasone propionate and formoterol/budesonide combinations in adults with persistent asthma. *Respir Med* 2006;100(7):1152-62.
- 129. Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinez-Jimenez NE, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract* 2007;61(5):725-36.
- 130. Ringdal N, Chuchalin A, Chovan L, Tudoric N, Maggi E, Whitehead PJ, et al. Evaluation of different inhaled combination therapies (EDICT): a randomised, double-blind comparison of seretide (50/250 microg bd Diskus vs. formoterol (12 microg bd) and budesonide (800 microg bd) given concurrently (both via turbuhaler) in patients with moderate-to-severe asthma. *Respir Med* 2002;96(11):851-61.
- 131. Vogelmeier C, D'Urzo A, Pauwels R, Merino JM, Jaspal M, Boutet S, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? *Eur Respir J* 2005;26(5):819-28.
- 132. Papi A, Paggiaro PL, Nicolini G, Vignola AM, Fabbri LM, Inhaled Combination Asthma Treatment versus SYmbicort (ICAT SY) Study Group. Beclomethasone/formoterol versus budesonide/formoterol combination therapy in asthma. *Eur Respir J* 2007;29(4):682-9.
- 133. Busse WW, Shah SR, Somerville L, Parasuraman B, Martin P, Goldman M. Comparison of adjustable- and fixed-dose budesonide/formoterol pressurized metered-dose inhaler and fixed-dose fluticasone propionate/salmeterol dry powder inhaler in asthma patients. *J Allergy Clin Immunol* 2008;121(6):1407-14.
- Papi A, Paggiaro P, Nicolini G, Vignola AM, Fabbri LM, ICAT SE study group. Beclomethasone/formoterol vs fluticasone/salmeterol inhaled combination in moderate to severe asthma. *Allergy* 2007;62(10):1182-8.
- 135. GlaxoSmithKline. Randomised, double-blind, parallel group study on the efficacy and tolerability of the salmeterol 50 mcg / fluticasone 250 mcg combination Diskus compared to the formoterol 6 mcg / budesonide 200 mcg combination Turbohaler administered twice daily in patients with moderate bronchial asthma. *GlaxoSmithKline (GSK) Clinical Study Register* 2005. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/997.pdf</u> (accessed 2009 Sep 18).
- 136. GlaxoSmithKline. A randomised, double blind, double-dummy, parallel-group, twelve week comparison of salmeterol/fluticasone propionate (FP) Diskus/Accuhaler 50/100mcg bd. with budesonide 200mcg bd. plus formoterol 4.5mcg bd. (both via breath-actuated dry powder inhaler [BADPI]) in adult and adolescent asthmatics. *GlaxoSmithKline (GSK) Clinical Study Register* 2004. Available: <u>http://www.gskclinicalstudyregister.com/files/pdf/3345.pdf</u> (accessed 2009 Sep 18).

- 137. Busse W, Koenig SM, Oppenheimer J, Sahn SA, Yancey SW, Reilly D, et al. Steroid-sparing effects of fluticasone propionate 100 microg and salmeterol 50 microg administered twice daily in a single product in patients previously controlled with fluticasone propionate 250 microg administered twice daily. *J Allergy Clin Immunol* 2003;111(1):57-65.
- 138. Kips JC, O'Connor BJ, Inman MD, Svensson K, Pauwels RA, O'Byrne PM. A long-term study of the antiinflammatory effect of low-dose budesonide plus formoterol versus high-dose budesonide in asthma. *Am J Respir Crit Care Med* 2000;161(3 Pt 1):996-1001.
- 139. Nielsen LP, Pedersen B, Faurschou P, Madsen F, Wilcke JT, Dahl R. Salmeterol reduces the need for inhaled corticosteroid in steroid-dependent asthmatics. *Respir Med* 1999;93(12):863-8.
- 140. Pauwels RA, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997;337(20):1405-11.
- 141. Pohl WR, Vetter N, Zwick H, Hrubos W. Adjustable maintenance dosing with budesonide/formoterol or budesonide: double-blind study. *Respir Med* 2006;100(3):551-60.
- 142. Schermer TR, Albers JM, Verblackt HW, Costongs RJ, Westers P. Lower inhaled steroid requirement with a fluticasone/salmeterol combination in family practice patients with asthma or COPD. *Fam Pract* 2007;24(2):181-8.
- 143. Self T. Does salmeterol facilitate 'step-down' therapy in patients with asthma receiving moderate to high doses of inhaled corticosteroids? *Curr Ther Res* 1998;59:803-11.
- 144. GlaxoSmithKline. A twelve week multi-centre, randomized, double-blind, parallel group, comparative trial of Advair 50/100 mcg Diskus inhalation device bid versus flovent 250 mcg Diskus inhalation device bid in adolescents and adults with persistent asthma (Program of Advair Control and Effectiveness - Advair Low Dose [PACE-ALD]. *GlaxoSmithKline (GSK) Clinical Study Register* 2005. Available: <u>http://www.gskclinicalstudyregister.com/files/pdf/23647.pdf</u> (accessed 2009 Sep 18).
- 145. GlaxoSmithKline. A multicentre, randomised, double-blind, parallel group comparison of the efficacy of seretide\* bd and fluticasone propionate bd (both via Diskus\*/Accuhaler\*, Inhaler) when tapering the inhaled corticosteroid dose in asthmatic adults. *GlaxoSmithKline (GSK) Clinical Study Register* 2004. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/991.pdf</u> (accessed 2009 Sep 18).
- 146. GlaxoSmithKline. A multicentre, randomised, double-blind, controlled, parallel-group, comparative investigation of the corticosteroid-saving potential of the combination therapy fluticasone propionate and salmeterol (Seretide) compared with fluticasone propionate alone, given to adult asthmatic subjects, when reducing the inhaled corticosteroid dose from an initially high level of 500 ig bd. *GlaxoSmithKline (GSK) Clinical Study Register* 2005. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/983.pdf</u> (accessed 2009 Sep 18).
- 147. GlaxoSmithKline. Efficacy and safety of salmeterol in patients with asthma controlled with inhaled corticosteroids. *GlaxoSmithKline (GSK) Clinical Study Register* 2006. Available: <u>http://www.gsk-clinicalstudyregister.com/files/pdf/2575.pdf</u> (accessed 2009 Sep 18).
- 148. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programs*. 3rd ed. New York: Oxford University Press; 2005.
- Jonsson B, Berggren F, Svensson K et al. An economic evaluation of combination treatment with budesonide and formoterol in patients with mild-to-moderate persistent asthma. *Respir Med* 2004;98:1146-54.
- 150. Andersson F, Stahl E, Barnes PJ, Löfdahl CG, O'Byrne PM, Pauwels RA. Adding fomoterol to budesonide in moderate asthma-health economic results from the FACET study. *Respir Med* 2001;95:505-12.
- 151. Briggs AH, Bousquet J, Wallace MV, Busse WW, Clark TJH, Pedersen SE, et al. Cost-effectiveness of asthma control: an economic evaluation appraisal of the GOAL study. *Allergy* 2006;61:531-6.

- 152. Johansson G. Cost-effectiveness analysis of salmeterol/fluticasone propionate 50/100 ug vs fluticasone propionate 100 ug in adults and adolescents with asthma III: results. *Pharmacoeconomics* 1999;16(Suppl 2):15-21.
- 153. Price MJ, Briggs AH. Development of an economic model to assess the cost effectiveness of asthma management strategies. *Pharmacoeconomics* 2002;20:183-94.
- 154. Lundbäck B, Jenkins C, Price MJ et al. Cost-effectiveness of salmeterol/fluticasone proprionate combination product 50/250 mug twice daily and budesonide 800 mug twice daily in the treatment of adults and adolescents with asthma. *Respir Med* 2000;94:724-32.
- Palmqvist M. Cost-effectiveness analysis of salmeterol/fluticasone propionate 50/250 ug vs fluticasone propionate 250 ug in adults and adolescents with asthma IV: results. *Pharmacoeconomics* 1999;16(Suppl 2):23-28.
- Pieters WR. Cost effectiveness of salmeterol/fluticasone propionate 50/500ug vs fluticasone propionate 500ug in patients with corticosteroid-dependent asthma V: results. *Pharmacoeconomics* 1999;16(Suppl 2):29-34.
- 157. EricssonK, Bantje TA, Huber RM et al. Cost-effectiveness analysis of budesonide/formoterol compared with fluticasone in moderate-persistent asthma. *Respir Med* 2006;100:586-94.
- 158. Price D, Haughney J, Lloyd A, Hutchinson J, Plumb J. An economic evaluation of adjustable and fixed dosing with budesonide/formoterol via a single inhaler in asthma patients: the ASSURE study. *Curr Med Res Opin* 2004;20(10):1671-9.
- 159. Bruggenjurgen B. Economic assessment of adjustable maintenance treatment with budesonide/formoterol in a single inhaler versus fixed treatment in asthma. *Pharmacoeconomics* 2005;23(7):723-731.
- 160. Rutten-van Molken M, van Doorslaer EKA, Till M. Cost-effectiveness analysis of fomoterol versus salmeterol in patients with asthma. *Pharmacoeconomics* 1998;14:671-84.
- 161. Johansson G, Andreasson EB, Larsson PE, Vogelmeier CF. Cost-effectiveness of budesonide/formoterol for maintenance and reliever therapy versus salmeterol/fluticasone plus salbutamol in the treatment of asthma. *Pharmacoeconomics* 2006;24(7):695-708.
- Miller E, Sears MR, McIvor A, Liovas A. Canadian economic evaluation of budesonide-formoterol as maintenance and reliever treatment in patients with moderate to severe asthma. *Can Respir J* 2007;14(5):269-75.
- Miller E, Fitzgerald JM. Canadian economic evaluation of budesonide-formoterol as maintenance and reliever treatment in patients with moderate to severe asthma. *Can J Clin Pharmacol* 2008;15(2):e165e176.
- 164. Shih YT, Mauskopf J, Borker R. Cost-effectiveness analysis of first-line controller therapies for persistent asthma. *Pharmacoeconomics* 2007;25:577-90.
- 165. Price D, Wiren A, Kuna P. Cost-effectiveness of budesonide/formoterol for maintenance and reliever asthma therapy. *Allergy* 2007;62:1189-98.
- 166. Canadian Agency for Drugs and Technologies in Health. *Guidelines for the economic evaluation of health technologies: Canada*. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2006. Available: <a href="http://www.cadth.ca/media/pdf/186\_EconomicGuidelines\_e.pdf">http://www.cadth.ca/media/pdf/186\_EconomicGuidelines\_e.pdf</a> (accessed 2007 Mar 12).
- 167. Briggs A, Sculpher M. An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics* 1998;13:397-409.
- Rowe BH, Voaklander DC, Wang D, Senthilselvan A, Klassen TP, Marrie TJ, et al. Asthma presentations by adults to emergency departments in Alberta, Canada: a large population-based study. *Chest* 2009;135:57-65.
- Seung SF, Mittmann N. Urgent care costs of uncontrolled asthma in Canada, 2004. Can Resp J 2005;12:435-6.

- 170. Ontario Ministry of Health and Long-Term Care. *Ontario drug benefit formulary/comparative drug index* [database online]. Toronto: Ontario Ministry of Health and Long-Term Care; 2009. Available: <u>http://www.health.gov.on.ca/english/providers/program/drugs/odbf\_mn.html</u> (accessed 2009 Apr).
- 171. Ontario Ministry of Health and Long-Term Care. *Ontario health insurance (OHIP) schedule of benefits and fees*. Toronto: Ontario Ministry of Health and Long-Term Care; 2009. Available: <a href="http://www.health.gov.on.ca/english/providers/program/ohip/sob/sob\_mn.html">http://www.health.gov.on.ca/english/providers/program/ohip/sob/sob\_mn.html</a> (accessed 2009 Sep 18).
- 172. Bank of Canada. *Bank of Canada inflation calculator*. Ottawa: Bank of Canada; 2009. Available: <u>http://www.bankofcanada.ca/en/rates/inflation\_calc.html</u> (accessed 2009 Apr 12).
- 173. Ontario Case Costing Initiative. *OCCI costing analysis tool, 2008.* Toronto: Ontario Case Costing Initiative; 2009. Available: <u>http://www.occp.com/</u> (accessed 2009 Mar).
- 174. Briggs AH, Sculpher MJ, Buxton MJ. Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. *Health Econ* 1994;3:95-104.
- 175. Doublilet P, Begg CB, Weinstein MC, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. *Med Decis Making* 1985;5(2):157-77.
- 176. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;10(8):779-87.
- 177. Beauchamp TL, Childress JF. *Principles of biomedical ethics*. 5th ed. New York: Oxford University Press; 2001.
- 178. Horne R, Price D, Cleland J, Costa R, Covey D, Gruffydd-Jones K, et al. Can asthma control be improved by understanding the patient's perspective? *BMC Pulm Med* 2007;7:7-8.
- 179. Chan AW, Krleža-Jeriæ K, Schmid I, Altman DG. Outcome reporting bias in randomized trials funded by the Canadian Institutes of Health Research. *Can Med Assoc J* 2004;171:735-40.
- 180. Jorgensen AW, Maric KL, Tendal B, Faurschou A, Gotzsche PC. Industry-supported meta-analyses compared with meta-analyses with non-profit or no support: differences in methodological quality and conclusions. *BMC Med Res Methodol* 2008;8(60).
- 181. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *Br Med J* 2003;326:1167-70.
- 182. Lemière C, Becker A, Boulet LP, Bowie D, Cartier A, Cockroft D, et al. Should combination therapy with inhaled corticosteroids and long-acting beta2-agonists be prescribed as initial maintenance treatment for asthma? *Can Med Assoc J* 2002;167:1008-9.
- 183. Furukawa TA, Watanabe N, Omori IM, Montori VM, Guyatt GH. Association between unreported outcomes and effect size estimates in Cochrane meta-analyses. *Jama* 2007;297:468-70.
- 184. Sismondo S. Pharmaceutical company funding and its consequences: A qualitative systematic review. *Contemp Clin Trials* 2008;29:109-13.
- 185. British Thoracic SocietyScottish, Intercollegiate Guideline Network. *British guideline on the management of asthma: quick reference guide*. London, UK: British Thoracic Society; 2008.
- 186. Buhl R, Kardos P, Richter K, Meyer-Sabellek W, Bruggenjurgen B, Willich SN, et al. The effect of adjustable dosing with budesonide/formoterol on health-related quality of life and asthma control compared with fixed dosing. *Curr Med Res Opin* 2004;20(8):1209-20.
- 187. Canonica GW. Adjustable maintenance dosing with budesonide/formoterol in a single inhaler provides effective asthma symptom control at a lower dose than fixed maintenance dosing. *Pulm Pharmacol Ther* 2004;17:239-47.
- 188. Ind PW, Haughney J, Price D, Rosen JP, Kennelly J. Adjustable and fixed dosing with budesonide/formoterol via a single inhaler in asthma patients: the ASSURE study. *Respir Med* 2004;98(5):464-75.

- Leuppi JD, Salzberg M, Meyer L, Bucher SE, Nief M, Brutsche MH, et al. An individualized, adjustable maintenance regimen of budesonide/formoterol provides effective asthma symptom control at a lower overall dose than fixed dosing. *Swiss Med Wkly* 2003;133(21-22):302-9.
- 190. Lundborg M, Wille S, Bjermer L, Tilling B, Lundgren M, Telg G, et al. Maintenance plus reliever budesonide/formoterol compared with a higher maintenance dose of budesonide/formoterol plus formoterol as reliever in asthma: an efficacy and cost-effectiveness study. *Curr Med Res Opin* 2006;22(5):809-21.
- 191. Stallberg B, Olsson P, Jorgensen LA, Lindarck N, Ekstrom T. Budesonide/formoterol adjustable maintenance dosing reduces asthma exacerbations versus fixed dosing. *Int J Clin Pract* 2003;57(8):656-61.
- 192. Bateman ED, Jacques L, Goldfrad C, Atienza T, Mihaescu T, Duggan M. Asthma control can be maintained when fluticasone propionate/salmeterol in a single inhaler is stepped down. *J Allergy Clin Immunol* 2006;117(3):563-70.
- 193. The AGREE Collaboration. Appraisal of guidelines for research and evaluation (AGREE) Instrument. London: The AGREE Collaboration; 2008. Available: <u>http://www.agreecollaboration.org/pdf/agreeinstrumentfinal.pdf</u> (accessed 2009 May 5).
- 194. Mayer D. Practice guidelines and clinical prediction rules. In: *Essential Evidence-Based Medicine*. Cambridge, UK: University Press; 2004. p.276-87.
- 195. Fervers B, Burgers JS, Haugh MC, Brouwers M, Browman G, Cluzeau F, et al. Predictors of high quality clinical practice guidelines: examples in oncology. *Int J Qual Health Care* 2005;17(2):123-32.
- 196. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part I: Critical appraisal of existing treatment guidelines and systematic review of current research evidence. *OsteoArthritis Cartilage* 2007;15:987-1000.
- 197. Boulet LP, Bai TR, Becker A, Berube D, Beveridge R, Bowie DM, et al. What is new since the last (1999) Canadian Asthma Consensus Guidelines? *Can Respir J* 2001;8(Suppl A):5A-27A.
- Boulet LP, Becker A, Berube D, Beveridge R, Ernst P. Canadian Asthma Consensus Report, 1999. CMAJ 1999;161(11 Suppl):S1-S62.
- 199. Boulet LP, Becker A, Berube D, Beveridge R, Ernst P. Summary of recommendations from the Canadian Asthma Consensus Report, 1999. *CMAJ* 1999;161(11 Suppl):S1-S12.
- Becker A, Lemière C, Bérubé D, Boulet LP, Ducharme F, FitzGerald M, et al. Summary of recommendations from the Canadian Asthma Consensus Guidelines, 2003. *CMAJ* 2005;173(6 Suppl):S1-S56.

# **APPENDIX 1: LITERATURE SEARCH STRATEGIES**

#### APPENDIX 1.1: LITERATURE SEARCH STRATEGY FOR CLINICAL EFFECTIVENESS STUDIES

Ovid
EBM Reviews – Cochrane Central Register of Controlled Trials <3rd Quarter 2008>
EMBASE <1988 to 2008>
Medline® <1950 to 2008>
31Jul08
Left open
2006-2008
At the end of a phrase, searches the phrase as a subject heading
Medical Subject Heading
Floating subheading
Explode a subject heading
Truncation symbol, or wildcard: retrieves plural or variations of a word
Indicates that the marked subject heading is a primary topic
Requires words are adjacent to each other (in any order)
Adjacency within # number of words (in any order)
Title
Abstract
Title, Abstract, Subject Heading, CAS Registry/EC Number Word
CAS registry number

## MULTI-FILE STRATEGY

	Search Strings	Results
N	MEDLINE/CENTRAL	345 / 140
1	l. exp Administration, Inhalation/ and exp Glucocorticoids/	
	2. (inhale*.mp. or "Administration, Inhalation"/) and (glucocorticoid* or corticosteroid* or	
	steroid*).mp.	
	3. ICS.ti,ab.	
	4. exp Beclomethasone/ or 4419-39-0.rn.	
	5. 90566-53-3.rn.	
6	5. exp Budesonide/ or 51333-22-3.rn.	
	7. (141845-82-1 or 83919-23-7).rn.	
	8. (beclomet* or budes* or flutic* or cicles* or mome?asone).mp.	
	9. (pulmicort or flovent or Flixotide or QVAR or alvesco or asthmanex or asmanex).mp.	
	10. or/1-9	
1	11. (exp Adrenergic beta-agonists/ or "Receptors, Adrenergic, beta-2"/) and (long adj	
	ucting).ti,ab.	
	12. (long adj5 (beta* or agonist* or bronchodilator*)).mp.	
	13. LABA.ti,ab.	
	14. salmeterol*.mp.	
	15. (serevent or serobid or salmetadur or arial or beglan or betanican or inaspir).mp.	
	16. 89365-50-4.rn.	
	17. formoterol*.mp.	
	18. (oxeze or oxis or foradil or foradile or forair or formatris or broncoteril or fortofan or	
	atimos or eolus or liferol or atock or modulate or perforomist).mp.	
	19. 73573-87-2.m.	
	20. or/11-19	
	21. (symbicort or seretide or advair or viani or adoair or seroflo or fostair or innovair).mp.	
	22. (fluticasone adj3 salmeterol).mp.	
	23. (budesonide adj3 formoterol).mp.	
	24. (LABA adj2 ICS).ti,ab.	
	25. or/21-24	
	26. exp Asthma/	
	27. asthma*.mp.	
	28. or/26-27	
	29. 10 and 20 and 28	
	30. 25 and 28	
	31. or/29-30	
	32. limit 31 to yr="2006 - 2008"	
E	EMBASE	792
1	. inhale*.ti,ab. or *inhalation drug administration/ or ih.fs.	
	2. exp *corticosteroid/ or (glucocorticoid* or corticosteroid* or steroid*).ti,ab.	
	3. 1 and 2	
4	4. *beclometasone/ or *beclometasone dipropionate/ or 4419-39-0.rn.	
	5. *fluticasone/ or *fluticasone furoate/ or *fluticasone propionate/ or 90566-53-3.rn.	
6	5. exp *Budesonide/ or 51333-22-3.rn.	
	7. exp *CICLESONIDE/ or 126544-47-6.rn.	
	3. exp *Mometasone Furoate/ or 83919-23-7.rn.	
	9. (beclomet* or budes* or flutic* or cicles* or mome?asone).ti,ab.	
	10. (pulmicort or flovent or Flixotide or QVAR or alvesco or asthmanex or asmanex).ti,ab.	
	11. ICS.ti,ab.	
	12. or/3-11	
	13. exp *salmeterol/ or exp *formoterol/	
	14. *beta adrenergic receptor stimulating agent/ and long?acting.ti,ab.	

Line #	Search Strings	Results
	15. (long adj5 (beta* or agonist* or bronchodilator*)).ti,ab.	
	16. salmeterol*.ti,ab.	
	17. (serevent or serobid or salmetadur or arial or beglan or betanican or inaspir).ti,ab.	
	18. 89365-50-4.rn.	
	19. formoterol*.ti,ab.	
	20. (oxeze or oxis or foradil or foradile or forair or formatris or broncoteril or fortofan or	
	atimos or eolus or liferol or atock or modulate or perforomist).ti,ab.	
	21. 73573-87-2.rn.	
	22. LABA.ti,ab.	
	23. or/13-22	
	24. exp *Fluticasone Propionate Plus Salmeterol/	
	25. exp *budesonide plus formoterol/	
	26. (symbicort or seretide or advair or viani or adoair or seroflo or fostair or innovair).ti,ab.	
	27. (fluticasone adj3 salmeterol).ti,ab.	
	28. (budesonide adj3 formoterol).ti,ab.	
	29. (LABA adj2 ICS).ti,ab.	
	30. or/24-29	
	31. exp Asthma/	
	32. asthma*.mp.	
	33. or/31-32	
	34. 12 and 23 and 33	
	35. 30 and 33	
	36. or/34-35	
	37. limit 36 to yr="2006 - 2008"	

OVERVIEW Interface:		
muuluuv.	Wiley	
Databases:	The Cochrane Library (Issue 3 2008)	
	<ul> <li>Cochrane Database of Systematic Reviews (CDSR)</li> </ul>	
	• Database of Abstracts of Reviews of Effects (DARE)	
	<ul> <li>Health Technology Assessment Database (HTA)</li> </ul>	
Date of Search:	05Sep08	
Study Types:	Controlled Trials, Systematic Reviews, Health Technology Assessmen	ts
Limits:	None	
SYNTAX		
GUIDE		
MeSH descriptor	Medical Subject Heading	
Explode all trees	Explode a subject heading	
*	Truncation symbol, or wildcard: retrieves plural or variations of a word	1
NEAR/#	Required words are adjacent to each other within # of words	
ti	Title	
ab	Abstract	
kw	Heading Word; usually includes subject headings and controlled vocab	oulary
MULTI-FILE STR	ATEGY	
Line	Search Strings	Results
#		
1 (ASTHMA	L*):ti,ab,kw	18 CDSR
		4 DARE
		5 HTA
	or hudges or fluties or gigless or momentaging or momentaging or	
2 (beclomet*	of budes of flutte of cicles of mometasone of mometasone of	
	or flovent or Flixotide or QVAR or alvesco or asthmanex or	
pulmicort ( asmanex):	or flovent or Flixotide or QVAR or alvesco or asthmanex or i,ab,kw	
pulmicort ( asmanex):	or flovent or Flixotide or QVAR or alvesco or asthmanex or	
	or budes* or flutic* or cicles* or mometasone or momethasone or	5 HTA

4	(#2 OR #3)
5	(formoterol or oxeze or oxis or foradil or foradile or forair or formatris or broncoteril or fortofan or atimos or eolus or liferol or atock or modulate or perforomis OR salmeterol or serevent or serobid or salmetadur or arial or beglan or betanican or inaspir):ti,ab,kw
6	(long NEAR/5 (beta* or agonist* or bronchodilator*)):ti,ab,kw or (LABA):ti,ab,kw
7	(#5 OR #6)
8	(#4 AND #7)
9	(symbicort or seretide or advair or viani or adoair or seroflo or fostair or innovair ):ti,ab,kw or (budesonide NEAR/3 formoterol):ti,ab,kw or (fluticasone NEAR/3 salmeterol ):ti,ab,kw or (ICS NEAR/3 LABA):ti,ab,kw
10	(#8 OR #9)
11	(#1 AND #10)

OVER	VIEW	
Interfac		
Databas		
	Search: 29Aug08	
Study T		
Limits:	Last 180 days	
	AX GUIDE	
MeSH	Medical Subject Heading terms	
RN	EC/RN Number	
TIAB *	Title/Abstract	
-	Truncation symbol, or wildcard: retrieves plural or variations of a word	
STRAT		
Line #	# Search Strings	Results
<u>55</u>	Search #51 AND #52 Limits: added to PubMed in the last 180 days	<u>81</u>
<u>53</u>	Search #51 AND #52	<u>1513</u>
<u>52</u>	Search Asthma*	<u>107649</u>
<u>51</u>	Search #49 OR #50	<u>2217</u>
<u>50</u>	Search symbicort OR seretide OR advair OR viani OR adoair OR seroflo OR fostair OR innovair OR "fluticasone/salmeterol" OR "salmeterol/fluticasone" OR "budesonide/formoterol" OR "formoterol/budesonide" OR "LABA + ICS" OR "LABA/ICS"[TIAB]	<u>571</u>
<u>49</u>	Search #37 AND #48	<u>1951</u>
<u>48</u>	Search #39 OR #44 OR #45	<u>104827</u>
<u>45</u>	Search LABA[TIAB] OR salmeterol* OR serevent OR serobid OR salmetadur OR arial OR beglan OR betanican OR inaspir OR 89365-50-4[RN] OR formoterol* OR oxeze OR oxis OR foradil OR foradile OR forair OR formatris OR broncoteril OR fortofan OR atimos OR eolus OR liferol OR atock OR modulate OR performist OR 73573-87-2[RN]	<u>67626</u>
<u>44</u>	Search long[tiab] AND (beta*[TIAB] OR agonist*[TIAB] OR bronchodilator*[TIAB])	<u>38894</u>
<u>39</u>	Search ("Adrenergic beta-agonists" [MESH] OR "Receptors, Adrenergic, beta-2"[MESH]) AND "long acting"[TIAB]	<u>907</u>
<u>37</u>	Search #33 OR #34 OR #35	<u>15523</u>
<u>35</u>	Search ICS [TIAB] OR Beclomethasone[MESH] OR 4419-39-0[RN] OR 90566-53-3[RN] OR Budesonide[MESH] OR 51333-22-3[RN] OR 141845-82-1[RN] OR 83919-23-7[RN] OR beclomet* OR budes* OR flutic* OR cicles* OR mometasone OR momethasone OR	<u>10622</u>

pulmicort OR flovent OR Flixotide OR QVAR OR alvesco OR asthmanex OR asmanex

- <u>34</u> Search ((inhale\* OR "Administration, Inhalation"[Mesh:noexp]) AND (glucocorticoid\* OR 9022 corticosteroid\* OR steroid\*)) <u>1121</u>
- Search "Administration, Inhalation" [Mesh] AND Glucocorticoids [Mesh] <u>33</u>

#### 

	VIEW	
Interface Databa		
Dutubu	Web of Science® (1909-2008)	
Date of	f Search: 28Aug08	
Study 7	6	
Limits:		
	AX GUIDE	
TS=	Topic	
SAME	Truncation symbol, or wildcard: retrieves plural or variations of a word	
SAME	Finds records containing terms in the title, the same sentence in the abstract, or the keyword phrase.	e same
TI=	Title of Article	
SO=	Source	
MULT	I-FILE STRATEGY	
Line #	Search Strings	Results
14	#13 AND #12	98 BIOSIS
14	$\pi_{13} \operatorname{And} \pi_{12}$	254 WOS
	TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation	
13	stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR	
	TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*)	
12	#11 AND #10	
11	TS=(asthma*)	
10	#9 OR #8	
	TS=(symbicort or seretide or advair or viani or adoair or seroflo or fostair or innovair) OR	
9	TS=(fluticasone SAME salmeterol) OR TS=(budesonide SAME formoterol) OR TS=(ICS	
	SAME LABA)	
8	#7 AND #4	
7	#6 OR #5	
6	TS=(long SAME (beta* or agonist* or bronchodilator*)) OR TI=(LABA)	
	TS=(formoterol or oxeze or oxis or foradil or foradile or forair or formatris or broncoteril or	
5	fortofan or atimos or eolus or liferol or atock or modulate or perforomis) OR TS=(salmeterol	
	or serevent or serobid or salmetadur or arial or beglan or betanican or inaspir)	
4	#3 OR #2 OR #1	
	TI=(iCS)	
3		
32	TS=(inhale*) AND TS=(glucocorticoid* or corticosteroid* or steroid*)	
	TS=(inhale*) AND TS=(glucocorticoid* or corticosteroid* or steroid*) TS=(beclomet* or budes* or flutic* or cicles* or mometasone or momethasone or pulmicort or	-

### OTHER DATABASES

Database	Search Strings	Results
ClinicalTrials.Gov Seached: 28Jul08	pulmicort OR flovent OR flixotide OR QVAR OR alvesco OR beclomet* OR budes* OR flutic* OR cicles*   asthma   salmeterol OR serevent OR serobid OR fomoterol OR oxeze OR oxis OR foradil OR seretide OR symbicort OR advair OR viani OR adoair OR seroflo   Adult	90
Australian New Zealand Clinical Trials Registry :: ANZCTR Searched: 30Jul08	Asthma*	134
Current Controlled Trials Searched: 05Sep08	(symbicort or seretide or advair or viani or adoair or seroflo or fostair or innovair) AND asthma%	1
ClinicalStudy Results.Org Searched: 27Aug08	Selected the following drugs from the search menu and scanned titles : Advair, Advair/Seretide, advair/seretide, Advair; Seretide, Symbicort, Pulmicort Turbuhaler, Fluticasone, Beclomethasone, Budesonide, Ciclesonide	116
Dissertation Abstracts (1637- 2008) Searched: 29Aug08	3. (Search symbicort OR seretide OR advair OR viani OR adoair OR seroflo OR fostair OR innovair OR "fluticasone/salmeterol" OR "salmeterol/fluticasone" OR "budesonide/formoterol" OR "formoterol/budesonide" OR "LABA/ICS") AND (asthma*)	1
	2. (inhale* and (glucocorticoid* or corticosteroid* or steroid*)) AND ("long acting" or LABA) AND (asthma*)	5
	1. (beclomet* or budes* or flutic* or cicles* or mometasone or momethasone or pulmicort or flovent or Flixotide or QVAR or alvesco or asthmanex or asmanex) AND (asthma*) AND ("long acting" or LABA)	1

## **ORGANIZATIONS AND SOCIETIES**

U.S.Food and Drug Administration www.fda.gov Searched Jully 22, 2008

European Medicines Agency (EMEA) www.emea.europa.eu/index/indexh1.htm

#### APPENDIX 1.2: LITERATURE SEARCH STRATEGY FOR COST-EFFECTIVENESS STUDIES

Interfa	COLEW	Wiley	
Databa		The Cochrane Library (Issue 3 2008)	
2 anaoa		<ul> <li>NHS Economic Evaluation Database (NHS EED)</li> </ul>	
Date of	f Search:	September 5, 2008	
Study '	Types:	Not required	
Limits		None	
SYNT. GUIDI			
	descriptor	Medical Subject Heading	
	de all trees	Explode a subject heading	
*		Truncation symbol, or wildcard: retrieves plural or variations of a word	
NEAR	/#	Required words are adjacent to each other within # of words	
ti		Title	
ab		Abstract	
kw		Heading Word; usually includes subject headings and controlled vocabul	ary
MULT	I-FILE STR	RATEGY	
Line		Search Strings	Results
#	( ) ( ) ) ) ) ) ) ) ) ) ) ) ) ) ) ) ) )		
1	(ASTHMA	x*):ti,ab,kw	27
2	(beclomet*	f or budes* or flutic* or cicles* or mometasone or momethasone or	
	(beclomet* pulmicort o	f or budes* or flutic* or cicles* or mometasone or momethasone or flovent or Flixotide or QVAR or alvesco or asthmanex or	
2	(beclomet* pulmicort of asmanex):t	f or budes* or flutic* or cicles* or mometasone or momethasone or flovent or Flixotide or QVAR or alvesco or asthmanex or i,ab,kw	
	(beclomet* pulmicort of asmanex):1 (inhale*) A	or budes* or flutic* or cicles* or mometasone or momethasone or flovent or Flixotide or QVAR or alvesco or asthmanex or i,ab,kw AND (glucocorticoid* or corticosteroid* or steroid*):ti,ab,kw or	
2	(beclomet* pulmicort of asmanex):t	or budes* or flutic* or cicles* or mometasone or momethasone or flovent or Flixotide or QVAR or alvesco or asthmanex or i,ab,kw AND (glucocorticoid* or corticosteroid* or steroid*):ti,ab,kw or kw	
2	(beclomet* pulmicort d asmanex):ti (inhale*) A (ICS):ti,ab (#2 OR #3	* or budes* or flutic* or cicles* or mometasone or momethasone or or flovent or Flixotide or QVAR or alvesco or asthmanex or i,ab,kw ND (glucocorticoid* or corticosteroid* or steroid*):ti,ab,kw or kw	
2 3 4	(beclomet* pulmicort of asmanex):tf (inhale*) A (ICS):ti,ab (#2 OR #3) (formotero	For budes* or flutic* or cicles* or mometasone or momethasone or for flovent or Flixotide or QVAR or alvesco or asthmanex or i,ab,kw AND (glucocorticoid* or corticosteroid* or steroid*):ti,ab,kw or kw I or oxeze or oxis or foradil or foradile or forair or formatris or broncoteril	
2 3 4	(beclomet* pulmicort c asmanex):t (inhale*) A (ICS):ti,ab (#2 OR #3) (formotero or fortofan	For budes* or flutic* or cicles* or mometasone or momethasone or flovent or Flixotide or QVAR or alvesco or asthmanex or i,ab,kw AND (glucocorticoid* or corticosteroid* or steroid*):ti,ab,kw or kw I or oxeze or oxis or foradil or foradile or forair or formatris or broncoteril or atimos or eolus or liferol or atock or modulate or perforomis OR	
2 3 4	(beclomet* pulmicort c asmanex):t (inhale*) A (ICS):ti,ab (#2 OR #3) (formotero or fortofan salmeterol inaspir):ti,a	For budes* or flutic* or cicles* or mometasone or momethasone or flovent or Flixotide or QVAR or alvesco or asthmanex or i,ab,kw AND (glucocorticoid* or corticosteroid* or steroid*):ti,ab,kw or ,kw I or oxeze or oxis or foradil or foradile or forair or formatris or broncoteril or atimos or eolus or liferol or atock or modulate or perforomis OR or serevent or serobid or salmetadur or arial or beglan or betanican or ab,kw	
2 3 4	(beclomet* pulmicort c asmanex):t (inhale*) A (ICS):ti,ab (#2 OR #3) (formotero or fortofan salmeterol inaspir):ti,a	For budes* or flutic* or cicles* or mometasone or momethasone or flovent or Flixotide or QVAR or alvesco or asthmanex or i,ab,kw AND (glucocorticoid* or corticosteroid* or steroid*):ti,ab,kw or kw I or oxeze or oxis or foradil or foradile or forair or formatris or broncoteril or atimos or eolus or liferol or atock or modulate or perforomis OR or serevent or serobid or salmetadur or arial or beglan or betanican or	
2 3 4 5	(beclomet* pulmicort c asmanex):t (inhale*) A (ICS):ti,ab (#2 OR #3) (formotero or fortofan salmeterol inaspir):ti,a	<ul> <li>a or budes* or flutic* or cicles* or mometasone or momethasone or per flovent or Flixotide or QVAR or alvesco or asthmanex or i,ab,kw</li> <li>AND (glucocorticoid* or corticosteroid* or steroid*):ti,ab,kw or gkw</li> <li>a or oxeze or oxis or foradil or foradile or forair or formatris or broncoteril or atimos or eolus or liferol or atock or modulate or performis OR or serevent or serobid or salmetadur or arial or beglan or betanican or ab,kw</li> <li>R/5 (beta* or agonist* or bronchodilator*)):ti,ab,kw or (LABA):ti,ab,kw</li> </ul>	
2 3 4 5 6	(beclomet* pulmicort of asmanex):ti (inhale*) A (ICS):ti,ab (#2 OR #3 (formotero or fortofan salmeterol inaspir):ti,d (long NEA	For budes* or flutic* or cicles* or mometasone or momethasone or flovent or Flixotide or QVAR or alvesco or asthmanex or i,ab,kw AND (glucocorticoid* or corticosteroid* or steroid*):ti,ab,kw or kw I or oxeze or oxis or foradil or foradile or forair or formatris or broncoteril or atimos or eolus or liferol or atock or modulate or perforomis OR or serevent or serobid or salmetadur or arial or beglan or betanican or ab,kw R/5 (beta* or agonist* or bronchodilator*)):ti,ab,kw or (LABA):ti,ab,kw	
2 3 4 5 6 7	(beclomet* pulmicort of asmanex):ti (inhale*) A (ICS):ti,ab (#2 OR #3 (formotero or fortofan salmeterol inaspir):ti,a (long NEA (#5 OR #6 (#4 AND #	For budes* or flutic* or cicles* or mometasone or momethasone or flovent or Flixotide or QVAR or alvesco or asthmanex or i,ab,kw AND (glucocorticoid* or corticosteroid* or steroid*):ti,ab,kw or kw I or oxeze or oxis or foradil or foradile or forair or formatris or broncoteril or atimos or eolus or liferol or atock or modulate or perforomis OR or serevent or serobid or salmetadur or arial or beglan or betanican or ab,kw R/5 (beta* or agonist* or bronchodilator*)):ti,ab,kw or (LABA):ti,ab,kw	
2 3 4 5 6 7 8	(beclomet* pulmicort of asmanex):ti (inhale*) A (ICS):ti,ab (#2 OR #3) (formotero or fortofan salmeterol inaspir):ti,3 (long NEA (#5 OR #6) (#4 AND # (symbicort ):ti,ab,kw of	For budes* or flutic* or cicles* or mometasone or momethasone or per flovent or Flixotide or QVAR or alvesco or asthmanex or i,ab,kw AND (glucocorticoid* or corticosteroid* or steroid*):ti,ab,kw or kw I or oxeze or oxis or foradil or foradile or forair or formatris or broncoteril or atimos or eolus or liferol or atock or modulate or perforomis OR or serevent or serobid or salmetadur or arial or beglan or betanican or ab,kw R/5 (beta* or agonist* or bronchodilator*)):ti,ab,kw or (LABA):ti,ab,kw F7) or seretide or advair or viani or adoair or seroflo or fostair or innovair or (budesonide NEAR/3 formoterol):ti,ab,kw or (fluticasone NEAR/3	
2 3 4 5 6 7 8	(beclomet* pulmicort of asmanex):t (inhale*) A (ICS):ti,ab (#2 OR #3) (formotero or fortofan salmeterol inaspir):ti,a (long NEA (#5 OR #6) (#4 AND # (symbicort ):ti,ab,kw of salmeterol	a or budes* or flutic* or cicles* or mometasone or momethasone or flovent or Flixotide or QVAR or alvesco or asthmanex or i,ab,kw AND (glucocorticoid* or corticosteroid* or steroid*):ti,ab,kw or kw I or oxeze or oxis or foradil or foradile or forair or formatris or broncoteril or atimos or eolus or liferol or atock or modulate or perforomis OR or serevent or serobid or salmetadur or arial or beglan or betanican or ab,kw R/5 (beta* or agonist* or bronchodilator*)):ti,ab,kw or (LABA):ti,ab,kw or seretide or advair or viani or adoair or seroflo or fostair or innovair or (budesonide NEAR/3 formoterol):ti,ab,kw or (fluticasone NEAR/3 ):ti,ab,kw or (ICS NEAR/3 LABA):ti,ab,kw	
2 3 4 5 6 7 8	(beclomet* pulmicort of asmanex):ti (inhale*) A (ICS):ti,ab (#2 OR #3) (formotero or fortofan salmeterol inaspir):ti,3 (long NEA (#5 OR #6) (#4 AND # (symbicort ):ti,ab,kw of	a or budes* or flutic* or cicles* or mometasone or momethasone or flovent or Flixotide or QVAR or alvesco or asthmanex or i,ab,kw AND (glucocorticoid* or corticosteroid* or steroid*):ti,ab,kw or kw I or oxeze or oxis or foradil or foradile or forair or formatris or broncoteril or atimos or eolus or liferol or atock or modulate or perforomis OR or serevent or serobid or salmetadur or arial or beglan or betanican or ab,kw R/5 (beta* or agonist* or bronchodilator*)):ti,ab,kw or (LABA):ti,ab,kw or seretide or advair or viani or adoair or seroflo or fostair or innovair or (budesonide NEAR/3 formoterol):ti,ab,kw or (fluticasone NEAR/3 ):ti,ab,kw or (ICS NEAR/3 LABA):ti,ab,kw	

OVER	RVIEW		
Interfa	nce:	Wiley	
Databa		HEED: Health Economic Evaluations Database	
Date of Search:		September 5, 2008	
	Types:	Not required	
Limits		None applied	
	AX GUIDE		
*		Truncation symbol, or wildcard: retrieves plural	l or variations of a word
AX		All Data	
CS		Combined search lines	
MULI	<b>FILE ST</b>	RATEGY	
ID		Search Strings	Results
1.	AX=asth	ma*	92
2.		omet* or budes* or flutic* or cicles* or mometason or QVAR or alvesco or asthmanex or asmanex	ne or momethasone or pulmicort or flovent or
3.	(AX=inh	ale* AND AX=glucocorticoid* or corticosteroid*	or steroid*) OR AX=ICS
4.	CS=2 or	3	
5.	atimos or	noterol or oxeze or oxis or foradil or foradile or for e eolus or liferol or atock or modulate or perforomis ur or arial or beglan or betanican or inaspir	
6.	(AX=lon	g AND AX=beta* or agonist* or bronchodilator*)	OR AX=LABA
7.	CS= 5 or	6	
8.	CS=4 an	.d 7	
9.		nbicort or seretide or advair or viani or adoair or se lesonide AND formoterol) OR (AX=fluticasone Al	
10.	CS= 8 or	9	
11.	CS=1 and	4.10	

# ORGANIZATIONS AND SOCIETIES

Centre for Health Economics and Policy Analysis (CHEPA), McMaster University <a href="http://www.chepa.org/">http://www.chepa.org/</a>

ISPOR (International Society for Pharmacoeconomics and Outcomes Research), 2003-2008 <a href="http://www.ispor.org/">http://www.ispor.org/</a>

## APPENDIX 2: EXCLUDED STUDIES—CLINICAL REVIEW

## **EXCLUDED STUDIES (N = 48)**

The following studies failed to meet at least one of the pre-specified inclusion criteria.

#### Publication type (N = 10)

The following studies were excluded because they were not reports of primary research.

Budesonide/formoterol (symbicort) for asthma. Med Lett Drugs Ther 2008;50(1279):9-11.

Bloom J. Fluticasone propionate/salmeterol 100/50mcg is inhaled steroid sparing in patients who require fluticasone propionate 250mcg for asthma stability [poster]. ATS Conference D034; 2003; Seattle. Poster no C33.

Bonnet-Gonod F. Superior efficacy of low daily dose of a new fixed combination of beclometasone dipropionate/formoterol pMDI compared to an increased daily dose of BDP in moderate persistent asthma a 3 month clinical study. *Eur Respir J* 2006;28(Suppl 50):207s.

Boulet LP. Efficacy of salmeterol/fluticasone proprionate HFA MDI versus high dose fluticasone proprionate HFA MDI in adolescent and adult asthma [poster]. ERS Meeting; 2003; Vienna.

Dahl R. EXCEL: regular maintenance therapy with salmeterol/fluticasone propionate combination (SFC) reduces exacerbations more effectively than with formoterol/budesonide combination (FBC) [abstract]. ERJ 2004;24(Suppl 48):309s.

Jenkins CR, Marks GB, Gibson PG, Wark PAB, Thien FC, Belousova EG, et al. A randomised controlled trial of two algorithms for maintaining asthma control on long acting bronchodilators (LABA) and inhaled corticosteroids (ICS) [abstract]. Thoracic Society of Australia and New Zealand Annual Scientific Meeting; 2008 March 25-28. Abstract TP044.

Matz J, Emmett A, Rickard K, Kalberg C. Addition of salmeterol to low-dose fluticasone versus higher-dose fluticasone: an analysis of asthma exacerbations. *J Allergy Clin Immunol* 2001;107(5):783-9.

O'Byrne PM, Naya IP, Kallen A, Postma DS, Barnes PJ. Increasing doses of inhaled corticosteroids compared to adding long-acting inhaled beta2-agonists in achieving asthma control. *Chest* 2008.

Rosenwasser L, Noonan M, Martin P, O'Dowd L, O'Brien C. Safety of budesonide and formoterol administered via one pressurized metered-dose inhaler (budesonide/formoterol pMDI) in patients (>= 12 years) with moderate to severe persistent asthma. *J Allergy Clin Immunol* 2007;119(1 Suppl 1).

Smozik Y. Effectiveness of adjustable maintenance dosing and fixed dosing with budesonide/formoterol single inhaler in a multi-ethnic asthma population [abstract]. *European Respiratory Society* 2004.

#### Study design (N = 2)

The following studies were excluded because they were not randomized controlled clinical trials.

Trautmann M. Achievement of total control of asthma in clinical practice using the combination of inhaled salmeterol and fluticasone propionate. *Eur Respir J* 2006;28(Suppl 50):616s.

Tsoi AN, Gavrishina EA, Lazareva NB, Arkhipov VV. Efficacy of the using budesonide formoterol in patients with bronchial asthma (BA): the study of routine clinical practice. *Eur Respir J* 2006;28(Suppl 50):499s.

#### Adult Population (N = 8)

The following studies were excluded because the study population was not >50% adult ( $\geq 12$  years).

Akpinarli A, Tuncer A, Saraclar Y, Sekerel BE, Kalayci O. Effect of formoterol on clinical parameters and lung functions in patients with bronchial asthma: a randomised controlled trial. *Arch Dis Child* 1999;81(1):45-8.

Hueck C. A randomized controlled trial of short term growth and collagen turnover in asthmatics with inhaled formoterol and bedesonide. *Arch Dis Child* 2000;83:334-9.

Meijer GG, Postma DS, Mulder PG, van Aalderen WM. Long-term circadian effects of salmeterol in asthmatic children treated with inhaled corticosteroids. *Am J Respir Crit Care Med* 1995;152(6 Pt 1):1887-92.

Ortega-Cisnero M. [Salmeterol and inhaled beclomethasone versus high dose inhaled beclomethasone in the control of pediatric patients with moderate asthma]. *Ann Allergy Asthma Immunol* 1998;80:131.

Russell G, Williams DA, Weller P, Price JF. Salmeterol xinafoate in children on high dose inhaled steroids. *Ann Allergy Asthma Immunol* 1995;75(5):423-8.

Tal A, Simon G, Vermeulen JH, Petru V, Cobos N, Everard ML, et al. Budesonide/formoterol in a single inhaler versus inhaled corticosteroids alone in the treatment of asthma. *Pediatr Pulmonol* 2002;34(5):342-50.

Verberne AA, Frost C, Duiverman EJ, Grol MH, Kerrebijn KF. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma. The Dutch Asthma Study Group. *Am J Respir Crit Care Med* 1998;158(1):213-9.

Zimmerman B, D'Urzo A, Berube D. Efficacy and safety of formoterol turbuhaler when added to inhaled corticosteroid treatment in children with asthma. *Pediatr Pulmonol* 2004;37(2):122-7.

#### Diagnosis of asthma (N = 1)

The following study was excluded because it did not report that the study population had been diagnosed with chronic persistent asthma.

Simons FE, Gerstner TV, Cheang MS. Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. *Pediatrics* 1997;99(5):655-9.

### Intervention not combination therapy (N = 3)

The following studies were excluded because the intervention of interest was not a combination LABA/ICS therapy.

Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;129(1):15-26.

Wolfe J, Kreitzer S, Chervinsky P, Lawrence M, Wang Y, Reilly D, et al. Comparison of powder and aerosol formulations of salmeterol in the treatment of asthma. *Ann Allergy Asthma Immunol* 2000;84(3):334-40.

Wolfe J, Laforce C, Friedman B, Sokol W, Till D, Della CG, et al. Formoterol, 24 microg bid, and serious asthma exacerbations: similar rates compared with formoterol, 12 microg bid, with and without extra doses taken on demand, and placebo. *Chest* 2006;129(1):27-38.

#### Trial period < 60 days (N = 11)

The following studies were excluded because the trial period was less than 60 days.

Fitzgerald JM, Sears MR, Boulet LP, Becker AB, McIvor AR, Ernst P, et al. Adjustable maintenance dosing with budesonide/formoterol reduces asthma exacerbations compared with traditional fixed dosing: a five-month multicentre Canadian study. *Can Respir J* 2003 Nov;10(8):427-34.

Hampel F, Martin P, Mezzanotte W. Early bronchodilatory effects of budesonide/formoterol pressurized metered-dose inhaler (pMDI) compared with fluticasone Propionate/Salmeterol dry powder inhaler (DPI) and albuterol pMDI in adults with asthma. *J Allergy Clin Immunol* 2008;121(2 Suppl. 1):S220-S221.

Houghton CM, Lawson N, Borrill ZL, Wixon CL, Yoxall S, Langley SJ, et al. Comparison of the effects of salmeterol/fluticasone propionate with fluticasone propionate on airway physiology in adults with mild persistent asthma. *Respir Res* 2007;8:52.

Leblanc P, Knight A, Kreisman H, Borkhoff CM, Johnston PR. A placebo-controlled, crossover comparison of salmeterol and salbutamol in patients with asthma. *Am J Respir Crit Care Med* 1996;154(2 Pt 1):324-8.

Lotvall J, Langley S, Woodcock A. Inhaled steroid/long-acting beta 2 agonist combination products provide 24 hours improvement in lung function in adult asthmatic patients. *Respir Res* 2006;7:110.

Norhaya MR, Yap TM, Zainudin BM. Addition of inhaled salmeterol to inhaled corticosteroids in patients with poorly controlled nocturnal asthma. *Respirology* 1999;4(1):77-81.

Pearlman DS, Stricker W, Weinstein S, Gross G, Chervinsky P, Woodring A, et al. Inhaled salmeterol and fluticasone: a study comparing monotherapy and combination therapy in asthma. *Ann Allergy Asthma Immunol* 1999;82(3):257-65.

Piccinno A. Tolerability of high cumulative doses of a new fixed combination of beclomethasone dipropionate/formoterol in asthmatic patients. *Eur Respir J* 2006;28(Suppl 50):316s.

Weersink EJM. Fluticasone proprionate, salmeterol xinaoate and their combination in the treatment of nocturnal asthma. *Am J Respir Crit Care Med* 1997;155:1241-6.

Zhong NS. Salmeterol/fluticasone propionate in a single inhaler is superior to budesonide alone in control of Chinese asthmatic adults - an open-label, randomised, 6-week study. *Clin Drug Invest* 2004;24:583-92.

Zugic V. Effects of adding salmeterol to inhaled corticosteroids on lung function and quality of life in patients with mild persistent asthma. *Eur Respir J* 2006;28(Suppl 50):499s.

#### Comparator not ICS monotherapy or combination therapy (N = 8)

The following studies did not compare the study treatment to ICS monotherapy or a different LABA/ICS combination therapy.

Bateman ED. Salmeterol/fluticasone combination inhaler: a new, effective and well tolerated treatment for asthma. *Clin Drug Invest* 1998;16(3):193-201.

Cowie RL, Boulet LP, Keith PK, Scott-Wilson CA, House KW, Dorinsky PM. Tolerability of a salmeterol xinafoate/fluticasone propionate hydrofluoroalkane metered-dose inhaler in adolescent and adult patients with persistent asthma: a 52-week, open-label, stratified, parallel-group, multicenter study. *Clin Ther* 2007;29(7):1390-402.

D'Urzo AD, Chapman KR, Cartier A, Hargreave FE, Fitzgerald M, Tesarowski D. Effectiveness and safety of salmeterol in nonspecialist practice settings. *Chest* 2001;119(3):714-9.

Holt S, Ryder-Lewis S, Masoli M, Weatherall M, Beasley R. Fixed and adjustable dose asthma action plans based on combination therapy: a pilot study. *Respirology* 2005;10(4):497-503.

Rosenhall L, Heinig JH, Lindqvist A, Leegaard J, Stahl E, Bergqvist PB. Budesonide/formoterol (symbicort) is well tolerated and effective in patients with moderate persistent asthma. *Int J Clin Pract* 2002;56(6):427-33.

Sears MR, Boulet LP, Laviolette M, Fitzgerald JM, Bai TR, Kaplan A, et al. Budesonide/formoterol maintenance and reliever therapy: impact on airway inflammation in asthma. *Eur Respir J* 2008;31(5):982-9.

Sears R. Budesonide/formoterol maintenance and reliever therapy for asthma compared to conventional best practice a randomised real life study. *Eur Respir J* 2006;28(Suppl 50):613s.

Shim JJ, Uh ST, Lee YC, Park Sk, Williams AE, Jung KS. Asthma-related quality of life with salmeterol/fluticasone propionate (SFC) in bronchial asthma: a randomised controlled study comparing SFC with current care. *Respirology* 2006;11(Suppl 5):A144-12.

#### Inconsistent use of additional therapy (N = 1)

The following study was excluded because the study population used variable doses of an additional cointervention.

Wronska J, Chazan R, Mazurek J, Droszcz W. Treatment with salmeterol and quality of life in patients with asthma. *Pneumonol Alergol Pol* 1998;66(3-4):193-7.

## LABA ICS run-in (N = 1)

The following study was excluded because the study participants were run-in on LABA/ICS combination therapy prior to randomization.

Godard P, Greiller P, Pigearias B, Nachbaur G, Desfougeres JL, Attali V. Maintaining asthma control in persistent asthma: comparison of three strategies in a 6-month double-blind randomized study. *Respir Med* 2008;102:1124-1131.

## No outcome data (N = 3)

The following studies were excluded because they did not report numeric data on an least one of the outcomes of interest (i.e., lung function, asthma control, or quality of life).

AstraZeneca. SALTO - symbicort single inhaler therapy use in adolescent adults and adults with persistent asthma [database online]. In. Bethesda (MD): *ClinicalTrials.gov*; 2006. p. NCT00290264. Available: <u>http://clinicaltrials.gov/ct2/show/NCT00290264</u> (accessed 2009 Sep 18).

Gardiner PV, Ward C, Booth H, Allison A, Hendrick DJ, Walters EH. Effect of eight weeks of treatment with salmeterol on bronchoalveolar lavage inflammatory indices in asthmatics. *Am J Respir Crit Care Med* 1994;150(4):1006-11.

Shamsul AI, Hadzri HM, Noradina AT, Fauzi MA, Hamid AJ, Rosalina AM. Step-down approach in chronic stable asthma; a comparison of reducing dose inhaled formoterol/budesonide with maintaining inhaled budesonide [abstract]. *Respirology* 2007;12(Suppl 4):A141.

## **REPORTS PENDING (N = 6)**

The following reports are pending retrieval or consensus assessment.

Bonnet-Gonod F. Beclometasone dipropionate/formoterol in a single inhaler improves lung function and clinically meaningful outcomes in moderate to severe asthma [abstract]. *Eur Respir* J 2006;28(Suppl 50):205s.

Chapman KR, Ringdal N, Backer V, Palmqvist M, Saarelainen S, Briggs M. Salmeterol and fluticasone propionate (50/250 microg) administered via combination Diskus inhaler: as effective as when given via separate Diskus inhalers. *Can Respir J* 1999;6(1):45-51.

Godard PA, V. Comparison of different treatment strategies in stepping down combination treatment withdrawing the LABA versus reducing the ICS dose. *Proc Am Thorac Soc* 2006;A213.

Kalberg CJ. A comparison of added salmeterol versus increased-dose fluticasone in patients symptomatic on low-dose fluticasone [abstract]. *J Allergy Clin Immunol* 1998;101(Suppl):S6.

Michilis A. SURF study: real-life effectiveness of budesonide/formoterol (B/F) adjustable maintenance dosing [abstract]. *Allergy Clin Immunol Int* 2003;15(Suppl 1):56. Abs P-2-39.

Paggiaro P. Efficacy and safety of the new beclomethasone dipropionate/formoterol combination vs fluticasone propionate /salmeterol pMDIs in moderate to severe persistent asthma [abstract]. *Eur Respir J* 2006;28(Suppl 50):205s.

## APPENDIX 3: EXCLUDED STUDIES—ECONOMIC REVIEW

## **EXCLUDED STUDIES (N = 35)**

The following studies failed to meet at least one of the pre-specified inclusion criteria.

#### Study Design (N = 2)

The following studies were excluded because they were not randomized controlled clinical trials.

Lundback B. Cost effectiveness of salmeterol/fluticasone propionate combination product and fluticasone propionate in patients with asthma I: introduction and overview. *Pharmacoeconomics* 1999;16(Suppl 2):1-8.

Peters DH. Salmeterol: an appraisal of its quality of life benefits and potential pharmacoeconomic positioning in asthma. *Pharmacoeconomics* 1995;7(6):562-574.

#### Adult Population (N = 1)

The following studies were excluded because the study population was not >50% adult ( $\geq 12$  years).

Bisgaard H. Cost-effectiveness of fluticasone propionate administered via metered-dose inhaler plus babyhaler spacer in the treatment of asthma in preschool-aged children. *Chest* 2001;120(6):1835-1842.

#### Intervention Not Combination Therapy (N = 21)

The following studies were excluded because the intervention of interest was not a combination LABA/ICS therapy.

Berggren F. A cost-effectiveness study comparing the as-needed use of formoterol (oxis) and terbutaline (bricanyl) in patients with moderate to severe asthma. *Respir Med* 2001;95:753-758.

Borker R. Determining economic feasibility of fluticasone propionate-salmeterol vs montelukast in the treatment of persistent asthma using a net benefit approach and cost-effectiveness acceptability curves. *Ann Allergy Asthma Immunol* 2005;95(2):181-189.

Busse W, Raphael GD, Galant S, Kalberg C, Goode-Sellers S, Srebro S, et al. Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: a randomized clinical trial. *J Allergy Clin Immunol* 2001; 107: 461-468.

Calhoun WJ, Nelson HS, Nathan RA, Pepsin PJ, Kalber C, Emmett A, et al. Comparison of fluticasone propionate-salmeterol combination therapy and montelukast in patients who are symptomatic on short-acting beta2-agonists alone. *Am J Respir Crit Care Med* 2001;164:759-763.

Connett GJ. The cost effectiveness of budesonide in severe asthmatics aged one to three years. *Br J Med Econom* 1993;6:127-134.

Davis R. Budesonide. An appraisal of the basis of its pharmacoeconomic and quality-of-life benefits in asthma. *Pharmacoeconomics* 1995;7(5):457-470.

Huse DM. Russell MW, Weiss ST, Hartz SC. Anti-inflammatory therapy reduces total costs of asthma care compared with bronchodilation: the asthma outcomes registry. *Am J Manag Care* 2000;6(9):1045-1050.

Meltzer EO, Lockey RF, Friedman BF, Kalberg C, Goode-Sellers S, Srebro S, et al. Efficacy and safety of low-dose fluticasone proprionate compared with montelukast for maintenance treatment of persistent asthma. *Mayo Clin Proc* 2002;77:437-445.

Nightingale CH. Cost comparison of beta2-agonist bronchodilators used in the treatment of asthma. *Pharmacotherapy* 1995;15(5):677-681.

O'Conner RD. Two-year retrospective economic evaluation of three dual-controller therapies used in the treatment of asthma. *Chest* 2002;121(4):1028-1035.

O'Connor RD. Cost effectiveness of fluticasone propionate plus salmeterol versus fluticasone propionate plus montelukast in the treatment of persistent asthma. *Pharmacoeconomics* 2004;22(12):815-825.

O'Connor RD. Effect of fluticasone propionate and salmeterol in a single device, fluticasone propionate, and montelukast on overall asthma control, exacerbations, and costs. *Ann Allergy Asthma Immunol* 2004;93(6):581-588.

Ollendorf D. An economic analysis of alternative step-up therapies in asthma patients receiving inhaled corticosteroids. P&T 2002;27(3):147-153.

Pearlman DS, White MV, Lieberman AK, Pepsin PJ, Kalberg C, Emmett A, et al. Fluticasone propionate/salmeterol combination compared with montelukast for the treatment of persistent asthma. *Ann Allergy Asthma Immunol* 2002;88:227-235.

Price DB. Salmeterol xinafoate: an analysis of outcomes and cost-effectiveness using a primary care database. *Respir Med* 1998;92:1302-1304.

Rutten-van Molken MP, Van Doorslaer EK, Jansen MC, Van Essen-Zandvliet EE, Rutten FF. Cost effectiveness of inhaled corticosteroid plus bronchodilator therapy versus bronchodilator monotherapy in children with asthma. *Pharmacoeconomics* 1993;4(4):235-310.

Rutten-van Molken MP, Van Doorslaer EK, Jansen MC, Kerstjens HA, Rutten FF. Costs and effects of inhaled corticosteroids and bronchodilators in asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1995;151:975-982.

Sheth K. Cost-effectiveness comparison of salmeterol/fluticasone propionate versus montelukast in the treatment of adults with persistent asthma. *Pharmacoeconomics* 2002;20(13):909-918.

Stahl E S. Bambuterol is a more cost-effective treatment strategy than salmeterol in asthmatic patients with nocturnal symptoms. *J Med Econ* 1999;2:117-122.

Stempel DA. Inhaled corticosteroids plus salmeterol or montelukast: effects on resource utilization and costs. *J Allergy Clin Immunol* 2002;109(3):433-439.

Stempel DA, Riedel AA, Carranza Rosenzweig JR, et al. Resource utilization with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies in children with asthma. *Curr Med Res Opin* 2006;22(3):463-470.

### Outcome Data (N = 7)

The following studies were excluded because they did not report data on cost or other outcomes of interest.

Delea TE, Hagiwara M, Stanford RH, Stempel DA. Effects of fluticasone proprionate/salmeterol combination on asthma-related health care resource utilization and costs and adherence in children and adults with asthma. *Clin Ther* 2008;30:560-571.

Detournay B. Budget impact model for determining the costs of introducing inhaled salmeterol/fluticasone propionate combination for the management of persistent asthma in France. *Eur J Health Econ* 2002;3:149-155.

Haycox A, Mitchell G, Niziol C, Featherstone R. Cost effectiveness of asthma treatment with a breath-actuated pressurised metered dose inhaler (BAI) - a prescribing claims study of 1,856 patients using a traditional pressurised metered dose inhaler (MDI) or a breath-actuated device. *J Med Econ* 2002;5:65-77.

Leversha AM. Costs and effectiveness of spacer versus nebulizer in young children with moderate and severe acute asthma. *J Pediatr* 2000;136:497-502.

O'Connor RD, Stanford A, Crim C, Yancey SW, Edwards L, Rickard KA, et al. Effect of fluticasone propionate and salmeterol in a single device, fluticasone propionate, and montelukast on overall asthma control, exacerbations, and costs. *Ann Allergy Asthma Immunol* 2004;93:581-588.

Rosenhall L. Budesonide/formoterol in a single inhaler (symbicort) reduces healthcare costs compared with separate inhalers in the treatment of asthma over 12 months. *Int J Clin Pract* 2003;57(8):662-667.

Stanford RH, Fuhlbrigge A, Riedel A, Rey GG, Stempel DA. An observational study of fixed dose combination fluticasone propionate/salmeterol or fluticasone propionate alone on asthma-related outcomes. *Curr Med Res Opin* 2008;24(11):3141-3148.

#### Publication Type (N = 4)

The following studies were excluded because there was only an abstract available.

Campbell LM, Berggren F, Emmas C. The cost effectiveness of eformoterol via turbohaler and salmeterol via propionate metered dose inhaler and metered dose powder inhaler in mild to moderate asthma. *Journal of Drug Assessment* 2000;3(2):133-44.

Gothard LR. Cost consequences of dual-controller therapy for asthma: inhaled corticosteroids used concurrently with either salmeterol or leukotriene modifiers [abstract]. *J Manag Care Pharm* 2000;6:358-364.

Ind P. Addition of salmeterol xinafoate to fluticasone proionate produces costeffective asthma management [abstract]. *Am J Respir Crit Care Med* 1999;159(3):A636.

Lucioni C, Mangrella M, Mazzi S, Negrini C, Vaghi A. Treatment of patients with asthma with a fixed combination of budesonide and formoterol: a pharmacoeconomic evaluation vs some therapeutic alternatives. *Pharmacoecon Ital Res Articles* 2002;4(1):15-23.

# **APPENDIX 4: FORMS**

Long-acting Beta Agonists (LABA) and Inhaled Corticosteroids (ICS) Combination

Therapy for Maintenance Therapy of Persistent Asthma

## LIBERAL SCREENING CRITERIA

A report is considered *not* relevant if it meets one of the following:

- letter to the editor, opinion piece, editorial or lay press article;
- clearly not a randomized controlled trial, i.e., it is clearly described as a nonrandomized study, cohort study, etc.
- clearly mainly pediatric study [majority (>50%) of study participants clearly <12years old];
- clearly not comparing LABA plus ICS or combination (LABA + ICS in one delivery device) therapy;
- clearly not on population with chronic asthma (screen out acute asthma or COPD studies).

### Long-acting Beta Agonists (LABA) and Inhaled Corticosteroids (ICS) Combination

#### Therapy for Maintenance Therapy of Persistent Asthma

#### INCLUSION/EXCLUSION FORM

Reviewer ID:Date://2008Record	I ID:		
Criteria	Yes	No	Unclear
1. PUBLICATION TYPE			
a. Report of primary research			
2. STUDY DESIGN			
a. Randomized controlled trial			
3. POPULATION			
a. >50% adult patients (≥12 years)			
b. Diagnosis of mild to severe persistent or "chronic" asthma (according to author). When severity not described % of $FEV_1$ is taken as proxy as defined in GINA p.22.			
<b>C.</b> Participants free of co-morbid pulmonary diseases (e.g., bronchitis, bronchiectasis, cystic fibrosis, chronic obstructive pulmonary disease [COPD])			
4. SETTING			
Study takes place in non-acute care			
5. INTERVENTION			
a. Combination therapy of LABA and ICS either as one or two agents and fixed or variable dose			
b. Trial period is $\geq 60$ days			
6. COMPARATOR			
a. ICS monotherapy of higher, equal or lower dose to that used in combination therapy or other LABA/ICS combination			
b. If used, dose of additional cointervention e.g., xanthines, anticholinergics and NSAIDs, consistent throughout study period. [ <i>Check "Yes" if no cointervention</i> ]			
7. OUTCOME			
Study reports numeric data on at least one outcome of interest (e.g., exacerbations requiring oral steroids, admission to hospital due to exacerbations, FEV1, PEF, symptom score, % symptom-free days, night time wakenings, rescue- free days, disease-specific quality of life [e.g., Asthma Quality of Life Questionnaire (AQLQ)] scores).			
Comments:			
REVIEWER'S DECISION : Include Exclude Unsure			
Non-English study requiring translation Language:			
FINAL DECISION: Include       Exclude       Unsure         NOTE: To exclude must have said "NO" for at least one of 1-7.			
<b>RELEVANT TO QUESTION(S):</b> I. What is the clinical effectiveness of LABA plus ICS maintenance therapy (eith ingredient products) compared to ICS monotherapy in newly diagnosed patients with			

naïve) aged 12 years or older?

II. What is the clinical effectiveness of LABA plus ICS maintenance therapy (as fixed dose or single ingredient products) compared to ICS monotherapy in patients with persistent asthma aged 12 years or older who have been stabilized on ICS?

III. What is the comparative effectiveness of salmeterol/fluticasone versus formoterol-budesonide maintenance therapy in patients with persistent asthma aged 12 years or older?

IV. Are there any differences in harm between combination ICS/LABA treatment (e.g., inhaled salmeterol/fluticasone and formoterol/budesonide combinations) and ICS monotherapy?

□ V. Is there evidence that adding a LABA to ICS allows reducing the ICS dose (i.e. do LABAs have a steroid sparing effect)? **NB:** Steroid sparing studies must report determining minimum effective dose (see Busse et al. 2003 for example)

□ VI. Doug Coyle will screen and apply IE criteria to results of economic search. We will exclude articles that contain only economic data and will pass these references to Doug Coyle to review. Please check "VI" to pass to Doug Coyle (DO NOT also check "include").

#### Long-acting Beta Agonists (LABA) and Inhaled Corticosteroids (ICS) Combination Therapy for Maintenance Therapy of Persistent Asthma

#### QUALITY ASSESSMENT

Reviewer ID: Record	I ID:			
Jadad Scale				
1.	2. YES	3. NO		
4. 1. Was the study described as randomized (this includes the use of words such as randomly, random and randomization)?	5. 1	6. 0		
7. 2. Was the study described as double-blind?	8. 1	9. 0		
10. 3. Was there a description of withdrawals and drop-outs?	11. 1	12. 0		
13. 4. Method to generate the sequence of randomization was described and was appropriate (e.g. table of random numbers, computer generated, coin tossing, etc.)	14. 1	15. 0		
<ol> <li>5. Method of double-blinding described and appropriate (identical placebo, active placebo, dummy)</li> </ol>	17. 1	18. 0		
19. 6. Method of randomization described and it was <b>in</b> appropriate (allocated alternately, according to date of birth, hospital number, etc.)	201	21. 0		
22. 7. Method of double-blinding described but it was <b>in</b> appropriate (comparison of tablet vs. injection with no double dummy)	231	24. 0		
25. OVERALL SCORE (Maximum 5)	2	6.		

#### **Concealment of treatment allocation – Schulz**

27. Concealment of treatment allocation		Adequate
		□ Inadequate
_		
28.	30.	
29. Adequate:	5	n; numbered/coded containers; drugs prepared by nd, opaque, sealed envelopes
32. Inadequate:	33. e.g. alternation, use of ca	se record numbers, dates of birth or day of week; open
	lists	
34. Unclear:	35. Allocation concealment a	oproach not reported or fits neither above category

## Decision Rules for Quality Assessment

**1. Randomization:** Award point if title, abstract, or body of text includes use of "randomly", "random", or "randomization".

2. Double-blind: Awarded point if title, abstract or body of text includes words "double blind".

**3. Withdrawals and dropouts:** Participants who were included in the study but did not complete the observation period (some may dropout or withdraw during non-treatment phase, e.g., washout or baseline phase) or who were not included in the analysis must be described. Award point if the number **and** reasons for withdrawal in each group must be stated or depicted in a CONSORT flow diagram. If there were no withdrawals, it should be stated in the article or easily deduced from Ns reported in tables.

**4. Method of randomization:** Awarded point if sequence generation is described and is appropriate, i.e., allowed each participant the same chance of receiving the intervention and the investigators could not predict which treatment was next. E.g., table of random numbers, computer generated.

*NB*: The Jadad scale emphasizes reporting over conduct. A large, multi-centre, multi-country trial with thousands of participants likely used a computer generated schedule, but no point is awarded if this fact is not reported.

**6.** Subtract point if inappropriate, e.g., allocated alternately, according to date of birth, hospital number, etc.

**5. Method of blinding:** Award an additional point if method of double-blinding was described and appropriate, e.g., identical placebo, active placebo, dummy, etc.

**NB:** Though identical placebo/dummy/etc. strictly ensures only participant blinding, for reporting purposes, this is considered adequate for this scale.

7. Subtract point if double-blind inadequate, e.g., injection without double dummy.

#### **Concealment of Treatment Allocation**

Concealment is of treatment allocation is essential if the rational for randomization is to be realized (balancing known and unknown prognostic factors and other potential confounders). For concealment to be judged ADEQUATE, the person who generates the allocation sequence should not be the person who determines the eligibility and entry of patients. If possible the mechanism for treatment allocation should use people not involved in the trial. E.g., central randomization; numbered/coded containers; drugs prepared by pharmacy. If these two conditions are not met, the only other plausible method of concealment is to enclose assignments in serially numbered, opaque, sealed envelopes (or equivalent).

**INADEQUATE:** e.g. alternation, use of case record numbers, dates of birth or day of week; open lists

**UNCLEAR:** Allocation concealment approach not reported or fits neither above category.

#### I. CODER INFORMATION

1. Reviewer initials:	2. Time to extract (to nearest minute):
3. Applies to question: 1 2 3 4 5	

#### **II. PUBLICATION**

4. Author:			5.Year of publication (last two digits):		
6.Country trial conducted (No. and complete list if >1):		7. Publication Type:	1- journal article		
99-NR				2-industry reported trial	
				3-abstract	
8. Funding:	1-government	3–Industry	D-Nycomed	4–No funding	
	2-institution	A–AZ	E-Novartis	5–other (describe)	
		B-GSK	F-other	99–NR	
		C-			
		Graceway			

#### **III. STUDY CHARACTERISTICS**

9. Type of trial:	1-parallel	10. Blinding:	1-open	A-double dummy
	2–cross-over		label	
			2-single	
			blind	
			3-dble	
			blind	
11. Number of centres:	0-multi centre (provide	1-single		
	number of centres if given)			

		99-NR		
12. Duration of treatment (mo. or wks):		13. Recruitment dates (mm/yy-mm/yy):		99/99–
				NR
			INIT	
14. Run-in phase duration (mo. or wks)				
re. Run in phase duration (no. or wits)				
15. Run-in treatment (describe):				

#### IV. TREATMENT GROUPS

		Group A	Group B	Group C	Group D	Total
16. Number of participants						
enrolled/randomized ( <i>n</i> )						
17. Number of partic	ipants analyzed ( <i>n</i> )					
18. Number of dropouts/withdrawals (n)						
20. Device: 1-single	drug 2-combo 3-					
separate						
21. Drug 1: name	21. Drug 1: name					
22. Delivery device:						
1 – diskhaler	3 – MDI					
2 – pMDI	4 – Turbuhaler					
* Do not record spacer	5-other					
use.						
23. Dosing: 1-fixed 2- variable 3-NR						
24. No.						

times/day:	3 – twice/day			
5	5			
1 – once AM	4 – other			
2 – once PM				
25. Total dose (mo	veh/ (nc			
20. 10101 0030 (110	59/7003			
26. Drug 2: name				
27. Delivery device	e: 3 – MDI			
1 – diskhaler	4 – Turbuhaler			
2 – pMDI	5-other			
* Do not record spacer				
use.				
28 Dosing: 1_fixe	d 2- variable 3-NR			
zu. Dusing. T-Inc				
29. No. times/day:				
1 – once AM	3 – twice/day			
2 – once PM	4 – other			
	4 – 001			
30. Total dose (mo	cq) /day			
31. Additional treatment allowed				
(describe)				
(40001120)				
32. Compliance measured 1-yes ND			1	ı
2-diary card 3-weight 4-internal				
counter 4-no				

	V. BASELINE CHARACTERISTICS	when	possible re	port data	post run-in/	pre-treatment)	)
--	-----------------------------	------	-------------	-----------	--------------	----------------	---

*Circle or describe	IARACTERISTICS a units		Group A	Group B	Group C	Group D	Total
33. Age (mean±S	D / SE; median(ra	nge); IQR)					
34. Males <i>n</i> (%)							
35. Duration of as	thma (mean±SD /	SE;					
median(range); IC	2R)						
36. Baseline	1-naive (and de	fine)					
ICS history:	2-maintenance	ICS					
37. Disease	1-stable						
stage (reported	2-symptomatic/u	unstable					
by author):	3-mixed						
	99-NR						
38. Disease	1-intermittent	4-severe					
severity:	2-mild	5–all					
(GINA p.22)	3-moderate	categories					
		99-NR					
39. ICS dose	1–low	4-other					
level:	2-medium	(e.g. CT)					
(GINA p.29)	3–high	and					
		describe					
40. ICS use (total	daily dose)	<u>                                     </u>					
41. SABA use (pu	iffs/day)						
42. Combo use 1-	never 2-time since	e use (enter)					

	1		
43. AM PEF L/min			
44. AM % pred PEF			
45. PM PEF L/min			
46. PM % pred			
47. % predicted PEF			
48. Reversibility			
49. FEV1 (mL/L)			
50. % predicted FEV <sub>1</sub>			
51. Symptom score			
52. DTS			
53. NTS			
54. Smoking habits			
55. Pc20 (eg, methacholine or histamine test)			
56. AQLQ/QoL			
57. SFD			
58. RFD			
59. FVC		<u></u>	
60. Other			
61. Other			
62. Other			

### VI. REPORTED OUTCOMES (outcomes with data reported)

Primary:		
63. PEF:	71. exacerbations:	82. Change in dose of ICS:
64. PEF:	72. Symptom score:	83. Composite:
65. PEF:	73. Symptom score:	84. Composite:
66. PEF:	74. Symptom score:	85. Composite:
67. FEV:	75. Symptom score:	86. Composite:
68. FEV:	76. Symptom score:	87. Other:
69. FEV:	77. BHR:	88. Other:
70. FEV:	78. QoL:	89. Other:
71. exacerbation:	79. QoL:	90. Other:
72. exacerbation:	80. Serious AEs:	
73. exacerbation:	81. SABA/reliever use:	

102. exacerbations:	113. Change in dose of
	ICS:
103. Symptom score:	114. Composite:
104. Symptom score:	115. Composite:
105. Symptom score:	116. Composite:
106. Symptom score:	117. Composite:
107. Symptom score:	118. Other:
108. BHR:	119. Other:
	103. Symptom score:         104. Symptom score:         105. Symptom score:         106. Symptom score:         107. Symptom score:

98. FEV:	109. QoL:	120. Other:
99. exacerbation:	110. QoL:	121. Other:
100. exacerbation:	111. Serious AEs:	
101. exacerbation:	112. SABA/reliever use:	

#### **VII. ADVERSE EVENTS**

AE (verbatim)	Group A	Group B	Group C	Group D	Total
122. Total AE					

#### VIII. CONCLUSIONS

Describe conclusions: (*Please, also describe such as: "Compared to B and C, A----was-superior/inferior in ----", or "There were no differences between A and B in -----, but B was superior/inferior to C"*)

123.		
123.		

### ADDITIONAL COMMENTS

124.

124.

# APPENDIX 5: METHODOLOGICAL QUALITY OF STUDIES INCLUDED IN CLINICAL REVIEW (N=107)

Author Year	1. Study described as randomized?	2. Study described as double- blind?	3. Description of withdrawals and drop- outs?	4. Method of randomization described and appropriate?	5. Method of double- blinding described and appropriate?	6. Method of randomization described but Inappropriate?	7. Method of double- blinding described but Inappropriate?	Overall Score: Jadad	Concealment of Treatment Allocation
Aalbers R 2004 <sup>127</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Aubier M 1999 <sup>75</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
Baraniuk J 1999 <sup>109</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Bateman ED 200198	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Bateman ED 2003 <sup>106</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Bateman ED 2004 <sup>29</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
Bergmann K-C 2004 <sup>108</sup>	Yes	Yes	Yes	Yes	No	No	No	4	Adequate
Boonsawat W 200856	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Bouros D 1999 <sup>107</sup>	Yes	No	Yes	No	No	No	No	2	Unclear
Bousquet J 2007 <sup>10</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
Boyd G 1995 <sup>73</sup>	Yes	No	Yes	No	Yes	No	No	4	Unclear
Buhl R 200372	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Buhl R 2004 <sup>186</sup>	Yes	No	Yes	No	No	No	No	2	Unclear
Busse W W 2003 <sup>137</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
Busse WW 2008 <sup>133</sup>	Yes	No	Yes	No	No	No	No	2	Unclear
Canonica GW 2004 <sup>187</sup>	Yes	No	Yes	No	No	No	No	2	Unclear
Chuchalin AG 2008 <sup>62</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Chuchalin AG 2002 <sup>46</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Condemi JJ 1999 <sup>110</sup>	Yes	Yes	Yes	No	No	No	No	2	Unclear
Corren J 2007 <sup>47</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
Creticos PS 1999 <sup>55</sup>	Yes	No	No	No	No	No	No	1	Unclear
Dahl R 2006 <sup>128</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Di Franco A 1999 <sup>54</sup>	Yes	No	Yes	No	No	No	No	2	Unclear
FitzGerald JM 199990	Yes	Yes	Yes	No	Yes	No	No	4	Unclear

	1. Study described as	2. Study described as double-	3. Description of withdrawals and drop-	4. Method of randomization described and	5. Method of double- blinding described and	6. Method of randomization described but	7. Method of double- blinding described but	Overall Score:	Concealment of Treatment
Author Year	randomized?	blind?	outs?	appropriate?	appropriate?	Inappropriate?	Inappropriate?	Jadad	Allocation
FitzGerald JM 2005 <sup>11</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Fowler SJ 2002 <sup>77</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
Greening AP 1994 <sup>111</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Grutters JC 1999 <sup>59</sup>	Yes	Yes	No	No	No	No	No	2	Unclear
Langton Hewer S 1995 <sup>83</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Ind PW 2003 <sup>76</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
Ind PW 2004 <sup>188</sup>	Yes	No	Yes	No	No	No	No	2	Unclear
Jenkins C 2000 <sup>80</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Jenkins C 2006 <sup>93</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Johansson G 2001 <sup>112</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Kavuru M 2000 <sup>81</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Kelsen SG 1999 <sup>114</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Kemp JP 1998 <sup>82</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Kerwin EM 2008 <sup>61</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Kips JC 2000 <sup>138</sup>	Yes	Yes	No	No	No	No	No	2	Unclear
Koenig SM 2008 <sup>95</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Koopmans JG 200678	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Kuna P 2006 <sup>45</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Kuna P 2007 <sup>129</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Lalloo UG 2003 <sup>113</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
Lemanske RF 200179	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Leuppi JD 2003 <sup>189</sup>	Yes	No	Yes	No	No	No	No	2	Unclear
Li X 1999 <sup>86</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
Lundback B 2006 <sup>84</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Adequate
Lundborg M 2006 <sup>190</sup>	Yes	No	Yes	Yes	No	No	No	3	Unclear
Mitchell C 2003 <sup>115</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Molimard M 2001 <sup>85</sup>	Yes	No	Yes	Yes	No	No	No	3	Adequate
Morice AH 2007 <sup>96</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Murray JJ 2004 <sup>64</sup>	Yes	Yes	Yes	Yes	No	No	No	4	Unclear

	1. Study described as	2. Study described as double-	3. Description of withdrawals and drop-	4. Method of randomization described and	5. Method of double- blinding described and	6. Method of randomization described but	7. Method of double- blinding described but	Overall Score:	Concealment of Treatment
Author Year	randomized?	blind?	outs?	appropriate?	appropriate?	Inappropriate?	Inappropriate?	Jadad	Allocation
Murray JJ 1999 <sup>117</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Nathan RA 2006 <sup>94</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Nelson HS 2003 <sup>57</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
Nielsen LP 1999 <sup>139</sup>	Yes	Yes	No	No	Yes	No	No	3	Unclear
Noonan M 2006 <sup>92</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
O'Byrne PM 2005 <sup>105</sup>	Yes	Yes	Yes	Yes	No	No	No	4	Unclear
O'Byrne PM 2001 <sup>58</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Overbeek SE 2005 <sup>70</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
Papi A 2007 <sup>132</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Papi A 2007 <sup>134</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Pauwels RA 1997 <sup>140</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Pearlman DS 2004 <sup>74</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Peters SP 2007 <sup>123</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Peters SP 2008 <sup>101</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
Pohl WR 2006 <sup>141</sup>	Yes	Yes	Yes	Yes	No	No	No	4	Unclear
Price D 2002 <sup>91</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Rabe KF 2006 <sup>122</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Ringdal N 2002 <sup>130</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Rojas RA 2007 <sup>60</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
SAM30002 <sup>124</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
SAM30007 <sup>146</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
SAM30013 <sup>126</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
SAM40008 <sup>145</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
SAM40010 <sup>136</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
SAM40034 <sup>66</sup>	Yes	Yes	Yes	Yes	No	No	No	4	Unclear
SAM40036 <sup>65</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
SAM40048 <sup>135</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
SAM40065 <sup>99</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
SAM40090 <sup>144</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear

Author Year	1. Study described as randomized?	2. Study described as double- blind?	3. Description of withdrawals and drop- outs?	4. Method of randomization described and appropriate?	5. Method of double- blinding described and appropriate?	6. Method of randomization described but Inappropriate?	7. Method of double- blinding described but Inappropriate?	Overall Score: Jadad	Concealment of Treatment Allocation
SAM40120 <sup>53</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
SAS30015 <sup>68</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
SAS30039 <sup>67</sup>	Yes	Yes	Yes	Yes	No	No	No	4	Unclear
SAS40026 <sup>49</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
SAS40036 <sup>102</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
SAS40068 <sup>69</sup>	Yes	Yes	Yes	Yes	No	No	No	4	Unclear
Schermer TRJ 2007 <sup>142</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Scicchitano R 2004 <sup>119</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Self T 1998 <sup>143</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
SFA103153 <sup>100</sup>	Yes	Yes	Yes	Yes	No	No	No	4	Unclear
Shapiro G 2000 <sup>87</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
SLGA5021 <sup>125</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
SLGF75/FLIC 14 <sup>103</sup>	Yes	Yes	Yes	Yes	No	No	No	4	Unclear
SLGQ97/SLGB4010 <sup>104</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
SLMF4002 (SMS40012) <sup>147</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
Stallberg B 2003 <sup>191</sup>	Yes	No	Yes	No	No	No	No	2	Unclear
Strand AM 2004 <sup>63</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
van der Molen T 1997 <sup>88</sup>	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
van Noord JA 1999 <sup>120</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
van Noord JA 200197	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Vermetten FAAM 1999 <sup>121</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
Vogelmeier C 2005 <sup>131</sup>	Yes	No	Yes	Yes	No	No	No	3	Unclear
Wallin A 2003 <sup>116</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
Woolcock A 1996 <sup>118</sup>	Yes	Yes	Yes	No	No	No	No	3	Unclear
Zetterstrom O 2001 <sup>89</sup>	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate

## APPENDIX 6: CHARACTERISTICS OF STUDIES INCLUDED IN CLINICAL REVIEW

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Study Author Year: Aalbers R 2004 <sup>127</sup> Pub status: Journal article No. countries: 6 No. centers: 93 Design: randomized, parallel, open label Funding: Industry: AstraZeneca	Participant characteristics Randomized: 658 Analyzed: 654 Withdrawals: 83 ITT analysis: yes Asthma stage and severity: symptomatic, mild to severe Baseline ICS use: non-naïve GROUP 1 N: 217 Age yr. (mean±SD): 47±16 Males %: 43 FEV1 % predicted (mean±SD): 84±23.8 PEF AM L/min (mean±SD): 372.2±144.3 Duration of asthma yr. (mean±SD): 13±18.3 Smoking status: all <10 pack-yr GROUP 2 N: 214 Age yr. (mean±SD): 46 yr.±18 Males %: 45 FEV1 % predicted (mean±SD): 372.2±144.3 Duration of asthma yr. (mean±SD): 12±18.8 Males %: 45 FEV1 % predicted (mean±SD): 372.2±144.3 Duration of asthma yr. (mean±SD): 12±14.8 Smoking status: all <10 pack-yr GROUP 3 N: 223 Age yr. (mean±SD): 46±16 Males %: 49 FEV1 % predicted (mean±SD): 85±21 PEF AM L/min (mean±SD): 85±21 PEF AM L/min (mean±SD): 35.7±150.8 Duration of asthma yr. (mean±SD): 12±15.3 Smoking status: all <10 pack-yr			Notes Study objective: to examine whether asthma control improved if patients adjusted the maintenance dose (AMD) of FORM/BUD according to asthma severity compared to a fixed dose regimen (FD) of FORM/BUD. Additional details: AMD group could increase dose to four inhalations bid for 7-10 days if control was insufficient. If could not step down after 14 days they contacted the investigator. Patients experiencing a 3 <sup>rd</sup> exacerbation were withdrawn from the study.

AQLQ = asthma quality of life questionnaire; BDP = beclomethasone dipropionate; bid = twice daily; BUD = budesonide; DTS = daytime symptom score; FEV<sub>1</sub>; forced expiratory volume in 1 second; FORM = formoterol fumarate; FP = fluticasone propionate; ICS = inhaled corticosteroid; ITT = intention to treat; LABA = long-acting beta<sub>2</sub>-agonist; mcg = microgram; MDI = metered-dose inhaler; LOE = lack of efficacy; NR = not reported; NTS = nighttime symptom score; PEF = peak expiratory flow; prn = as required; PLA = placebo; RFD = rescue-free days; RFN = rescue-free nights; SABA = short-acting beta<sub>2</sub>-agonist; SAL = salmeterol xinafoate; SFD = symptom-free days; SD = standard deviation; TAA = triamcinolone acetonide

			Clinical	
<b>e</b> / 1		Treatment	outcomes	<b>N</b> (
Study	Participant characteristics	characteristics	reported	Notes
Author Year: Aubier M 1999 <sup>75</sup>	Randomized: 503 Analyzed: 403	GROUP 1 Drug mcg/day:	Definition of exacerbation: NR	Study objective: To determine if
	Withdrawals: 100	SAL/FP 100/1000		SAL/FP in a
Pub status:		+ PLA	Clinical	combination
Journal article	ITT analysis: all available data	Dosing: fixed	outcomes	Diskus <sup>®</sup> inhaler
	Asthma stage and severity:	Treatment	reported:	would be superior
No. countries:	symptomatic, intermittent to	duration: 28 wk.	Primary	to FP alone or to
3	severe	Device: Diskus <sup>®</sup> :	PEF AM	the same doses of
No. centers: 55	Baseline ICS use: non-naïve	one Withdraw LOE:	0	SAL and FP in
Design: randomized.	GROUP 1	NR	Secondary	separate inhalers in patients who were
parallel, double	<b>N</b> : 136		PEF PM     FEV	symptomatic on
blind, double	Age yr. (mean±SD): 46±16.5	GROUP 2	• FEV <sub>1</sub>	current ICS tx.
dummy	Males %: 59	Drug mcg/day:	<ul> <li>FEV<sub>1</sub> %</li> </ul>	
	FEV <sub>1</sub> % predicted (mean±SD):	SAL 100 + FP	<ul><li>predicted</li><li>asthma</li></ul>	
Funding:	73±15.5	1000	symptom	
Industry:	PEF AM L/min (mean±SD):	Dosing: fixed	score (5 pt.	
GlaxoSmithKline	359 <b>±</b> 95.6	Treatment	scale)	
	Duration of asthma yr. %: 47	duration: 28 wk.	<ul> <li>SFD</li> </ul>	
	<b>(</b> <10 yr.); 53 (>10 yr.)	<b>Device:</b> Diskus <sup>®</sup> :	SFN	
	Smoking status	two	RFD	
	(never/past/current %):	Withdraw LOE:	RFN	
	42/38/15	NR		
	GROUP 2	GROUP 3		
	<b>N:</b> 143	Tx/dose/day: FP		
	Age yr. (mean±SD): 48±15	1000 + PLA		
	Males %: 50	Dosing: fixed		
	FEV <sub>1</sub> % predicted (mean±SD):	Treatment duration: 28 wk.		
	73±15.7 PEF AM L/min (mean±SD):	<b>Device:</b> Diskus <sup>®</sup>		
	345±86.3	Withdraw LOE:		
	Duration of asthma yr. %: 43	NR		
	(<10yr.); 57 (>10yr.)			
	Smoking status	Reliever Tx:		
	(never/past/current %):	salbutamol as		
	44/40/16	needed		
		Run-in Tx:		
	GROUP 3	continued same		
	N: 124	dose of current		
	Age yr. (mean±SD): 50±16	ICS, other asthma		
	Males %: 53	drugs taken continued		
	FEV <sub>1</sub> % predicted (mean±SD): 73±18.0	unchanged.		
	PEF AM L/min (mean±SD):	Run-in duration:		
	351±104.1	2 wk.		
	Duration of asthma yr. %: 46			
	(<10yr.); 54 (>10yr.)			
	Smoking status			
	(never/past/current %):			

<b>.</b>	<b>-</b>	Treatment	Clinical outcomes	<b>N</b> <i>i</i>
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 680	GROUP 1	Definition of	Study objective:
Baraniuk J	Analyzed: 630	Drug mcg/day:	exacerbation: NR	To compare the
1999 <sup>109</sup>	Withdrawals: 50	SAL/FP 100/200		efficacies of
Pub status:		Dosing: fixed	List of clinical	medium dose FP
Journal article	ITT analysis: yes	Treatment	outcomes	and TAA and low-
	Asthma stage and severity:	duration: 12 wk.	reported:	dose FP + SAL in
No. countries:	symptomatic, moderate, severe	Device: MDI	Primary	patients
1	Baseline ICS use: non-naïve	Withdraw LOE n	<ul> <li>FEV<sub>1</sub> AM</li> </ul>	uncontrolled on low
No. centers: 50		: 2		dose ICS.
Design:	GROUP 1		Secondary	
randomized,	N: 231	GROUP 2	<ul> <li>FEV<sub>1</sub> %</li> </ul>	Additional details:
parallel, double	Age yr. (mean±SD): 41±16.8	Drug mcg/day:	predicted	All groups used
blind, triple	Males %: 41	FP 500 + PLA	PEF AM	MDI with CFC
dummy	FEV <sub>1</sub> % predicted (mean±SD):	Dosing: fixed	PEF PM	propellant
	63.1±11.9	Treatment	<ul> <li>PEF %</li> </ul>	
Funding:	PEF AM L/min (mean±SD):	duration: 12 wk.	predicted	
Industry:	361±121.6	Device: MDI	SABA use	
GlaxoSmithKline	Duration of asthma: NR	Withdraw LOE n:	<ul> <li>RFD</li> </ul>	
	Smoking status: all non-	2		
	smokers		1 3	
		GROUP 3	SABA	
	GROUP 2	Drug mcg/day:	asthma	
	N: 223	TAA 1200 + PLA	symptom	
	Age yr. (mean±SD): 40±15.5	Dosing: fixed	score (5 pt.	
	Males %: 39	Treatment	scale)	
	FEV <sub>1</sub> % predicted (mean±SD):	duration: 12 wk.	<ul> <li>SFD</li> </ul>	
	63.1±12.3	Device: MDI	<ul> <li>physician</li> </ul>	
	PEF AM L/min (mean±SD):	Withdraw LOE n:	global	
	344±104.5	9	assessment	
	Duration of asthma: NR	·		
	Smoking status: all non-	Reliever Tx:		
	smokers	albuterol as		
		needed		
	GROUP 3	Run-in Tx:		
	N: 226	Continued usual		
	Age yr. (mean±SD): 39±14.8	daily dose ICS.		
	Males %: 35	Fixed dose		
	FEV <sub>1</sub> % predicted (mean±SD):	theophylline		
	63.4±12.0	allowed if already		
	PEF AM L/min (mean±SD):	on it.		
	349±105.2	Run-in duration:		
	Duration of asthma: NR	2 wk.		
		∠ WK.		
	Smoking status: all non- smokers			
	SHUKEIS			

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year:	Randomized: 3,416	GROUP 1	Definition of	Study objective:
Bateman ED	Analyzed: 3,416		exacerbation:	To compare the
2004 <sup>29</sup>		Drug mcg/day,		
	Withdrawals: 526	stratum 1/2/3:	Required OCS	efficacy of
Pub status:		SAL100 + FP	and/or	increasing the dos
Journal article	ITT analysis: yes	200-1000 or FP	hospitalization or	of FP alone or in
	Asthma stage and severity:	200-1000 or 500-	ED visit	combination with
No. countries:	symptomatic, intermittent-	1000		SAL to achieve
44	severe	Dosing: fixed	List of clinical	asthma control as
No. centers:	Baseline ICS use, stratum	Treatment	outcomes	defined by GINA
326	1/2/3: naïve/non-naïve/non-	duration: 52 wk.	reported:	guidelines.
Design:	naïve	Device: diskhaler	Primary	galaointee.
randomized,	haive	Withdraw LOE:	well-controlled	Additional details
parallel, double	GROUP 1	NR	asthma during	This was the
blind	N, stratum 1/2/3: 548/ 585/ 576		phase 1.	GOAL study.
	Age yr. (mean±SD) stratum	GROUP 2	- ·	Stratum 1
Funding:	1/2/3:	Drug mcg/day,	Secondary	participants not on
Industry:	36.1±15.6/40.4±16.4/44.1±15.9	stratum 1/2/3: FP	<ul> <li>time to</li> </ul>	ICS pre study.
GlaxoSmithKline	Males %, stratum 1/2/3:	200-1000 or 200-	asthma	Stratum 2
	43/42/43	1000 or 500-1000	control	participants on BD
	FEV <sub>1</sub> % predicted (mean±SD),	Dosing: fixed	exacerbation:	≤ 500 mcg daily or
	stratum 1/2/3:	Treatment	rate/yr.	equivalent.
	77±18.7/78±18.2/75±18.6	duration: 52 wk.	<ul> <li>AQLQ score</li> </ul>	Stratum 3
	PEF AM L/min (mean±SD),	Device: diskhaler		participants on BD
	stratum 1/2/3:	Withdraw LOE:	<ul> <li>FEV<sub>1</sub> AM</li> </ul>	500 – 1000 mcg
	344±91.2/349±98.4/345±98.7		<ul> <li>DTS</li> </ul>	
		NR	<ul> <li>SABA use</li> </ul>	daily or equivalent
	<b>Duration of asthma:</b> $\geq$ 6 mo.	<b>.</b>	<ul> <li>PEF AM</li> </ul>	Phase 1: tx
	Smoking status: all < 10 pack-	Reliever Tx: NR	<ul> <li>NTA</li> </ul>	stepped up every
	yr	Run-in Tx: Usual		12 wk. until total
		dose ICS (if any)		asthma control
	GROUP 2	Run-in duration:		achieved or SAL/F
	N, stratum 1/2/3: 550/ 578/ 579	4 wk.		100/1000 mcg or
	Age yr. (mean±SD) stratum			FP 1000 mcg
	1/2/3:			reached.
	36.4±15.6/40.3±16.6/42.7±15.7			Phase 2: remained
	Males %, stratum 1/2/3:			on phase 1 tx until
	43/40/41			end of year 1. No
	FEV <sub>1</sub> % predicted, mean±SD,			step down tx
	stratum 1/2/3:			performed in this
	79±18.8/77±18.4/76±17.6			phase.
	PEF AM L/min (mean±SD),			
	stratum 1/2/3:			
	345±92.8/344±93.6/348±96.3			
	Duration of asthma: ≥ 6 mo.			
	Smoking status: all <10 pack-			
	•			
	yr			

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 344	GROUP 1	Definition of	Study objective:
Bateman ED	Analyzed: 309	Drug mcg/day:	exacerbation:	To compare the
2003 <sup>106</sup>	Withdrawals: 35	FORM/BUD	Mild: awakened	efficacy of
Pub status:		12/400 + PLA	due to asthma,	FORM/BUD to high
Journal article	ITT analysis: yes	Dosing: fixed	AM PEF at least	dose FP in
	Asthma stage and severity:	Treatment	20% below	moderate-persistent
No. countries:	moderate persistent	duration: 12 wk.	baseline, or need	asthma.
6	Baseline ICS use: non-naïve	Device:	to use at least 4	
No. centers: 37		Turbuhaler <sup>®</sup>	inhalations of	Additional details:
Design:	GROUP 1	Withdraw LOE n:	rescue	Both groups
randomized,	<b>N:</b> 168	3	medication over	received both types
parallel, double	Age yr. (mean±SD): 42.6±14.3		baseline use on	of inhalers.
blind, double	Males %: 42	GROUP 2	2 consecutive	
dummy	FEV <sub>1</sub> % predicted (mean):	Tx/dose/day: FP	days or nights.	
•	77.2	500 + PLA	Severe: need for	
Funding:	PEF AM L/min (mean): 354	Dosing: fixed	OCS, AM PEF at	
Industry:	Duration of asthma yr.	Treatment	least 30% below	
AstraZeneca	(mean±SD): 16.3±16.5	duration: 12 wk.	baseline on 2	
	Smoking status	Device: Diskus <sup>®</sup>	consecutive	
	(never/past/current %):	Withdraw LOE n:	days, or	
	69.6/25/5.4	8	discontinued	
			study due to	
	GROUP 2	Reliever Tx:	worsening	
	<b>N:</b> 176	terbutaline or	asthma.	
	Age yr. (mean±SD): 41.8±14.3	albuterol as		
	Males %: 78 (44)	needed.	List of clinical	
	FEV <sub>1</sub> % predicted (mean):	Run-in Tx: BUD	outcomes	
	79.2	400 mcg + PLA	reported:	
	PEF AM L/min (mean): 363	Run-in duration:	Primary	
	Duration of asthma yr. (mean±SD): 16.3±16.3	2 wk.	PEF AM	
	Smoking status		Secondary	
	(never/past/current %):		PEF PM	
	71/22.2/6.8		<ul> <li>FEV<sub>1</sub> (L)</li> </ul>	
			• FVC	
			<ul> <li>SABA use</li> </ul>	
			RFD	
			<ul> <li>asthma</li> </ul>	
			control days	
			%	
			SFD	
			NTA	
			• mild	
			exacerbations	
			<ul> <li>severe</li> </ul>	
			<ul> <li>severe exacerbations</li> </ul>	
			CAUCIDATIONS	

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 484	GROUP 1	Definition of	Study objective:
Bateman ED	Analyzed: 484	Drug mcg/day:	exacerbation:	To determine if
2006 <sup>192</sup>	Withdrawals: 10	SAL/FP 100/200	NR	SAL or FP dose
Pub status:		Dosing: fixed		can be reduced
Journal article	ITT analysis: yes	Treatment	List of clinical	without loss of
	Asthma stage and severity:	duration: 12 wk.	outcomes	asthma control
No. countries:	asymptomatic, moderate	Device:	reported:	once control is
12	Baseline ICS use: pre run-in	Diskus <sup>®</sup> /Accuhaler™	Primary	obtained with
No. centers: 68 Design:	naïve; post run-in non-naïve	Withdraw LOE: NR	PEF AM	SAL/FP 100/500 mcg/d.
randomized,	GROUP 1	GROUP 2	Secondary	
parallel, double	N: 246	Drug mcg/day: FP	PEF PM	Additional
blind	Age yr. (mean±SD):	500	<ul> <li>FEV<sub>1</sub></li> </ul>	details:
	40.3±15.9	Dosing: fixed	<ul> <li>SABA use</li> </ul>	Phase 1 open label
Funding:	Males %: 39	Treatment	daytime	tx with SAL/FP
Industry:	FEV <sub>1</sub> % predicted	duration: 12 wk.	SABA use	100/500 mcg; in
GlaxoSmithKline	(mean±SD): 69.6±6.4	Device:	nighttime	the randomized
	PEF AM L/min (mean±SD):	Diskus <sup>®</sup> /Accuhaler™	• well	phase Grp 1 had
	327±89	Withdraw LOE: NR	controlled	FP stepped down,
	<b>Duration of asthma:</b> ≥ 6 mo.		asthma	Grp 2 had SAL
	Smoking status: all ≤ 10		<ul> <li>total asthma</li> </ul>	stopped.
	pack-yr	Reliever Tx:	control	
		salbutamol as	<ul> <li>SFD</li> </ul>	Definition of total
	GROUP 2	needed	<ul> <li>SFN</li> </ul>	and well
	N: 238	Run-in Tx: SAL/FP	RFD	controlled
	Age yr. (mean±SD): 40.7±15.1	100/500 mcg	RFN	asthma: used the
	<b>Males %:</b> 42	Run-in duration: 2		criteria in the
	FEV <sub>1</sub> % predicted	wk.		GOAL study
	(mean±SD): 70.5±6.4			
	PEF AM L/min (mean±SD):			
	332±92			
	<b>Duration of asthma:</b> $\geq$ 6 mo.			
	Smoking status: all $\leq 10$			
	pack-yr			
	μασιτ-γι			

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 497	GROUP 1	Definition of	Study objective:
Bateman ED	Analyzed: 497	Tx Drug	exacerbation: NR	To demonstrate
2001 <sup>98</sup>	Withdrawals: 67	mcg/day:		equivalent efficacy
Pub status:		SAL/FP 100/200	List of clinical	and comparable
Journal article	ITT analysis: yes	+ PLA	outcomes	safety of the lowest
	Asthma stage and severity:	Dosing: fixed	reported:	strength SAL/FP
No. countries:	symptomatic, mild-moderate	Treatment	Primary	100/200 MDI and
10	Baseline ICS use: non-naïve	duration: 12 wk.	<ul> <li>PEF AM</li> </ul>	Diskus <sup>™</sup> and to
No. centers: 69		Device: MDI <sub>HFA</sub> +	- ·	show that SAL/FP
Design:	GROUP 1	PLA Diskus	Secondary	100/200 MDI <sub>HFA</sub>
randomized,	N: 165	Withdraw LOE n:	<ul> <li>PEF PM</li> </ul>	was more
parallel, double	Age yr. (mean±SD): 40.7±16.8	1	<ul> <li>diurnal</li> </ul>	efficacious than FP
blind, double	Males %: 44		variation %	200 via MDI <sub>CFC</sub>
dummy	FEV <sub>1</sub> % predicted (mean): 75	GROUP 2	predicted	
	PEF AM L/min (mean): 353	Drug mcg/day:	<ul> <li>FEV<sub>1</sub></li> </ul>	
Funding:	Duration of asthma yr. %: 53	SAL/FP 100/200	<ul> <li>FEV<sub>1</sub> %</li> </ul>	Additional details:
Industry:	(<10 yr.); 47 ( ≥10 yr.)	+ PLA	predicted	Grp 1 combination
GlaxoSmithKline	Smoking status (past/current	Dosing: fixed	<ul> <li>SFD</li> </ul>	SAL/FP was
	<b>%):</b> 17/13 (all < 10 pack-yr.)	Treatment	<ul> <li>SFN</li> </ul>	delivered by an MDI
		duration: 12 wk.	RFD	using HFA
	GROUP 2	Device: Diskus		propellant, Grp 3
	N: 167	+ PLA MDI <sub>HFA</sub>		FP was delivered in
	Age yr. (mean±SD): 38.6±17 Males %: 47	Withdraw LOE n:		an MDI using CFC
		2		propellant
	FEV <sub>1</sub> % predicted (mean): 76	GROUP 3		
	PEF AM L/min (mean): 373 Duration of asthma yr. %:			
	48.5 (<10 yr.); 51.5 (≥ 10 yr.)	Drug mcg/day: FP 200 + PLA		
	Smoking status (past/current	<b>Dosing:</b> fixed		
	%): 25/9 (all < 10 pack-yr.)	Treatment		
	70): 23/3 (all < 10 pack-yl.)	duration: 12 wk.		
	GROUP 3	Device: MDI <sub>CFC</sub> +		
	<b>N</b> : 165	PLA Diskus		
	Age yr. (mean±SD): 39.5±16	Withdraw LOE n:		
	Males %: 41	0		
	<b>FEV</b> <sub>1</sub> % predicted (mean): 76	Ū		
	PEF AM L/min (mean): 354	Reliever Tx:		
	Duration of asthma yr. %: 49	salbutamol as		
	(<10 yr.); 51 (≥10 yr.)	needed		
	Smoking status (past/current	Run-in Tx: Usual		
	%): 21/11 (all < 10 pack-yr.)	ICS 400-500		
	· · · · · · · · /	mcg/d BDP		
		equivalent or FP		
		200-250 mcg/d		
		Run-in duration:		
		12 wk.		

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Bergmann KC 2004 <sup>108</sup> Pub status: Journal article No. countries: 1 No. centers: 76 Design: randomized, parallel, double blind Funding: Industry: GlaxoSmithKline	Randomized: 365 Analyzed: 347 Withdrawals: 29 ITT analysis: yes Asthma stage and severity: symptomatic, moderate Baseline ICS use: non-naïve GROUP 1 N: 170 Age yr. (mean±SD): 49.8±14.2 Males %: 49.4 FEV <sub>1</sub> % predicted (mean±SD): 74.5±19.3 PEF AM L/min (mean±SD): 318±111 Duration of asthma yr.: 1-19 Smoking status: all non or ex- smokers GROUP 2 N: 177 Age yr. (mean±SD): 48.9±13.9 Males %: 43.5 FEV <sub>1</sub> % predicted (mean±SD): 75.7±20.2 PEF AM L/min (mean±SD): 316±102 Duration of asthma, yr.: 1-19 Smoking status: all non or ex- smokers	GROUP 1 Drug mcg/day: SAL/FP 100/500 Dosing: fixed Treatment duration: 12 wk. Device: Diskus <sup>®</sup> Withdraw LOE: NR GROUP 2 Drug mcg/day: FP 1000 Dosing: fixed Treatment duration: 12 wk. Device: Diskus <sup>®</sup> Withdraw LOE: NR Reliever Tx: salbutamol as needed Run-in Tx: Continued usual asthma medications and BDP or BUD 800- 1000 mcg/d or FP 500 mcg/d Run-in duration: 2 wk.	Definition of exacerbation: NR List of clinical outcomes reported: Primary • PEF AM • PEF AM % predicted • PEF PM • PEF PM % predicted • FEV1 • FEV1 % predicted • FVC % predicted • asthma symptom score (5 pt. scale) • SABA use • SFD • AQOL • MD assessment • patient assessment (5 pt. scale)	Study objective: To study the efficacy and safety of SAL/FP combination compared to doubling the dose of FP alone in patients with moderate, symptomatic asthma.

<b>•</b> / 1		Treatment	Clinical outcomes	
Study Author Year: Boonsawat W 2008 <sup>56</sup> Pub status: Journal article No. countries: 9 No. centers: 69 Design: randomized, parallel, double blind	Participant characteristics Randomized: 464 Analyzed: 458 Withdrawals: 25 ITT analysis: yes Asthma stage and severity: asymptomatic, intermittent-mild Baseline ICS use: naïve GROUP 1 N: 149 Age yr. (mean±SD): 34.7±15.3 Males %: 46	characteristics GROUP 1 Drug mcg/day: SAL/FP 50/100 Dosing: fixed Treatment duration: 12 wk. Device: MDI Withdraw LOE n: 0 GROUP 2 Drug mcg/day: FP 100	reported Definition of exacerbation: moderate: a deterioration requiring a short course of OCS based on AM PEF > 30% below baseline for ≥2 days. Severe: a deterioration requiring	Notes Study objective: To compare the efficacy and tolerability of once/d SAL/FP with once/d FP. Additional details: If courses of OCS were separated by > 1 wk. they were counted as
Funding: Industry: GlaxoSmithKline	FEV <sub>1</sub> % predicted (mean±SD): 94.3±14.5 PEF AM L/min (mean±SD): 441.1±114.9 Duration of asthma: $\geq$ 6 mo. Smoking status: all <10 pack- yr GROUP 2 N: 154 Age yr. (mean±SD): 34.0±14 Males %: 44 FEV <sub>1</sub> % predicted (mean±SD): 96.1±15.3 PEF AM L/min (mean±SD): 448.6±108.3 Duration of asthma: $\geq$ 6 mo. Smoking status: all <10 pack- yr GROUP 3 N: 155 Age yr. (mean±SD): 33.4±15.3 Males %: 54 FEV <sub>1</sub> % predicted (mean±SD): 95.6±14.6 PEF AM, L/min, (mean±SD): 458.7±109.4 Duration of asthma: $\geq$ 6 mo. Smoking status: all <10 pack- yr.	Dosing: fixed Treatment duration: 12 wk. Device: MDI Withdraw LOE n: 2 GROUP 3 Drug mcg/day: PLA Dosing: fixed Treatment duration: 12 wk. Device: MDI Withdraw LOE n: 1 Reliever Tx: salbutamol as needed Run-in Tx: salbutamol as needed Run-in duration: 2 wk.	hospitalization. List of clinical outcomes reported: Primary • PEF AM Secondary • PEF PM • FEV1 • SFD • RFD • symptom control • well controlled asthma • FEF25.75 • exacerbations	separate moderate exacerbations. Patients were withdrawn if had > 2 exacerbations requiring OCS or were hospitalized. Definition of well controlled asthma:

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Bouros D 1999 <sup>107</sup> Pub status: Journal article No. countries: 1 No. centers: 11 Design:	Randomized: 134 Analyzed: 132 Withdrawals: 10 ITT analysis: no Asthma stage and severity: symptomatic, mild-severe Baseline ICS use: non-naïve GROUP 1	GROUP 1 Drug mcg/day: FORM/BDP 24/500 Dosing: fixed Treatment duration: 12 wk. Device: MDI Withdraw LOE n: 1	Definition of exacerbation: Patients requiring OCS List of clinical outcomes reported: Primary • PEE AM	Study objective: To study if adding FORM to a low dose ICS could have similar results to increasing the dose of ICS alone in patients symptomatic on ICS.
randomized, parallel, open label	N: 69 PEF AM L/min (mean±SD): 380.4±108.8	GROUP 2 Drug mcg/day: BDP 1000	<ul> <li>FEF AM</li> <li>Secondary</li> <li>PEF PM</li> <li>FEV<sub>1</sub></li> </ul>	100.
Funding: Industry: Novartis	GROUP 2 N: 65 PEF AM L/min (mean±SD): 356.4±96.2 Total population Age yr. (mean±SD): 43±14	Dosing: fixed Treatment duration: 12 wk. Device: MDI Withdraw LOE n: 1	<ul> <li>DTS</li> <li>NTS</li> <li>SABA use</li> </ul>	
	Males %: 34.3 FEV <sub>1</sub> % predicted (mean±SD): NR Duration of asthma yr. (mean±SD): NR Smoking status (never/past/current %): NR	Reliever Tx: salbutamol as needed Run-in Tx: BDP 500 mcg/d Run-in duration: 2 wk.		

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 2,309	GROUP 1	Definition of	Study objective: to
Bousquet J	Analyzed: 2,304	Drug mcg/day:	exacerbation:	assess efficacy of
2007 <sup>10</sup>	Withdrawals: 208	FORM/BUD	severe:	FORM/BUD plus
Pub status:		24/800 + PLA	deterioration	FORM/BUD as
Journal article	ITT analysis: all available data	Dosing: fixed	leading to	needed to SAL/FP
	Asthma stage and severity:	Treatment	hospitalization/ED	plus SABA as
No. countries:	symptomatic, intermittent to	duration: 6 mo.	tx and/or OCS $\geq$ 3	needed.
17	severe	Device:	days	noodod.
No. centers:	Baseline ICS use: non-naïve	Turbuhaler® +	aayo	
184	Bucchine lee use. Hell halve	Diskus	List of clinical	Additional details:
Design:	GROUP 1	Withdraw LOE:	outcomes	Each participant
randomized,	<b>N</b> : 1151	NR	reported:	received 2 inhalers
parallel, double	Age yr. (mean±SD): 40±17		Primary	for maintenance: 1
	Males %: 38	GROUP 2	•	Turbuhaler <sup>®</sup> either
blind, double-			• exacerbation:	
dummy	FEV <sub>1</sub> % predicted (mean±SD):	Drug mcg/day:	time to 1 <sup>st</sup>	active or PLA and 1
F	70.2±17.3	SAL/FP 100/1000	severe	Diskus <sup>™</sup> either
Funding:	PEF AM L/min (mean): 330.1	+ PLA Baain an fina d	exacerbation	active or PLA plus
Industry:	Duration of asthma yr.	Dosing: fixed	<ul> <li>exacerbation:</li> </ul>	1 Turbuhaler <sup>®</sup> either
AstraZeneca	(mean±SD): 14±16.5	Treatment	time to 2 <sup>nd</sup>	FORM/BUD or PLA.
	Smoking status	duration: 6 mo.	severe	
	(never/past/current %):	Device: Diskus	exacerbation	Definition of
	82/13/4 (all < 10 pack-yr.)	+ Turbuhaler®		asthma control
		Withdraw LOE:		day: day and night
	GROUP 2	NR	Secondary	with no asthma
	<b>N:</b> 1153		PEF AM	symptoms, no
	Age yr. (mean±SD): 39±17		PEF PM	awakenings due to
	Males %: 38	Reliever Tx:	<ul> <li>FEV<sub>1</sub></li> </ul>	asthma symptoms
	FEV <sub>1</sub> % predicted (mean±SD):	terbutaline as	<ul> <li>exacerbation:</li> </ul>	and no use of as-
	71.0±44.3	needed	rate of severe	needed medication
	PEF AM L/min (mean): 329.0	Run-in Tx:	<ul> <li>exacerbation:</li> </ul>	
	Duration of asthma yr.	Current ICS	time to 1 <sup>st</sup>	
	(mean±SD): 13±19	maintenance tx +		
	Smoking status	LABA if already	hospitalization /ED treatment	
	(never/past/current %):	on it		
	82/13/5 (all < 10 pack-yr.)	Run-in duration:	<ul> <li>exacerbation:</li> </ul>	
		2 wk.	rate of	
			hospitalization	
			/ED	
			treatments	
			<ul> <li>exacerbation:</li> </ul>	
			total events	
			<ul> <li>ACQ-5</li> </ul>	
			<ul> <li>asthma</li> </ul>	
			control days	
			<ul> <li>NTA</li> </ul>	
			SFD	
			<ul> <li>asthma</li> </ul>	
			symptoms	
			<ul> <li>SABA use</li> </ul>	
			<ul> <li>RFD</li> </ul>	
			<ul> <li>change in ICS dose</li> </ul>	

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year: Boyd G 1995 <sup>73</sup> Pub status: Journal article No. countries: 1 No. centers: 15 Design: randomized, parallel, double	Randomized: 119 Analyzed: 97 Withdrawals: 22 ITT analysis: yes Asthma stage and severity: symptomatic, severe Baseline ICS use: non-naïve GROUP 1 N: 47	GROUP 1 Drug mcg/day: Usual asthma medications + SAL 200 Dosing: SAL was fixed; usual care NR Treatment duration: 12 wk. Device:	Definition of exacerbation: an acute episode requiring ED treatment or a short course of OCS. List of clinical outcomes reported:	Study objective: To investigate the efficacy and safety of SAL in the management of chronic asthmatics currently being considered for OCS.
blind Funding: Industry (ND)	Age yr. (mean±SD): 47±15.3 Males %: 40 FEV <sub>1</sub> % predicted (mean±SD): 66±18	Diskhaler <sup>®</sup> <b>Withdraw LOE n:</b> 2	<ul><li>Primary</li><li>PEF AM</li><li>PEF PM</li></ul>	Additional details: Patients carried on with current asthma treatment
	PEF AM L/min (mean±SD): 267±94 Duration of asthma: NR Smoking status: NR GROUP 2 N: 50 Age yr. (mean±SD): 47±13.8 Males %: 45.3 FEV <sub>1</sub> % predicted (mean±SD): 66±24.8 PEF AM L/min (mean±SD): 289±111 Duration of asthma: NR Smoking status: NR	GROUP 2 Drug mcg/day: Usual asthma medications + PLA Dosing: PLA was fixed; usual care NR Treatment duration: 12 wk. Device: Diskhaler <sup>®</sup> Withdraw LOE n: 2	Secondary • FEV <sub>1</sub> • exacerbations • FVC • DTS • NTS • SFD • SFN • SABA use	throughout the study.
		Reliever Tx: salbutamol as needed Run-in Tx: current high dose ICS (1500 mcg or equivalent) plus other current asthma therapy		

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 3,297	GROUP 1	Definition of	Study objective: to
Buhl R 2004 <sup>186</sup>	Analyzed: 3,027	Drug mcg/day:	exacerbation:	assess whether
Pub status:	Withdrawals: 260	FORM/BUD	required a course	adjustable dosing
Journal article		24/800	of OCS and were	maintained HRQL
	ITT analysis: yes	Dosing: fixed	withdrawn from the	and asthma control
No. countries:	Asthma stage and severity:	Treatment	study.	as effectively as
1	asymptomatic after run-in (mild-	duration: 12 wk.	olddy.	fixed dosing using
No. centers:	moderate for inclusion)	Device:	List of clinical	questionnaires and
1051	Baseline ICS use: non-naïve	Turbuhaler®	outcomes	clinical measures of
Design:		Withdraw LOE n:	reported:	asthma control.
randomized,	GROUP 1	14	Primary	
parallel, open	N: 1491		<ul> <li>change in</li> </ul>	Additional details:
label	Age yr. (mean±SD): 37.6±10	GROUP 2	AQLQ score	Patients in the
	Males %: 44	Drug mcg/day:		variable group
Funding:	FEV <sub>1</sub> % predicted (mean±SD):	FORM/BUD	Secondary	instructed to step up
Industry:	NR	12/400	<ul> <li>PEF AM</li> </ul>	FORM/BUD to
AstraZeneca	PEF AM L/min (mean±SD):	Dosing: variable	PEF PM	24/800 x 1 wk. if AM
/ lott all office d	356±89.4	Treatment		PEF was $< 80\%$ of
	<b>Duration of asthma:</b> $\geq$ 6 mo.	duration: 12 wk.	eymptom	baseline, or
	Smoking status: <10 pack-yr.	Device:	severity score	required reliever $\geq 3$
	and non-smoking for at least 2	Turbuhaler®	(4 pt scale)	inhalations/24 hr.
	yrs. pre-enrolment	Withdraw LOE n:	• SF-36	period, or had a
	Jiel pro emonitent	8	SABA use	nocturnal
	GROUP 2	0	<ul> <li>NTA</li> </ul>	awakening due to
	N: 1546		<ul> <li>SFD</li> </ul>	asthma. If asthma
	Age yr. (mean±SD): 37.3±10.2	Reliever Tx:	<ul> <li>asthma</li> </ul>	improved stepped
	Males %: 43.2	terbutaline as	control days	down to 12/400
	FEV <sub>1</sub> % predicted (mean±SD):	needed	%	again. If above
	NR	Run-in Tx:	<ul> <li>use of study</li> </ul>	criteria still met after
	PEF AM L/min (mean±SD):	FORM/BUD	medication	7 days they
	355±84.6	24/800 mcg/d	<ul> <li>step-up tx</li> </ul>	increased dose a
	<b>Duration of asthma:</b> $\geq$ 6 mo.	Run-in duration:	required	second time to
	Smoking status: <10 pack-yr.	4 wk.		48/1600 x 1 wk. If
	and non-smoking for at least 2	4 WK.		not controlled they
	yrs. pre-enrolment			contacted
	yrs. pre-enronnent			
				investigator. If controlled stepped
				down to 24/800
				again.
				Definition of an
				asthma control
				day:
				24 h with no asthma
				symptoms and no
				use of reliever
				medication

			Clinical	
Oterales	Deuticia autokona deutetia a	Treatment	outcomes	Natas
Study	Participant characteristics	characteristics	reported	Notes
Author Year: Buhl R 2003 <sup>72</sup>	Randomized: 523	GROUP 1	Definition of	Study objective: to
Pub status:	Analyzed: 523 Withdrawals: 43	Drug mcg/day: FORM/BUD	exacerbation: Mild: NTA due to	examine the
Journal article	Withurawais. 43	12/400 + PLA	asthma, or PEF ≤	efficacy of FORM/BUD 6/200
Journal article	ITT analysis: yos			
No. countries:	ITT analysis: yes Asthma stage and severity:	Dosing: fixed (bid)	20% of baseline, or ≥ 4 inhalations	mcg given bid to FORM/BUD 12/400
9	symptomatic- mixed	Treatment	of reliever/24 hr.	and BUD 400 mcg
No. centers: 56	asymptomatic and	duration: 12 wk.	for 2 consecutive	given once a day
Design:	symptomatic, mild	Device:	days.	(OD) to show that
randomized,	Baseline ICS use: non-naïve	Turbuhaler®	Severe:	one inhaler once a
parallel. double	Dasenne 100 use. non-narve	Withdraw LOE n:	deterioration	day is effective in
blind, double	GROUP 1 (FORM/BUD bid)	4	requiring OCS, or	patients with
dummy	<b>N</b> : 176	7	PEF $\leq$ 30% of	moderate persistent
dunniny	Age yr. (mean±SD): 44.8±14	GROUP 2	baseline for 2	asthma.
Funding:	Males %: 36.4	Drug mcg/day:	consecutive days,	astinna.
Industry:	FEV <sub>1</sub> % predicted (mean±SD):	FORM/BUD	or discontinuation	
AstraZeneca	77.6±17	12/400 + PLA	due to worsening	Additional details:
Astrazencea	PEF AM L/min (mean±SD):	Dosing: fixed	asthma.	To ensure blinding
	351±135	(OD PM)	astinna.	all patients took
	Duration of asthma	Treatment	List of clinical	active drug and/or
	(mean±SD): 12.3±15.5	duration: 12 wk.	outcomes	PLA twice a day. In
	Smoking status	Device:	reported:	groups 2 and 3
	(never/past/current %):	Turbuhaler®	Primary	once a day (OD)
	70.5/20.5/9.0 (all < 10 pack-yr.)	Withdraw LOE n:	<ul> <li>PEF AM</li> </ul>	active drug was
	10.0/20.0/0.0 (all 110 paok 31.)	5		given in the
	GROUP 2 (FORM/BUD OD)	0	Secondary	evening, PLA taken
	<b>N</b> : 176	GROUP 3	PEF PM	in the morning.
	Age yr. (mean±SD): 42.7±14.8	Drug mcg/day:	<ul> <li>FEV1</li> </ul>	g.
	Males %: 38	BUD 400 + PLA	<ul> <li>asthma</li> </ul>	Definition of a well
	FEV <sub>1</sub> % predicted (mean±SD):	Dosing: fixed	symptom	controlled asthma
	77.1±20.5	(OD PM)	score (0-6	week:
	PEF AM L/min (mean±SD):	Treatment	scale)	
	350±146.3	duration: 12 wk.	<ul> <li>asthma</li> </ul>	
	Duration of asthma yr.	Device:	control days	
	(mean±SD): 12.7±15.5	Turbuhaler®	<ul> <li>asthma</li> </ul>	
	Smoking status	Withdraw LOE	control week	
	(never/past/current %):	<b>n:</b> 5	SABA use	
	79.5/14.8/5.7 (all < 10 pack-yr.)		<ul> <li>SFD</li> </ul>	
		Reliever Tx:		
	GROUP 3 (BUD OD)	terbutaline as	NTA	
	<b>N:</b> 171	needed	RFD	
	Age yr. (mean±SD): 45.5±15	Run-in Tx: BUD	<ul> <li>time to 1st</li> </ul>	
	Males %: 39.8	400 mcg/d	mild	
	FEV <sub>1</sub> % predicted (mean±SD):	Run-in duration:	exacerbation	
	77.6±24.8	2 wk.	<ul> <li>exacerbation</li> </ul>	
	PEF AM L/min (mean±SD):		mild and	
	344±129.3		severe	
	Duration of asthma yr.		incidence	
	(mean±SD): 14.5±15.5			
	Smoking status			
	(never/past/current %):			
	74.3/17.5/8.2 (all < 10 pack-yr.)			

Study	Particinant charactoristics	Treatment characteristics	Clinical outcomes reported	Notes
Study Author Year: Busse W 2003 <sup>137</sup> Pub status: Journal article No. countries: 1 (United States) No. centers: 90 Design: randomized, parallel, double blind Funding: Industry: GlaxoSmithKline	Participant characteristicsRandomized: 558Analyzed: 558Withdrawals: 100ITT analysis: yesAsthma stage and severity: asymptomatic, moderateBaseline ICS use: non-naïveGROUP 1N: 281 for 12 wk.; 155 for 24 wk.Age yr. (mean±SD): 38±16.3 Males %: 41FEV1 % predicted (mean±SD): $80.5\pm(9.7)$ PEF AM L/min (mean±SD): $458.0\pm145.8$ Duration of asthma % (≥ 15 yr.): 5 Smoking status (never/past/current %): NRGROUP 2 N: 277 for 12 wk.; 153 for 24 wk. Age yr. (mean±SD): 39±15 Males %: 43 FEV1 % predicted (mean±SD): $80.9 (9.4)$ PEF AM L/min (mean±SD): $457.4\pm148.1$	<ul> <li>characteristics</li> <li>GROUP 1</li> <li>Drug mcg/day: SAL/FP 100/200</li> <li>Dosing: fixed</li> <li>Treatment</li> <li>duration: 12-24</li> <li>wk.</li> <li>Device: Diskus™</li> <li>Withdraw LOE n:</li> <li>wk. 1-12. n=14;</li> <li>wk. 13-24 n=3</li> <li>GROUP 2</li> <li>Drug mcg/day:</li> <li>FP 500</li> <li>Dosing: fixed</li> <li>Treatment</li> <li>duration: 12-24</li> <li>wk.</li> <li>Device: Diskus™</li> <li>Withdraw LOE n:</li> <li>wk. 13-24 n=3</li> <li>GROUP 2</li> <li>Drug mcg/day:</li> <li>FP 500</li> <li>Dosing: fixed</li> <li>Treatment</li> <li>duration: 12-24</li> <li>wk.</li> <li>Device: Diskus™</li> <li>Withdraw LOE n:</li> <li>wk. 1-12 n= 20;</li> <li>wk. 13-24 n=4</li> <li>Reliever Tx:</li> <li>albuterol as</li> <li>needed</li> <li>Run-in Tx: P1</li> <li>(10-14 d) FP 500</li> <li>mcg/d or</li> <li>equivalent; P2 (5-28 d) FP 200</li> </ul>		Notes Study objective: to determine if SAL/FP 100/200 mcg/d combination can be used to reduce ICS dose in patients stable on medium dose ICS and remain stable. Additional details: Study had 3 run-in phases to determine minimum effective dose. Only asthma study medications allowed.
	457.4±148.1 Duration of asthma % (≥ 15 yr.): 7 Smoking status (never/past/current %): NR	28 0) FP 200 mcg/d; P3 (4 wk. FP 500 mcg (to regain control)) <b>Run-in duration:</b> 12-24 wk.		

			Clinical	
		Treatment	outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year: Canonica GW 2004 <sup>187</sup> Pub status: Journal article No. countries: 1 No. centers: 154 Design: randomized,	Randomized: 2,358 Analyzed: 2,063 Withdrawals: 479 ITT analysis: all available data Asthma stage and severity: asymptomatic, mild intermittent to severe Baseline ICS use: non-naïve GROUP 1 (adjustable dose) N: 1,030	GROUP 1 Drug mcg/day: FORM/BUD 24/400 to 800 Dosing: variable Treatment duration: 12 wk. Device: Turbuhaler® Withdraw LOE: NR	Definition of exacerbation: asthma-related serious adverse event; hospitalization/ED treatment or course of OCS ≥ 5 d; withdrawal from study due to lack of effect or a need for other asthma	Study objective: To evaluate efficacy, tolerability, and costs of adjustable dose FORM/BUD (single inhaler) compared to fixed dosing in moderate-to-severe asthma.
parallel, open label Funding: Industry: AstraZeneca	Age yr. (mean±SD): 42.6±17 Males %: 48.4 FEV <sub>1</sub> % predicted (mean): ~85±20 PEF AM L/min (mean±SD): 372±144.6 Duration of asthma yr. (mean±SD): 11.2±11.1 Smoking status current %): 11.2 GROUP 2 (fixed dose) N: 1,033 Age yr. (mean±SD): 42.7±16.9 Males %: 46.1 FEV <sub>1</sub> % predicted (mean±SD): ~86±20 PEF AM L/min (mean±SD): 372.3±143.9 Duration of asthma: 10.6±10.7 Smoking status (current %): 12.1	GROUP 2 Drug mcg/day: FORM/BUD 12 to 24/200 to 1600 Dosing: fixed Treatment duration: 12 wk. Device: Turbuhaler® Withdraw LOE: NR Reliever Tx: NR Run-in Tx: dependant on current ICS use either FORM/BUD 24/800 mcg/d or 24/400 mcg/d Run-in duration: 4 wk.	<ul> <li>medications.</li> <li>List of clinical outcomes reported: Primary <ul> <li>exacerbation: frequency</li> <li>change in asthma symptom severity</li> </ul> </li> <li>Secondary <ul> <li>PEF % predicted</li> <li>FEV1 % predicted</li> <li>SFD %</li> <li>NTA #/d</li> <li>symptom score (scale 0-3)</li> <li>SABA use</li> <li>asthma control wk. %</li> <li>step-up/step-down tx.</li> <li>study medication use</li> <li>patient satisfaction (scale 1-10)</li> <li>doctor satisfaction (scale 1-10)</li> <li>days with lost activity</li> </ul> </li> </ul>	Additional details: Symptom severity assessed using National Heart, Lung and Blood Institute definitions. FEV1 % predicted estimated from a graph Definition of asthma control week: a symptom- free and SABA-free week. Adjustable dose instructions: Patients could step- down to FORM/BUD 12/200 or 12/400 mcg/d if in previous 7 d: SABA required on ≤ 2 d and no NTA. Patients could step- up to FORM/BUD 48/1600 or 48/3200 mcg/d until symptoms resolved if: required SABA ≥ 3 times/d or experienced NTA on 2 consecutive days. If no improvement in 14 days or worsened, they received alternative therapy or called an investigator. If experienced 2 exacerbations they were withdrawn from the study.

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 2,280	GROUP 1	Definition of	Study objective:
Chuchalin A	Analyzed: 2,258	Drug mcg/day:	exacerbation:	to test the
2008 <sup>62</sup>	Withdrawals: 315	SAL/FP 50/100 (AM)	Mild: AM PEF >	hypothesis that
Pub status:		+ PLA (PM)	20% below	once daily
Journal article	ITT analysis: yes (also per	Dosing: fixed	baseline; SABA	SAL/FP 50/100
	protocol populations)	Treatment duration:	use greater than	mcg is non-
No. countries:	Asthma stage and severity:	52 wk.	baseline on more	inferior to twice
28	symptomatic, mild	Device:	than 3	daily FP 100 mcg
No. centers:	Baseline ICS use: naïve	Diskus™/Accuhaler™	occasions/24 hrs.;	as initial therapy
175	Dasenne 100 use. nave	Withdraw LOE n: 7	or NTA; all on $\ge 2$	in mild asthma.
-	GROUP 1		•	in milu asunna.
Design:	N: 973	GROUP 2	consecutive days.	Additional
randomized,			Moderate:	
parallel, double	Age yr. (mean±SD): 33.8	Drug mcg/day: FP	required OCS	details:
blind, double	±15.8	100 (AM) + FP 100	based on AM PEF	Only study drugs
dummy	Males %: 44	(PM)	> 30% below	allowed except
	FEV <sub>1</sub> % predicted	Dosing: fixed	baseline on $\geq 2$	OCS for an
Funding:	(mean±SD): 96.7±20.7	Treatment duration:	consecutive days.	exacerbation.
Industry:	PEF AM L/min (mean±SD):	52 wk.	Severe: required	
GlaxoSmithKline	400.4 <b>±</b> 99.2	Device:	hospitalization	Definition of we
	Duration of asthma yr.: ≥6	Diskus™/Accuhaler™		controlled and
	mo.	Withdraw LOE n: 5	List of clinical	totally controlle
	Smoking status		outcomes	asthma:
	(never/past/current %):	GROUP 3	reported:	Composite
	77/15/9	Drug mcg/day: PLA	Primary	measures based
		(AM + PM)	• PEF AM	on GINA and NIF
	GROUP 2	Dosing: fixed	exacerbation:	guidelines
	N: 970	Treatment duration:	<ul> <li>exacerbation.</li> <li>rate</li> </ul>	guidennes
	Age yr. (mean±SD): 33.8±16	52 wk.		
	Males %: 42	Device:	(moderate/se	
	FEV <sub>1</sub> % predicted	Diskus™/Accuhaler™	vere)	
		Withdraw LOE n: 8	•	
	(mean±SD): 96.1±14.2		Secondary	
	PEF AM L/min (mean±SD):		<ul> <li>FEV<sub>1</sub></li> </ul>	
	395.1±96.1	Reliever Tx:	<ul> <li>exacerbation:</li> </ul>	
	Duration of asthma yr.: ≥6	Salbutamol as	hospitalizatio	
	mo.	needed	n/ER visits	
	Smoking status	Run-in Tx: SABA as	<ul> <li>exacerbation:</li> </ul>	
	(never/past/current %):	needed	outpatient/pra	
	78/15/8	Run-in duration: 2	ctice visits	
		wk.	<ul> <li>asthma</li> </ul>	
	GROUP 3		symptom	
	<b>N:</b> 315		score (6 pt	
	Age yr. (mean±SD):		scale)	
	35.0±16.5			
	Males %: 39		• NTA	
	FEV <sub>1</sub> % predicted		ACQ	
	(mean±SD): 98.0±19.0		<ul> <li>SABA use</li> </ul>	
	PEF AM L/min (mean±SD):		<ul> <li>asthma</li> </ul>	
	<b>393.8±</b> 96.4		control	
	Duration of asthma yr.: ≥6		<ul> <li>SFD %</li> </ul>	
	-		<ul> <li>FEV<sub>25-75</sub></li> </ul>	
	mo Smoking status		• well	
			controlled	
	(never/past/current %):		asthma	
	78/14/7		<ul> <li>totally</li> </ul>	
			<ul> <li>controlled</li> </ul>	
			asthma	
			asinma	

Study         Participant characteristics         characteristics         reported         Notes           Author Year:         Randomized: 333         GROUP 1         Definition of exacerbation: NR         Study objective:           Chuchalin AG         Analyzed: 333         Drug mcg/day:         exacerbation: NR         To evaluate the safety and efficacy           2002 <sup>46</sup> Withdrawals: 17         FORM/BUD         List of clinical         of FORM plus BUD           Journal article         ITT analysis: yes (also per protocol populations Asthma         Treatment         reported:         alone in mild-to- moderate asthma.           No. countries:         stage and severity: mild-to- moderate         Device:         •         PEF AM           No. centers:         Baseline ICS use: naïve         Turbuhaler®: two         Secondary         Only study drugs           Design:         GROUP 1         1         •         FEV ( PEF PM         Additional details:           Oummy         FEV, % predicted (mean±SD):         BUD 400 + PLA         SABA use         Only study drugs           Jouration of asthma yr.         Device:         •         FEF AM         FVC         PEF PM           Jou pack-yr         GROUP 2         Drug mcg/day: investigator         •         SAGA         SAGA <td< th=""><th></th><th></th><th>Treatment</th><th></th><th></th></td<>			Treatment		
Author Year: Chuchalin AG 2002 <sup>40</sup> Randomized: 333 (Mithdrawals: 17)       GROUP 1 Drug mcg/day: 24/400       Definition of moderate       Study objective: To evaluate the safety and efficacy of FORM plus BUD compared to BUD         Journal article Journal article       ITT analysis: yes (also per protocol populations Asthma stage and severity: mild-to- moderate       Dosing: fixed Treatment moderate       List of clinical oucomes       Study objective: To evaluate the safety and efficacy of FORM plus BUD compared to BUD         No. countries:       Baseline ICS use: naïve       Turbuhaler®: two Withdraw LOE n:       Def Additional details: Secondary         No. centers:       Baseline ICS use: naïve       Turbuhaler®: two Males %: 22.5       Drug mcg/day: Treatment Males %: 22.5       Secondary Drug mcg/day: BUD 400 + PLA Dosing: fixed Treatment duration: 12 wk.       SABA use symptoms (4 pt scale)         Funding: NR       PEF AM L/min (mean±SD): NR       Turbuhaler®: two Males %: 28.1       Drug mcg/day: trubuhaler®       AQLQ         GROUP 2 NR       Turbuhaler®       Withdraw LOE n:       AQLQ         Smoking status       GROUP 3       Drug mcg/day: investigator choice of non- steroid treatment TEV1 % predicted (mean±SD): NR       Drug mcg/day: investigator choice of non- steroid treatment TEV1 % predicted (mean±SD): NR       Withdraw LOE n:         GROUP 2 N285-7889.4       Duration of asthma yr. (mean±SD): 2 6 mo. Smoking status       Withdraw LOE n:       Eliv. Scale       Autorice in con- steroid treatment Treatm	Study	Particinant characteristics			Notes
Chuchalin AG 2002 <sup>16</sup> Analyzed: 333 Withdrawals: 17       Drug mcg/day: FORM/BUD 24/400       exacerbation: NR safety and efficacy outcomes protocol populations Asthma moderate       To evaluate the safety and efficacy outcomes         Journal article       ITT analysis: yes (also per protocol populations Asthma moderate       Dosing: fixed Treatment       List of clinical outcomes       outcomes         No. countries:       stage and severity: mild-to- moderate       Dosing: fixed Treatment       Pirmary       moderate         No. conters:       Baseline ICS use: naive       Turbuhaler®: two Withdraw LOE n:       Verice:       PEF AM         NR       GROUP 1       1       FEV.1       Secondary       Only study drugs allowed.         Journation of asthma yr.       GROUP 2       Drug mcg/day: moderate       PEF PM       SABA use         Funding: NR       PEF AM L/min (mean±SD): NR       Burd ato: 12 wk.       PEF PM       SABA use         Funding: NR       GROUP 2 (mean±SD): 2 6 mo.       Turbuhaler®       Withdraw LOE n:       SF-36         GROUP 2 (mean±SD): 2 6 mo.       Turbuhaler®       Withdraw LOE n:       SF-36         GROUP 2 (neen±SD): NR       GROUP 3 Drug mcg/day: investigator       SF-36       AQLQ         Vithdraw LOE n:       285.7±89.4       Duration of asthma yr.       Choice of non- steroid treatment       SABA </th <th></th> <th></th> <th></th> <th></th> <th></th>					
10 pack-yr       Run-in Tx: terbutaline as needed         GROUP 3       needed         N: 108       Run-in duration:         Age yr. (mean±SD): 43.6 ±12       2 wk.         Males %: 22.2       2 wk.         FEV1 % predicted (mean±SD):       NR         PEF AM L/min (mean±SD):       Vertical sectors	Author Year: Chuchalin AG 2002 <sup>46</sup> Pub status: Journal article No. countries: 1 No. centers: NR Design: randomized, parallel, double blind, double dummy	Randomized: 333 Analyzed: 333 Withdrawals: 17ITT analysis: yes (also per protocol populations Asthma stage and severity: mild-to- moderate Baseline ICS use: naïveGROUP 1 N: 111 Age yr. (mean±SD): 44.1±9 Males %: 22.5 FEV1 % predicted (mean±SD): 288.0±89.4 Duration of asthma yr. (mean±SD): $\geq 6$ mo. Smoking status (never/past/current %): all < 10 pack-yr	GROUP 1 Drug mcg/day: FORM/BUD 24/400 Dosing: fixed Treatment duration: 12 wk. Device: Turbuhaler®: two Withdraw LOE n: 1 GROUP 2 Drug mcg/day: BUD 400 + PLA Dosing: fixed Treatment duration: 12 wk. Device: Turbuhaler® Withdraw LOE n: 4 GROUP 3 Drug mcg/day: investigator choice of non- steroid treatment Treatment duration: 12 wk. Withdraw LOE n: 6 Reliever Tx: terbutaline as needed Run-in Tx: terbutaline as needed Run-in duration:	Definition of exacerbation: NR List of clinical outcomes reported: Primary • PEF AM Secondary • FEV <sub>1</sub> • FVC • PEF PM • SABA use • asthma symptoms (4 pt scale) • SF-36	Study objective: To evaluate the safety and efficacy of FORM plus BUD compared to BUD alone in mild-to- moderate asthma. Additional details: Only study drugs

Pub status: Journal articleITT analysis: yes Asthma stage and severity: symptomatic, moderate, severe Baseline ICS use: non-naïveDosing: fixed Treatment duration: 24 wk. Device: 2 MDIsrequired treatment with OCS or parenteral CSof adding SAL is compared to doubling the do of FP in patient who remain symptomatic or dose FP.No. centers: 36 Design: randomized, parallel, double dummyGROUP 1 N: 221 Males %: 38Dosing: fixed Treatment duration 24 wk. Device: 2 MDIsrequired treatment with OCS or parenteral CSdoubling the do of FP in patient who remain symptomatic or dose FP.Funding: Industry: GlaxoSmithKlinePEF AM L/min (mean±SD): 10 motation of asthma ≥ 10yr. %: 77/23/0GROUP 2 N: 216 Age yr. (mean±SD): 36.8±13.2Dosing: fixed Treatment duration 24 wk. Device: 2 MDIsPrimary • PEF PMAdditional detFunding: Industry: GlaxoSmithKlinePEF AM L/min (mean±SD): T7/23/0Dosing: fixed Treatment 6 (3%)Primary • PEF PMAdditional detGROUP 2 N: 216 Age yr. (mean±SD): 36.8±13.2Reliever Tx: albuterol as needed Run-in Tx: FP 200 mcg/d• pts exacerbation exacerbation• pts exacerbation exacerbation	Study Author Year:	Participant characteristics Randomized: 437	Treatment characteristics GROUP 1	Clinical outcomes reported Definition of	Notes Study objective:
<ul> <li>FEV₁ % predicted (mean±SD): 61.8±10.9</li> <li>PEF AM L/min (mean±SD): 36.07±111.7</li> <li>Duration of asthma ≥ 10yr. %: 78</li> <li>Smoking status (never/past/current %): 80/20/0</li> <li>Cough (5 pt scale)</li> <li>combined symptoms (5 pt scale)</li> <li>SABA use</li> <li>NTA</li> <li>nights with 0 awakenings</li> </ul>	1999 <sup>110</sup> <b>Pub status:</b> Journal article <b>No. countries:</b> 1 <b>No. centers:</b> 36 <b>Design:</b> randomized, parallel, double blind, double dummy <b>Funding:</b> Industry:	Withdrawals: 39 ITT analysis: yes Asthma stage and severity: symptomatic, moderate, severe Baseline ICS use: non-naïve GROUP 1 N: 221 Age yr. (mean $\pm$ SD): 36.9 $\pm$ 13.4 Males %: 38 FEV <sub>1</sub> % predicted (mean $\pm$ SD): 60.9 $\pm$ 11.0 PEF AM L/min (mean $\pm$ SD): 363.6 $\pm$ 116.0 Duration of asthma $\geq$ 10yr. %: 76 Smoking status (never/past/current %): 77/23/0 GROUP 2 N: 216 Age yr. (mean $\pm$ SD): 36.8 $\pm$ 13.2 Males %: 40 FEV <sub>1</sub> % predicted (mean $\pm$ SD): 61.8 $\pm$ 10.9 PEF AM L/min (mean $\pm$ SD): 36.07 $\pm$ 111.7 Duration of asthma $\geq$ 10yr. %: 78 Smoking status (never/past/current %):	SAL/FP 100/200 Dosing: fixed Treatment duration: 24 wk. Device: 2 MDIs Withdraw LOE n: 2 (<1%) GROUP 2 Drug mcg/day: FP 500 + PLA Dosing: fixed Treatment duration: 24 wk. Device: 2 MDIs Withdraw LOE n: 6 (3%) Reliever Tx: albuterol as needed Run-in Tx: FP 200 mcg/d Run-in duration:	asthma event that required treatment with OCS or parenteral CS List of clinical outcomes reported: Primary • PEF AM Secondary • PEF PM • FEV1 AM • pts experiencing 1 exacerbation • pts experiencing 2 1 exacerbation • wheeze (5 pt scale) • SOB (5 pt scale) • chest tightness (5 pt scale) • cough (5 pt scale) • cough (5 pt scale) • combined symptoms (5 pt scale) • SABA use • NTA • nights with 0	efficacy and safety of adding SAL to FP compared to doubling the dose of FP in patients who remain symptomatic on low dose FP. Additional details: Withdrawal criteria: Patients with >2 exacerbations or had 2 exacerbations within a 30 day

			Clinical	
		Treatment	outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 480	GROUP 1	Definition of	Study objective:
Corren J 200747	Analyzed: 454	Drug mcg/day:	exacerbation:	To compare efficacy
	Withdrawals: 133	FORM/BUD	worsening asthma	and tolerability of
Pub status:		24/400 + PLA	requiring ED	FORM/BUD
Journal article	ITT analysis: all available data	Dosing: fixed	treatment,	combined to FORM
	Asthma stage and severity:	Treatment	hospitalization, or	and BUD and PLA
No. countries:	asymptomatic, mild-moderate	duration: 12 wk.	non-study drugs.	alone.
1	Baseline ICS use: non-naïve	Device: MDI		
No. centers: 56		Withdraw LOE n:	List of clinical	Additional details:
Design:	GROUP 1	9	outcomes	All groups received
randomized,	<b>N:</b> 123		reported:	an MDI and a
parallel, double	Age yr. (mean±SD): 37.2±15.7	GROUP 2	-	Turbuhaler <sup>®</sup> .
blind, double-	Males %: 37.4	Drug mcg/day:	Primary	Only study
dummy	FEV <sub>1</sub> % predicted (mean±SD):	BUD 400 + PLA	<ul> <li>FEV<sub>1</sub> AM</li> </ul>	medications
5	70.6±10.3	Dosing: fixed	• FEV <sub>1</sub> 12 hr.	allowed.
Funding:	PEF AM L/min	Treatment	mean	
Industry:	(mean±SD):350±95	duration: 12 wk.	mean	Criteria for
AstraZeneca	Duration of asthma yr.	Device: MDI	Secondary	worsening
	(mean±SD): 20.2±12.5	Withdraw LOE n:	PEF AM	asthma:
	Smoking status: all < 10 pack-	8		A decrease in
	yr	0	PEF PM	<ul> <li>A decrease in AM FEV1 ≥</li> </ul>
	y i	GROUP 3	DTS (4 pt	20% of
	GROUP 2	Drug mcg/day:	scale)	baseline or a
	N: 121	FORM 24 + PLA	<ul> <li>NTS (4 pt</li> </ul>	
			scale)	decrease to <
	Age yr. (mean±SD): 37.1±15.9 Males %: 38	Dosing: fixed Treatment	<ul> <li>asthma</li> </ul>	45% predicted.
	FEV <sub>1</sub> % predicted (mean±SD):	duration: 12 wk.	symptom	• ≥ 12 uses of
	70.0±10.1	Device:	score (4 pt	SABA/d on $\geq 3$
	PEF AM L/min (mean±SD):	Turbuhaler®	scale)	of 7
	353±82	Withdraw LOE n:	<ul> <li>SABA use</li> </ul>	consecutive
			<ul> <li>worsening</li> </ul>	days.
	Duration of asthma yr.	21	asthma	A decrease in
	(mean±SD): 19.5±13.0		<ul> <li>awakening</li> </ul>	AM PEF ≥ 20%
	Smoking status: all < 10 pack-	GROUP 4	free nights	of baseline on a
	yr	Drug mcg/day:	SFD	3 of 7
		PLA + PLA	••• =	consecutive
	GROUP 3	Dosing:		days.
	N: 114	Treatment		<ul> <li>Night</li> </ul>
	Age yr. (mean±SD): 35.3±16.0	duration: 12 wk.		awakenings
	Males %: 36.87.9.1	Device: MDI		requiring SABA
	FEV <sub>1</sub> % predicted (mean±SD):	Withdraw LOE:		on ≥ 2 of 7
	70.6±10.1	40		consecutive
	PEF AM L/min (mean±SD):			nights.
	359±87	Reliever Tx:		<ul> <li>Exacerbation</li> </ul>
	Duration of asthma yr.	albuterol as		requiring ED
	(mean±SD): 19.7± 12.3	needed		treatment,
	Smoking status: all < 10 pack-	Run-in Tx: PLA.		hospitalization,
	yr	All current asthma		or non-study
		medications		drugs.
	GROUP 4	discontinued		÷
	N: 122	Run-in duration:		
	Age yr. (mean±SD): 36.1±14.5	1-3 wk.		
	Males %: 38.5			
	FEV <sub>1</sub> % predicted (mean±SD):			
	69.7±9.8			
	PEF AM L/min (mean±SD):			
	· =· / =/			
	350±93			
	350±93			

Study Author Year: Creticos PS	Participant characteristics	charactoristics	roportod	Notes
Creticos PS		characteristics	reported	
	Randomized: 46	GROUP 1	Definition of	Study objective: to
55	Analyzed: NR	Drug mcg/day:	exacerbation: NR	examine effects of
1999 <sup>55</sup>	Withdrawals: NR	SAL/TAA 100/800		primary therapy with
Pub status:		Dosing: fixed	List of clinical	TAA compared to
Journal article	ITT analysis: not clear	Treatment	outcomes	SAL alone and to
	Asthma stage and severity:	duration: 24 wk.	reported:	SAL plus TAA in
No. countries:	symptomatic, mild-moderate	Device: NR	Primary	symptomatic
1 (United	Baseline ICS use: naïve	Withdraw LOE:	methacholine	asthma
States)		NR	sensitivity	dottinid
No. centers: 1	GROUP 1		Sensitivity	Additional details:
			0	
Design:	N: NR	GROUP 2	Secondary	Very little data
randomized,	FEV <sub>1</sub> % predicted (mean±SD):	Drug mcg/day:	<ul> <li>FEV<sub>1</sub></li> </ul>	reported
parallel	NR	TAA 800		
	PEF AM L/min (mean±SD): NR	Dosing: fixed		
Funding: NR	Duration of asthma yr.	Treatment		
	(mean±SD): NR	duration: 24 wk.		
	Smoking status	Device: NR		
	(never/past/current %): NR	Withdraw LOE:		
		NR		
	GROUP 2			
	N: NR	GROUP 3		
	FEV <sub>1</sub> % predicted (mean±SD):	Drug mcg/day:		
	NR	SAL 100		
	PEF AM L/min (mean±SD): NR	Dosing: fixed		
	Duration of asthma yr.	Treatment		
	(mean±SD): NR	duration: 24 wk.		
	Smoking status	Device: NR		
	(never/past/current %): NR	Withdraw LOE:		
	, I ,	NR		
	GROUP 3			
	N: NR	Reliever Tx: NR		
		Run-in Tx:		
	FEV <sub>1</sub> % predicted (mean±SD):			
	NR	observational		
	PEF AM L/min (mean±SD): NR	period		
	Duration of asthma yr.	Run-in duration:		
	(mean±SD): NR	2 wk.		
	Smoking status			
	(never/past/current %): NR			
	Total population			
	N: 46			
	Age yr. (mean): 35			
	Males %: 43.5			
	FEV <sub>1</sub> % predicted (mean): all			
	≥ 65			

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year:	Randomized: 1,397	GROUP 1	Definition of	Study objective:
Dahl R 2006 <sup>128</sup>	Analyzed: 1,391 (ITT)	Drug mcg/day:	exacerbation:	To compare the
Pub status:	Withdrawals: 133	FORM/BUD 24/800 +	Mild: AM PEF >	efficacy of
Journal article		PLA	20% below	FORM/BUD
	ITT analysis: yes	Dosing: fixed	baseline; SABA	24/800 mcg/d to
No. countries:	Asthma stage and severity:	Treatment duration:	use greater than	SAL/FP 100/500
18	symptomatic, moderate	24 wk.	baseline on more	mcg/d in patients
No. centers:	Baseline ICS use: non-naïve	Device: Turbuhaler <sup>®</sup>	than 3	with persistent
178		Withdraw LOE: 2	occasions/24	asthma currently
Design:	GROUP 1		hrs.; or NTA; all	on ICS 1000-2000
randomized,	N: 697	GROUP 2	on $\geq 2$	mcg/d.
parallel, double	Age yr. (mean±SD):	Drug mcg/day:	consecutive days.	
blind, double	47.1±16.0	SAL/FP 100/500 +	Moderate:	Additional
dummy	Males %: 41	PLA	required OCS 40-	details:
	FEV <sub>1</sub> % predicted	Dosing: fixed	60 mg/d x 7-10	To ensure blinding
Funding:	(mean±SD): 78.5±18.2	Treatment duration:	days based on	each group
Industry:	PEF AM L/min (mean±SD):	24 wk.	AM PEF > 30%	received both
GlaxoSmithKline	348.4±111.47	Device:	below baseline	inhalers
	Duration of asthma: 6 mo. to	Diskus™/Accuhaler™	on $\geq 2$	
	≥ 25 yr	Withdraw LOE: 5	consecutive days	Well controlled
	Smoking status		or clinical	asthma week
	(never/past/current %): all <		deterioration	defined as: at
	10 pack-yr	Reliever Tx:	assessed by	least 2 of 3 of the
		salbutamol as	investigator.	following:
	GROUP 2	required	Severe: required	symptom score >
	N: 694	Run-in Tx: current	hospitalization	1 on no more than
	Age yr. (mean±SD):	ICS 1000-2000		2 days; no more
	45.6±18.3	mcg/d. No LABAs x 4	List of clinical	than 2 days of
	Males %: 44	wk. prior to study	outcomes	SABA use
	FEV <sub>1</sub> % predicted	Run-in duration: 2	reported:	(maximum 4
	(mean±SD): 78.7±17.9	wk.	Primary	x/wk.); AM PEF ≥
	PEF AM L/min (mean±SD):		exacerbation:	80% predicted
	357.6±122.45		rate/24	every day plus all
	Duration of asthma yr.		weeks	of the following: no
	(mean±SD): 6 mo. to ≥ 25 yr			NTA,
	Smoking status		Secondary	exacerbations, ED
	(never/past/current %): all <		<ul> <li>PEF AM</li> </ul>	visits, or treatment
	10 pack-yr		PEF AM %	related AEs
			predicted	forcing a change
			<ul> <li>FEV<sub>1</sub></li> </ul>	in therapy.
			exacerbation	
			requiring	
			OCS	
			<ul> <li>exacerbation</li> </ul>	
			requiring	
			hospital	
			admission	
			<ul> <li>DTS</li> </ul>	
			<ul> <li>DTS</li> <li>NTS</li> </ul>	
			<ul> <li>SABA use</li> </ul>	
			SFD	
			SFN	
			• RFD	
			• well-	
			controlled	
			asthma week	

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 33	GROUP 1	Definition of	Study objective:
DiFranco A	Analyzed: 24	Drug mcg/day:	exacerbation: NR	To compare efficacy
1999 <sup>54</sup>	Withdrawals: 9	SAL/BDP		of SAL/BDP to BDP
Pub status:		100/1000	List of clinical	alone and NS
Journal article	ITT analysis: yes	Dosing: fixed	outcomes	alone.
	Asthma stage and severity:	Treatment	reported:	
No. countries:	symptomatic, mild	duration: 52 wk.	Primary	Additional details:
1 (Italy) No. centers: 1	Baseline ICS use: naïve	Device: MDI Withdraw LOE:	<ul> <li>FEV<sub>1</sub> % pred</li> </ul>	2 participants withdrew due to
Design:	GROUP 1	NR	Secondary	asthma
randomized,	<b>N</b> : 10		PEF	exacerbation.
parallel, open	Age yr. (mean±SD): 32±8.5	GROUP 2	<ul> <li>asthma</li> </ul>	Group not reported.
label, single	Males %: 91	Drug mcg/day:	symptom	
blind	FEV <sub>1</sub> % predicted	BDP 1000	score	
	(median±SD): 99±16.5	Dosing: fixed	<ul> <li>PC<sub>20</sub></li> </ul>	
Funding: NR	PEF AM L/min (mean±SD): NR	Treatment		
	Duration of asthma yr.	duration: 52 wk.		
	(mean±SD): 10±5.8	Device: MDI		
	Smoking status	Withdraw LOE:		
	(never/past/current %): 91/9/0	NR		
	GROUP 2	GROUP 3		
	<b>N:</b> 5	Drug mg/day:		
	Age yr. (mean±SD): 42±13.5	nedocromil		
	Males (%): 27.3	sodium 16		
	FEV <sub>1</sub> % predicted (mean±SD):	Dosing: fixed		
	92±10.8	Treatment		
	PEF AM L/min (mean±SD): NR	duration: 52 wk.		
	Duration of asthma yr.	Device: MDI		
	(mean±SD): 10±7.3	Withdraw LOE:		
	Smoking status	NR		
	(never/past/current %):			
	36.4/54.5/9	Reliever Tx: NR		
		Run-in Tx: SABA		
	GROUP 3	as needed		
	N: 9	Run-in duration:		
	Age yr. (mean±SD): 26±11.8	2 wk.		
	Males %: 63.6			
	FEV <sub>1</sub> % predicted (mean±SD):			
	95±5.3			
	PEF AM L/min (mean±SD): NR			
	Duration of asthma yr.			
	(mean±SD): 8±3.7 Smoking status			
	(never/past/current %):			
	72.7/18.9/9			

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Study Author Year: Fitzgerald JM 2005 <sup>11</sup> Pub status: Journal article No. countries: 15 No. centers: 91 Design: randomized, parallel, double blind, double dummy Funding: Government, institution, industry: GlaxoSmithKline	Participant characteristics Randomized: 706 Analyzed: 688 Withdrawals: 173 ITT analysis: yes Asthma stage and severity: symptomatic, intermittent- moderate Baseline ICS use: non-naïve GROUP 1 N: 344 Age yr. (mean±SD): 44±14 Males %: 37 FEV <sub>1</sub> % predicted (mean±SD): 81±13 Mean PEF AM (mean±SD): 362±100 Duration of asthma (mean±SD): 200±58 Smoking status: <10 pack-yr. GROUP 2 N: 344 Age yr. (mean±SD): 46±14 Males %: 41 FEV <sub>1</sub> % predicted (mean±SD): 82±21 Mean PEF AM (mean±SD): 357±103 Duration of asthma (mean±SD): 197±57 Smoking status: <10 pack-yr.	characteristics GROUP 1 Drug mcg/day: FORM/BUD 24/800, 12/400, 6 /200 Dosing: variable Treatment duration: 52 wk. Device: Turbuhaler <sup>®</sup> Withdraw LOE: 4 GROUP 2 Drug mcg/day: SAL/FP 100/500 Dosing: fixed Treatment duration: 52 wk. Device: diskhaler Withdraw LOE: 3 Reliever Tx: salbutamol prn Run-in Tx: current asthma tx; salbutamol Run-in duration: 2 wk.	reported Definition of exacerbation: Worsening of asthma requiring hospital treatment or treatment with oral corticosteroids, either in the opinion of the investigator or based on a morning PEF <70% of the mean of the last 7 days in weeks 1 through 4 for >2 consecutive days. List of clinical outcomes reported: Primary SFD Secondary PEF AM daily score reliever use RFD NTA asthma	Notes Study objective: To compare the efficacy of 2 treatment approaches: stable dosing SAL/FP and patient adjustable maintenance dose of FORM/BUD in adults with persistent asthma. Additional Details: Step-down treatment administered by Turbuhaler®: FF/BUD 24 /800 mcg/day (wk. 1-4), 12 /400 mcg/day (wk. 4-16), 6 /200 mcg/day (wk. 16- 52).
			control weeks	

			Clinical	
Study	Participant characteristics			Notos
Study Author Year: Fitzgerald JM 1999 <sup>90</sup> Pub status: Journal article No. countries: 1 (Canada) No. centers: 15 Design: randomized, parallel, double blind Funding: Industry: Novartis	Participant characteristics Randomized: 271 Analyzed: 271 Withdrawals: 54 ITT analysis: no Asthma stage and severity: asymptomatic, mild,moderate Baseline ICS use: non-naïve GROUP 1 N: 89 Age yr. (mean±SD): 36±13 Males %: 53 FEV1 % predicted (mean±SD): 79.1±16.3 Mean PEF AM (mean±SD): 442±90 Duration of asthma (mean±SD): NR Smoking status: non-smokers GROUP 2 N: 91 Age yr. (mean±SD): 36±13 Males %: 40 FEV1 % predicted (mean±SD): 80.4±15.7 Mean PEF AM (mean±SD): 447±91 Duration of asthma (mean±SD): NR Smoking status: non-smokers GROUP 3 N: 91 Age yr. (mean±SD): 36±12 Males %: 36 FEV1 % predicted (mean±SD): 79.7±16.4 Mean PEF AM (mean±SD): 438±86	Treatment characteristics GROUP 1 Drug mcg/day: FORM/BDP or BUD or FP 24/400-1200 Dosing: fixed Treatment duration: 24 wk. Device: Aeroliser Withdraw LOE: NR GROUP 2 Drug mcg/day: BDP or BUD or FP 400-1200 (equal to pre- study ICS) Dosing: fixed Treatment duration: 26 wk. Device: Aeroliser Withdraw LOE: NR GROUP 3 Drug mcg/day: BDP or BUD or FP: equal to pre- study ICS/PLA 400-1200 mcg/day: whatever was taken pre-study Dosing: fixed Treatment duration: 26 wk. Device: Aeroliser Withdraw LOE: NR	Clinical outcomes reported Definition of exacerbation: Exacerbation days – a 24-hour period during which more than 8 puffs of rescue albuterol were inhaled and/or any asthma symptom score equaled 4. List of clinical outcomes reported: Primary • PC <sub>20</sub> Secondary • change in FEV <sub>1</sub> • FEV <sub>1</sub> • FEV <sub>1</sub> • asthma symptom score • daytime SABA use • nighttime SABA use • frequency of exacerbation days	Notes Study objective: to compare the effect of twice daily formoterol, 4 times daily albuterol, and on-demand albuterol on bronchial hyperresponsiveness (BHR), lung function measurements, symptoms, and other indicators of disease control over 6 months in patients with asthma of moderate or greater severity receiving concomitant inhaled corticosteroids.
	Mean PEF AM (mean±SD): 438±86 Duration of asthma (mean±SD): NR Smoking status: non-smokers	<b>Reliever Tx:</b> albuterol prn <b>Run-in Tx:</b> PLA dry powder 4x/day; albuterol		
		Run-in Tx: PLA dry powder		

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Fowler SJ 2002 <sup>77</sup> Pub status: Journal article No. countries: 1 (Scotland) No. centers: 1 Design: randomized, parallel, double dummy Funding: Institution	Randomized: 39 Analyzed: 39 Withdrawals: 0 ITT analysis: yes Asthma stage and severity: asymptomatic and symptomatic, mild to moderate Baseline ICS use: non-naïve Males %: 21.3 GROUP 1 N: 19 Age: 16-70 Males %: NR FEV <sub>1</sub> % predicted (mean±SD): NR Duration of asthma: NR Smoking status: NR GROUP 2 N: 20 Age: 16-70 Males %: NR FEV <sub>1</sub> % predicted (mean (5% CI)): 1.5 (1.1-2.0) Mean PEF AM (mean±SD): NR Duration of asthma: NR Smoking status: NR	GROUP 1 Drug mcg/day: SAL/FP 100/200 Dosing: fixed Treatment duration: 12 wk. Device: Diskus <sup>®</sup> Withdraw LOE: NA GROUP 2 Drug mcg/day: BDP (HFA) 400 Dosing: variable Treatment duration: 12 wk. Device: Autohaler® Withdraw LOE: NA Reliever Tx: albuterol Run-in Tx: BDP 2000 mcg bid Run-in duration: 4 wk.	Definition of exacerbation: NR List of clinical outcomes reported: Primary • PC <sub>20</sub> Secondary • PEF % predicted • PEF AM • PEF PM • PEF 25-75 • FEV1 • FEV1 % predicted • symptom score • AQLQ • Reliever use	Study objective: To evaluate step- down therapy with a fluticasone propionate- salmeterol (FP-SM) combination administered through a dry powder inhaler versus a medium dose of hydrofluoroalkane 143a- beclomethasone dipropionate (HFA- BDP) administered through a breath- actuated pressurized metered-dose inhaler. Additional • Comparison of HFA propellant with diskus

Author Year:RaGreening APAn199411WPub status:WJournal articleITAsAsNo. countries:sy1 (UnitedseKingdom)BaNo. centers:1Design:Glrandomized,N:parallel, doubleAgblindMa	Participant characteristics andomized: 429 nalyzed: 426 /ithdrawals: 136 T analysis: yes sthma stage and severity: /mptomatic, intermittent to evere aseline ICS use: non-naïve ROUP 1 : 220 ge yr. (mean±SD): 48±15	characteristics GROUP 1 Drug mcg/day: SAL/BDP 100 /400 Dosing: fixed Treatment duration: 26 wk. Device: diskhaler Withdraw LOE: NR GROUP 2	reported Definition of exacerbation: Mild = increased use of relief medication. Moderate = requiring a short course of oral corticosteroids. Severe = requiring hospital admission.	Notes Study objective: To compare two options in a randomized controlled trial – an increase in the inhaled corticosteroid dose and the addition of salmeterol xinafoate.
Greening AP 1994 <sup>111</sup> W Pub status: Journal article IT As No. countries: sy 1 (United se Kingdom) Ba No. centers: 1 Design: Gl randomized, N: parallel, double Ag blind Ma	nalyzed: 426 Vithdrawals: 136 T analysis: yes sthma stage and severity: ymptomatic, intermittent to evere aseline ICS use: non-naïve ROUP 1 : 220	Drug mcg/day: SAL/BDP 100 /400 Dosing: fixed Treatment duration: 26 wk. Device: diskhaler Withdraw LOE: NR GROUP 2	exacerbation: Mild = increased use of relief medication. Moderate = requiring a short course of oral corticosteroids. Severe = requiring	To compare two options in a randomized controlled trial – an increase in the inhaled corticosteroid dose and the addition of salmeterol
Funding: Ma Industry: 34 GlaxoSmithKline Du [ra Sr ne 10 Gl N: 57 Ne 10 Gl N: 57 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne 10 Ne Ne N Ne 10 Ne 10 Ne 10 Ne 10 Ne Ne Ne Ne Ne Ne Ne Ne Ne Ne Ne Ne Ne	ales %: 46 EV <sub>1</sub> % predicted: NR ean PEF AM (mean $\pm$ SD): 49 $\pm$ 109 uration of asthma (median ange]): 11.1 yr. (0.7-53) moking status – ever/prev/current (n [%]): 04(47) / 57(26) / 59(27) ROUP 2 : 206 ge yr. (mean $\pm$ SD): 47 $\pm$ 15 ales %: 41 EV <sub>1</sub> % predicted: NR ean PEF AM (mean $\pm$ SD): 39 $\pm$ 99 uration of asthma (median ange]): 11 yr. (0.1-62.6) moking status – ever/prev/current (n [%]): 06(51) / 46(22) / 54(26)	Drug mcg/day: BDP 1000 + PLA Dosing: fixed Treatment duration: 26 wk. Device: NR Withdraw LOE: NR Reliever Tx: salbutamol prn Run-in Tx: BDP 400 mcg/day Run-in duration: 2 wk.	List of clinical outcomes reported: • PEF AM Primary • PEF PM • total number of exacerbations • number of mild exacerbations • number of moderate exacerbations • number of severe exacerbations • number of severe exacerbations • self-reported symptom frequency • NTA • SABA use • AE Secondary	
			No secondary outcome measures reported	

		Tuestar	Clinical	
C to all a	Deuticineut cheve stavistics	Treatment	outcomes	Nataa
Study	Participant characteristics	characteristics	reported	Notes
Author Year: Grutters J	Randomized: 40	GROUP 1	Definition of exacerbation: NR	Study objective:
1999 <sup>59</sup>	Analyzed: 40 Withdrawals: 0	Drug mcg/day: SAL/BDP	exacerbation: NR	To investigate whether regular
Pub status:	withdrawais: 0	5AL/BDP 100/800	List of clinical	antiasthma
Journal article	ITT analysis: yes	Dosing: fixed	outcomes	treatment including
	Asthma stage and severity:	Treatment	reported:	salmeterol could
No. countries:	asymptomatic, intermittent-	duration: 8 wk.	Primary	modulate the
1 (The	moderate	Device:	• FEV <sub>1</sub> %	priming-sensitive
Netherlands)	Baseline ICS use: naïve	Diskhaler <sup>®</sup>	• predicted	cytotoxic
No. centers: 2	Daseline 105 use. naive	Withdraw LOE: 0	predicted	mechanisms of
Design:	GROUP 1		Secondary	human eosinophils.
randomized,	N: 12	GROUP 2	•	numan eosinophiis.
parallel, double	Age yr. (mean±SD): 27± 20.8	Drug mcg/day:	<ul> <li>response to allergens</li> </ul>	
blind	Males %: 6 (50)	BDP 800	<ul> <li>inflammatory</li> </ul>	
biirid	FEV <sub>1</sub> % predicted (mean±SD):	Dosing: fixed	responses	
Funding:	79±17.3	Treatment	responses	
Industry:	Mean PEF AM (mean±SD): NR	duration: 8 wk.		
GlaxoSmithKline	Duration of asthma: NR	Device:		
	Smoking status: NR	Diskhaler®		
	j	Withdraw LOE: 0		
	GROUP 2			
	N: 15	GROUP 3		
	Age yr. (mean±SD): 26±19.4	Drug mcg/day:		
	Males %: 62	SAL 100		
	FEV <sub>1</sub> % predicted (mean±SD):	Dosing: fixed		
	86±15.5	Treatment		
	Mean PEF AM (mean±SD): NR	duration: 8 wk.		
	Duration of asthma: NR	Device:		
	Smoking status: NR	Diskhaler <sup>®</sup>		
	-	Withdraw LOE: 0		
	GROUP 3			
	<b>N:</b> 13	Reliever Tx:		
	Age yr. (mean±SD): 31±25.2	salbutamol 400		
	Males %: 38	mcg prn		
	FEV <sub>1</sub> % predicted (mean±SD):	Run-in Tx: SAL		
	79±10.8	prn		
	Mean PEF AM (mean±SD): NA	Run-in duration:		
	Duration of asthma: NR	2 wk.		
	Smoking status: NR			

<b>.</b>	<b>_</b>	Treatment	Clinical outcomes	
Study Author Year: Ind PW 2004 <sup>188</sup> Pub status: Journal article No. countries: 1 (United Kingdom) No. centers: 365 Design: randomized, parallel, open label Funding: Industry: AstraZeneca	Participant characteristics Randomized: 1,553 Analyzed: 1,553 Withdrawals: 14 ITT analysis: yes Asthma stage and severity: asymptomatic, intermittent to moderate Baseline ICS use: non-naïve GROUP 1 N: 771 Age (mean [range]): 48 (18- 87) Males %: 41 FEV <sub>1</sub> % predicted: NR PEF AM (mean±SD): NR Duration of asthma: NR Smoking status: NR GROUP 2 N: 782 Age (mean [range]): 48.7 (18- 81) Males %: 38 FEV <sub>1</sub> % predicted: NR PEF AM (mean±SD): NR Duration of asthma: NR Smoking status: NR	Treatment characteristics GROUP 1 Drug mcg/day: FORM/BUD 18/640 Dosing: fixed Treatment duration: 12 wk. Device: Turbuhaler <sup>®</sup> Withdraw LOE: 8 GROUP 2 Drug mcg/day: FORM/BUD 9- 36/320-1,280 Dosing: variable Treatment duration: 12 wk. Device: Turbuhaler <sup>®</sup> Withdraw LOE: 6 Reliever Tx: terbutaline 0.5 mg Run-in Tx: FP/BUD 6/80 mcg bid or 6/200 mcg bid depending on maintenance ICS dose at enrollment Run-in duration: 4 wk.	outcomes reported Definition of exacerbation: Treatment failure: a serious asthma exacerbation leading to use of non-study medication (excluding a course of oral steroids lasting <5 days). Clinical outcomes reported: Primary • treatment failure • treatment success Secondary • PEF PM • asthma-free days • SABA use • nighttime awakening	Notes Study objective: To examine the effect of a symptom-driven, self-management plan in a large asthma population receiving budesonide/formotero in a single inhaler. Additional Details: Patients in the adjustable-dosing group were instructed how to alter their therapy (stepping up or stepping down), according to their level of symptoms.

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 502	GROUP 1	Definition of	Study objective:
Ind PW 2003 <sup>76</sup>	Analyzed: 496	Drug mcg/day:	exacerbation:	To see whether the
	Withdrawals: 64	SAL/FP 100/500	Mild = requiring	benefit of adding
Pub status:		Dosing: fixed	clinically significant	salmeterol was
Journal article	ITT analysis: no	Treatment	increase in relief	superior to that of
	Asthma stage and severity:	duration: 24 wk.	medication.	doubling the dose
No. countries:	symptomatic, intermittent to	Device: MDI	Moderate =	of FP to 500 mcg
6	severe	Withdraw LOE:	requiring the use	bid, while also
No. centers:	Baseline ICS use: non-naïve	12	of additional	including a control
100	Duschine loo use. Hon haive	12	corticosteroid.	group who
	GROUP 1	GROUP 2		continued treatment
Design:	N: 171		Severe = requiring	with low-dose FP
randomized,		Drug mcg/day:	emergency	
parallel, double	Age yr. (mean±SD): 44.8±15.6	FP 1000 mcg	hospital treatment.	(250 mcg bid).
blind, double	Males %: 41	Dosing: fixed		
dummy	FEV <sub>1</sub> % predicted: NR	Treatment	List of clinical	
	<b>PEF AM (mean±SD)</b> : 347±93	duration: 24 wk.	outcomes	
Funding:	Duration of asthma: 12 (0.2-	Device: MDI	reported:	
Industry:	64) (median(range))	Withdraw LOE:	Primary	
GlaxoSmithKline	Smoking status –	NR	<ul> <li>PEF AM</li> </ul>	
	prev/current (n [%]):			
	48(40)/23(13)	GROUP 3	Secondary	
		Drug mcg/day:	PEF PM	
	GROUP 2	FP 500	<ul> <li>total</li> </ul>	
	<b>N</b> : 160	Dosing: fixed	exacerbations	
	Age yr. (mean±SD): 43.9±14.9	Treatment	<ul> <li>number mild</li> </ul>	
	Males %: 50	duration: 24 wk.	exacerbations	
	FEV <sub>1</sub> % predicted: NR	Device: MDI		
	<b>PEF AM (mean±SD):</b> 357±104	Withdraw LOE:	number	
	Duration of asthma (median	NR	moderate	
	[range]): 11 (0.4-65)		exacerbations	
	Smoking status –	Reliever Tx:	<ul> <li>number</li> </ul>	
	prev/current (n [%]): 48 (29)/	salbutamol prn,	severe	
		unblended FP	exacerbations	
	39 (24)		<ul> <li>SFD</li> </ul>	
	GROUP 3	250 mcg, oral	<ul> <li>SFN</li> </ul>	
		prednisolone for	<ul> <li>medication</li> </ul>	
	N: 165	use in an	free days	
	Age yr. (mean±SD): 45.7±15.2	exacerbation	,	
	Males %: 49	Run-in Tx: FP		
	FEV <sub>1</sub> % predicted: NR	250 bid and		
	PEF AM (mean±SD): 347±101	salbutamol prn		
	Duration of asthma (median	Run-in duration:		
	[range]): 15 (1-68)	4 wk.		
	Smoking status –			
	prev/current (n [%]): 51			
	(32)/25 (16)			

	Treatment	Clinical outcomes	Nataa
			Notes
			Study objective: to
			compare the
Withdrawais: 59			efficacy and
	-		tolerability of a
			SAL/FP
		0,	combination (SFC
		•	50/250 mcg bid)
Baseline ICS use: non-naïve			with a three-fold
	Withdraw LOE: 7		higher microgram
			dose (3:1 ratio) of
			inhaled
Age (mean [range]): 45 (16-		corticosteroids,	corticosteroid
75)		bronchodilators	(budesonide 1600
Males %: 50	Dosing: fixed	and/or oral	mcg/day) in patients
FEV <sub>1</sub> % predicted (mean	Treatment	corticosteroids.	with moderate to
[range]): 68 (33-105)	duration: 24 wk.	Mild = a	severe persistent
PEF AM (mean±SD): NR	Device:	deterioration in	asthma remaining
Duration of asthma (n(%) 0-	Turbuhaler®	asthma requiring	symptomatic on a
1vr./1-5vr./5-10vr./>10vr.):		an increase in the	moderate to high
			corticosteroid dose
	Reliever Tx:		(800-1200 mcg/day
emoning othere in the			(000 1200 1109/04)
GROUP 2			
		clinically relevant.	
		List of clinical	
,			
	∠ WK.		
		-	
		•	
		PEF AM	
		<ul> <li>PEF PM</li> </ul>	
Smoking status: NR		<ul> <li>PEF % diurnal</li> </ul>	
		variation	
		● FEV <sub>1</sub>	
		•	
		<ul> <li>RFD</li> </ul>	
		<ul> <li>SAE</li> </ul>	
	Males %: 50 FEV <sub>1</sub> % predicted (mean [range]): 68 (33-105) PEF AM (mean±SD): NR	Participant characteristicscharacteristicsRandomized: 353GROUP 1Analyzed: 353Drug/mcg per d.:Withdrawals: 59SAL/FP 100/500Dosing: fixedTreatmentITT analysis: yesAsthma stage and severity:Moderate to severeBaseline ICS use: non-naïveBaseline ICS use: non-naïveDiskhaler®Withdraw LOE: 7GROUP 1N: 180GROUP 2Age (mean [range]): 45 (16-Diskhaler®75)GROUP 1Males %: 50GROUP 2FEV1 % predicted (mean [range]): 68 (33-105)Dosing: fixedPEF AM (mean±SD): NR Duration of asthma (n(%) 0- 1yr./1-5yr./5-10yr./>10(5)/34(19)/31(17)/105(58)Device: Turbuhaler®Smoking status: NRReliever Tx: salbutamol prn Run-in Tx: usual ICS and salbutamol prn Run-in duration: 2 wk.Males %: 50FEV1 % predicted (mean [range]): 72 (37-109)PEF AM (mean±SD): NR Duration of asthma (n(%) 0- 	Participant characteristicsreportedRandomized: 353GROUP 1Definition ofAnalyzed: 353Drug/mcg per d.:SAL/FP 100/500Withdrawals: 59SAL/FP 100/500Severe =Asthma stage and severity: moderate to severeTreatment duration: 24 wk.asthma requiring emergency hospital treatment.Baseline ICS use: non-naiveDiskhaler®Moderate =GROUP 1 N: 180GROUP 2Diskhaler®Moderate =Age (mean [range]): 45 (16- 75)GROUP 2Drug/mcg per d.: BUD 1600 + PLADosing: fixed Treatment duration: 24 wk.Moderate =PEF AM (meantSD): NR Duration of asthma (n(%) 0- 1yr./1-5yr./5-10yr./>10(5)/34(19)/31(17)/105(58)Reliever Tx: salbutamol prn Run-in Tx: usual ICS and salbutamol prnmedication which the physician considered to be colicically relevant.Males %: 50 FEV % predicted (mean [range]): 72 (37-109) PEF AM (meantSD): NR Duration of asthma (n(%) 0- 1yr./1-5yr./5-10yr./>10(6)/28(16)/28(16)/106(62)Reliever Tx: salbutamol prn Run-in duration: 2 wk.List of clinical outcomes reported: Primary • PEF AMMales %: 50 FEV1 % predicted (mean [range]): 72 (37-109) PEF AM (meantSD): NR Duration of asthma (n(%) 0- 1yr./1-5yr./5-10yr./>*10(6)/28(16)/106(62)Smoking status: NRList of clinical outcomes reported: Primary • PEF PMSmoking status: NRSECOndary • PEF MPEF % diurnal variationSFD • SFN • SFD • SFN • REDSFN • SFN

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 456	GROUP 1	Definition of	Study objective:
Jenkins C	Analyzed: 451	Drug mcg/day:	exacerbation:	To assess the
2006 <sup>93</sup>	Withdrawals: 57	FORM/BUD	Mild exacerbation	efficacy and safety
Pub status:		36/1600	day – a day with	of a higher dose of
Journal article	ITT analysis: ves	Dosing: fixed	one of the	BUD/FORM in
	Asthma stage and severity:	Treatment	following: ≥20%	patients with
No. countries:	symptomatic, moderate	duration: 12 wk.	decrease in	persistent
6	Baseline ICS use: non-naïve	Device:	morning PEF from	symptomatic
No. centers: 54	Buschine loo use. non naive	Turbuhaler®	baseline; night-	asthma.
Design:	GROUP 1	Withdraw LOE:	time awakening(s)	asunna.
randomized,	N: 222			
			due to asthma; or	
parallel, double	<b>Age yr. (mean [range])</b> : 46	GROUP 2	an increase of ≥4	
blind	(13-79)	Drug mcg/day:	inhalations of	
	Males %: 36	FORM/BUD	reliever medication	
Funding:	FEV <sub>1</sub> % predicted:	(separate	over a 24-hr period	
Industry:	PEF AM (mean±SD): NR	inhalers) 36/1600	compared with	
AstraZeneca	Duration of asthma (mean	Dosing: fixed	baseline. Mild	
	[range]): 8 (1-56)	Treatment	exacerbation – two	
	Smoking status: NR	duration: 12 wk.	consecutive mild	
	-	Device: NR	exacerbation days	
	GROUP 2	Withdraw LOE:	of the same type.	
	N: 114		of the same type.	
	Age yr. (mean [range]): 47	GROUP 3	List of clinical	
	(12-79)	Drug mcg/day:		
	Males %: 40	BUD 1600	outcomes	
	FEV <sub>1</sub> % predicted: NR	Dosing: fixed	reported:	
			Primary	
	PEF AM (mean±SD): NR	Treatment	<ul> <li>PEF AM</li> </ul>	
	Duration of asthma (mean	duration: 12 wk.		
	[range]): 10 yr. (1-66)	Device: NR	Secondary	
	Smoking status: NR	Withdraw LOE:	<ul> <li>PM PEF</li> </ul>	
			<ul> <li>FEV<sub>1</sub> %</li> </ul>	
	GROUP 3	Reliever Tx:	predicted	
	<b>N:</b> 115	terbutaline 0.5	<ul> <li>exacerbations</li> </ul>	
	Age yr. (mean [range]): 46	mcg prn		
	(13-74)	Run-in Tx:	DTS	
	Males %: 43	current ICS	<ul> <li>NTS</li> </ul>	
	FEV <sub>1</sub> % predicted: NR	therapy	<ul> <li>total daily</li> </ul>	
	PEF AM (mean±SD): NR	Run-in duration:	symptom	
			score (0-6)	
	Duration of asthma (mean	2 wk.	nighttime	
	[range]): 8 yr. (1-61)		SABA use	
	Smoking status: NR		daytime SABA	
			SFD	
			<ul> <li>RFD</li> </ul>	

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year:	Randomized: 349	GROUP 1	Definition of	Study objective: To
Author Year: Johansson G 2001 <sup>112</sup> <b>Pub status:</b> Journal article <b>No. countries:</b> 6 <b>No. centers:</b> 39 <b>Design:</b> randomized, parallel, double blind, double dummy <b>Funding:</b> Industry: GlaxoSmithKline	Analyzed: 349 Analyzed: 349 Withdrawals: 38 ITT analysis: yes Asthma stage and severity: symptomatic, mild to moderate Baseline ICS use: non-naïve GROUP 1 N: 176 Age yr. (mean±SD): 36±16 Males %: 38 FEV1 % predicted (mean±SD): 77±10 PEF AM (mean±SD): 383±92 Duration of asthma: NR Smoking status: ≤10 pack- year HX GROUP 2 N: 173 Age yr. (mean±SD): 36±17 Males %: 48 FEV1 % predicted (mean±SD): 76±11 PEF AM (mean±SD): 382±94 Duration of asthma: NR Smoking status: ≤10 pack- year HX	GROUP 1 Drug mcg/day: SAL/FP 100/200 Dosing: fixed Treatment duration: 12 wk. Device: Diskhaler <sup>®</sup> Withdraw LOE: 0 GROUP 2 Drug mcg/day: BUD 800 + PLA Dosing: fixed Treatment duration: 12 wk. Device: Diskhaler <sup>®</sup> Withdraw LOE: 1 Reliever Tx: salbutamol prn Run-in Tx: current ICS and salbutamol Run-in duration: 2 wk.	<ul> <li>bernitton of exacerbation: Mild = increased relief medication use. Moderate = additional corticosteroids (inhaled and/or oral). Severe = emergency hospital treatment.</li> <li>List of clinical outcomes reported: Primary</li> <li>PEF AM</li> <li>Secondary</li> <li>PEF PM</li> <li>PEF diurnal variation</li> <li>FEV<sub>1</sub></li> <li>number of exacerbations</li> <li>DTS</li> <li>NTS</li> <li>SFD</li> <li>SFN</li> <li>SABA use</li> <li>AE</li> </ul>	study objective: To compare the efficacy and tolerability of a salmeterol/fluticasone propionate (FP) combination product (50/100 mcg twice daily) with budesonide (BUD) at a four-fold higher microgram dose (400 mcg twice daily) in patients with mild-to- moderate asthma uncontrolled on existing therapy.

			Clinical	
		Treatment	outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 356	GROUP 1	Definition of	Study objective:
Kavuru M	Analyzed: 335	Drug mcg/day:	exacerbation:	To compare the
2000 <sup>81</sup>	Withdrawals: 126	SAL/FP 100/200	Clinical	efficacy and safety
Pub status:		Dosing: fixed	exacerbation –	of SAL/FP 50
Journal article	ITT analysis: yes	Treatment	requiring	mcg/100 mcg in a
	Asthma stage and severity:	duration: 12 wk.	emergency	combination dry
No. countries:	asymptomatic, intermittent to	<b>Device:</b> Diskus <sup>®</sup>	treatment,	powder product
1 (United	moderate	Withdraw LOE: 3	hospitalization, or	administered twice
States)	Baseline ICS use: non-naïve		asthma medication	daily with that of FP
No. centers: 42		GROUP 2	not allowed by	or SAL at the same
Design:	GROUP 1	Drug mcg/day:	protocol.	doses in patients
randomized,	N: 87	FP 200		previously treated
parallel, double	Age yr. (mean [range]): 38	Dosing: fixed	List of clinical	with low doses of
blind, double	(12-70)	Treatment	outcomes	inhaled
dummy	Males %: 59	duration: 12 wk.	reported:	corticosteroids or
,	FEV <sub>1</sub> % predicted (mean): 64	Device: diskhaler	Primary	SAL.
Funding:	<b>PEF AM (mean±SD):</b> 393±98.9	Withdraw LOE: 9	mean change	_
Industry:	Duration of asthma: NR		FEV <sub>1</sub>	
GlaxoSmithKline	Smoking status: NR	GROUP 3	<ul> <li>probability of</li> </ul>	
	••••••••••••••••••	Drug mcg/day:	remaining in	
	GROUP 2	SAL 100	study over	
	N: 85	Dosing: fixed	time	
	Age yr. (mean [range]): 39	Treatment	ume	
	(12-67)	duration: 12 wk.	Secondary	
	Males %: 52	Device: diskhaler	•	
	FEV <sub>1</sub> % predicted (mean): 64	Withdraw LOE:	inean enange	
	PEF AM (mean±SD):	30	in PEF PM	
	374±104.2	50	<ul> <li>% days no</li> </ul>	
	Duration of asthma: NR	GROUP 4	symptoms	
	Smoking status: NR	Drug mcg/day:	% nights no	
	Smoking status: NK	PLA	awakenings	
	GROUP 3	Dosing: fixed	<ul> <li>asthma</li> </ul>	
	N: 86	Treatment	symptoms 0-5	
	Age yr. (mean [range]): 37	duration: 12 wk.	<ul> <li>SABA use</li> </ul>	
		<b>Device:</b> single		
	(12-67) <b>Males %:</b> 51	-		
		drugs Withdraw LOE:		
	FEV <sub>1</sub> % predicted (mean): 64			
	PEF AM (mean±SD): 369±88.1	38		
	Duration of asthma: NR	Della de Tra		
	Smoking status: NR	Reliever Tx:		
		albuterol prn		
	GROUP 4	Run-in Tx: PLA		
	N: 77	Run-in duration:		
	Age yr. (mean [range]): 35	2 wk.		
	(12-66)			
	Males %: 51			
	FEV <sub>1</sub> % predicted (mean): 64			
	PEF AM (mean±SD):			
	382±102.7			
	Duration of asthma: NR			
	Smoking status: NR			

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year:	Randomized: 483	GROUP 1	Definition of	Study objective:
Kelsen SG	Analyzed: 476	Drug mcg/day:	exacerbation:	To evaluate the
1999 <sup>114</sup>	Withdrawals: 97	SAL/BDP 100	Asthma	efficacy of SAL
Pub status:		/400	exacerbation = any	administered via
Journal article	ITT analysis: yes	Dosing: fixed	event requiring	metered-dose
	Asthma stage and severity:	Treatment	treatment with oral	inhaler in the
No. countries:	symptomatic, moderate	duration: 24 wk.	or parenteral	management of
1 (United	Baseline ICS use: non-naïve	Device: MDI	corticosteroids or	asthma in adults
States)		Withdraw LOE:	any other asthma	symptomatic while
No. centers: 34	GROUP 1		medication not	receiving inhaled
Design:	N: 236	GROUP 2	allowed as	BDP at a dosage
randomized,	Age yr. (mean±SD): 42.2±13.8	Drug mcg/day:	concurrent therapy	less than 400 mcg
parallel, double	Males %: 43	BDP 800	during study	daily compared with
blind	FEV <sub>1</sub> % predicted (mean±SD):	Dosing: fixed	participation.	doubling the dose
	64.93±10.1	Treatment		of BDP.
Funding:	PEF AM (mean±SD): NR	duration: 24 wk.		
Industry:	Duration of asthma: NR	Device: MDI	List of clinical	
GlaxoSmithKline	Smoking status: non-smoking	Withdraw LOE:	outcomes reported:	
	GROUP 2	Reliever Tx:		
	N: 240	albuterol	Primary	
	Age yr. (mean±SD): 42.0±12.4 Males %: 35	Run-in Tx: BDP 400 mcg/day and	• FEV <sub>1</sub>	
	FEV <sub>1</sub> % predicted (mean±SD):	albuterol prn	Secondary	
	64.14±10.1	Run-in duration:	• PEF PM	
	PEF AM (mean±SD): NR	2 wk.	DTS	
	Duration of asthma: NR		<ul> <li>exacerbations</li> </ul>	
	Smoking status: non-smoking		<ul> <li>daytime</li> </ul>	
			albuterol use	
			<ul> <li>nightime</li> </ul>	
			awakenings	
			<ul> <li>nighttime</li> </ul>	
			albuterol use	

			Clinical	
<b>a</b>		Treatment	outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 844	GROUP 1	Definition of	Study objective:
Kerwin EM	Analyzed: 844	Drug mcg/day:	exacerbation: NR	To assess the
2008 <sup>61</sup>	Withdrawals: 140	SAL/FP 50/250		effectiveness of
Pub status:		Dosing: fixed	List of clinical	FL/SAL via a single
Journal article	ITT analysis: yes – all who	Treatment	outcomes	inhaler (FSC)
No. countries:	were randomized and received at least one dose of double-	duration: 12 wk. Device: Diskus <sup>®</sup>	reported: Primary	administered once daily compared with
2 (Canada,	blind study medication	Withdraw LOE: 4	• PEF PM %	FP once daily, FSC
United States)	Asthma stage and severity:		• predicted	twice daily, or
No. centers:	symptomatic, intermittent-	GROUP 2	predicted	placebo.
103	severe	Drug mcg/day:	Secondary	pidoobo.
Design:	Baseline ICS use: naïve	SAL/FP 100/200	PEF PM	
randomized,		Dosing: fixed	PEF AM	
parallel, double	GROUP 1	Treatment	<ul> <li>2 hr post-dose</li> </ul>	
blind	<b>N:</b> 210	duration: 12 wk.	PM PEF	
	Age yr. (mean±SD): 33.4±12.9	<b>Device:</b> Diskus <sup>®</sup>	<ul> <li>FEV1</li> </ul>	
Funding:	Males %: 40	Withdraw LOE: 4	<ul> <li>withdrawal</li> </ul>	
Industry:	FEV1 % predicted: 74.4±10.8		due to	
GlaxoSmithKline	PEF AM (mean±SD): 348±5.5	GROUP 3	exacerbation	
	Duration of asthma: > 3 mo	Drug mcg/day:	• 24-h	
	Smoking status: NR	FP 250	symptom	
		Dosing: fixed	score	
	GROUP 2 N: 210	Treatment duration: 12 wk.	<ul> <li>SABA use</li> </ul>	
		<b>Device:</b> Diskus <sup>®</sup>	<ul> <li>withdrawal</li> </ul>	
	Age yr. (mean±SD): 33.5±13.4 Males %: 50	Withdraw LOE:	due to	
	<b>FEV</b> <sub>1</sub> % <b>predicted:</b> 72.8±10.3	6	worsening	
	<b>PEF AM (mean±SD):</b> 349±5.6	0	asthma	
	Duration of asthma: > 3 mo	GROUP 4		
	Smoking status: NR	Drug mcg/day:		
		PLA		
	GROUP 3	Dosing: fixed		
	N: 212	Treatment		
	Age yr. (mean±SD): 31.7±12.7	duration: 12 wk.		
	Males %: 47	Device: single		
	FEV <sub>1</sub> % predicted: 74.5±10.5 PEF AM (mean±SD): 348±5.7	drugs Withdraw LOE:		
	Duration of asthma: > 3 mo	17		
	Smoking status: NR	17		
	ensing outdo. mit	Reliever Tx:		
	GROUP 4	albuterol		
	N: 212	Run-in Tx:		
	Age yr. (mean±SD): 33±13.7	albuterol prn +		
	Males %: 48	PLA		
	FEV1 % predicted: 73.2±10.8	Run-in duration:		
	PEF AM (mean±SD): 344±5.0	2 wk.		
	Duration of asthma: > 3 mo			
	Smoking status: NR			

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 60	GROUP 1	Definition of	Study objective:
Kips JC 2000 <sup>138</sup>	Analyzed: NR	Drug mcg/day:	exacerbation:	To compare in
Pub status:	Withdrawals: NR	FORM/BUD	Mild – 1) morning	patients with
Journal article		24/200	or evening PEF	asthma the effect of
	ITT analysis: yes	Dosing: fixed	>20% below	a 1-yr treatment
No. countries:	Asthma stage and severity:	Treatment	baseline; 2) rescue	with budesonide
3	asymptomatic, intermittent to	duration: 52 wk.	terbutaline use of	(100 mcg, twice
No. centers: 3	severe	Device:	more than four	daily) plus the LA
Design:	Baseline ICS use: non-naïve	Turbuhaler <sup>®</sup>	inhalations per 24h	β2-agonist
randomized,		Withdraw LOE:	above baseline; 3)	formoterol (12 mcg,
parallel, double	GROUP 1	NR	awakenings due to	twice daily) versus
blind	N: NR		asthma. Severe -	budesonide (400
	Age yr. (mean [range]): 34.7	GROUP 2	if OCS were	mcq, twice daily) on
Funding:	(19-59)	Drug mcg/day:	required either as	markers of airway
Industry:	Males %: 41.4	BUD 800 + PLA	judged by the	inflammation in
AstraZeneca	FEV <sub>1</sub> % predicted (mean±SE):	Dosing: fixed	investigator or	induced sputum.
, lott all official	84.4±3.6	Treatment	after a decrease in	
	PEF AM (mean±SE):	duration: 52 wk.	morning or	
	414.7±22.3	Device:	evening peak flow	
	Duration of asthma: ≥6 mo.	Turbuhaler®	by more than 30%	
	Smoking status: NR	Withdraw LOE:	below baseline on	
	omoking otatao. Ark	NR	two consecutive	
	GROUP 2		days.	
	N: NR	Reliever Tx:	uuyo.	
	Age yr. (mean [range]): 37.6	terbutaline	List of clinical	
	(19-69)	Run-in Tx: BUD	outcomes	
	Males %: 38.7	800 mcg bid +	reported:	
	FEV <sub>1</sub> % predicted (mean±SE):	terbutaline prn	Primary	
	82.2±2.9	Run-in duration:	•	
	PEF AM (mean±SE):	4 wk.		
	396.3±18.6	4 WK.	clinical	
	<b>Duration of asthma:</b> ≥6 mo.		outcomes	
			0	
	Smoking status: NR		Secondary	
			<ul> <li>FEV<sub>1</sub> %</li> </ul>	
			predicted	
			<ul> <li>mild</li> </ul>	
			exacerbations	
			<ul> <li>severe</li> </ul>	
			exacerbations	
			<ul> <li>episode-free</li> </ul>	
			days	
			-	

- · ·		Treatment	outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 466	GROUP 1	Definition of	Study objective: To
Koenig SM	Analyzed: 466	Drug mcg/day:	exacerbation:	determine whether
2008 <sup>95</sup>	Withdrawals: 145	SAL/FP (BHR)	Exacerbation –	adding a LABA to an
Pub status:		Class 1: PLA;	worsening asthma	ICS would control
Journal article	ITT analysis: no	Class 2 to 4:	for which	bronchial
	Asthma stage and severity:	100/200; Class 3:	treatment with	hyperresponsiveness
No. countries:	NR, moderate	100/500; Class 4:	medication other	(BHR) at an overall
3	Baseline ICS use: non-naïve	100/1000	than the double-	lower dose of ICS
No. centers: 55		Dosing: variable	blind study drugs	when titration of
Design:	GROUP 1	Treatment	or study-provided	medication was
randomized,	<b>N</b> : 156	duration: 40 wk.	albuterol was	based upon the
parallel, double	Age yr. (mean [range]): 34.8	Device: diskhaler	necessary, and	assessment of
blind	(12-81)	Withdraw LOE:	was treated with	routine clinical
	Males %: 38	NR	the prednisone	measures with or
Funding:	FEV <sub>1</sub> % predicted			without the
Industry:	(mean±SD): 77±119.9	GROUP 2	List of clinical	measurement of
GlaxoSmithKline	Mean PEF AM (mean±SD):	Drug mcg/day:	outcomes	BHR.
	401±168.6	FP Class 1: PLA;	reported:	
	Duration of asthma: > 3 mo	Class 2: 200;	Primary	
	Smoking status: NR	Class 3: 500;	<ul> <li>average daily</li> </ul>	
		Class 4: 1000	ICS dose	
	GROUP 2	Dosing: variable		
	<b>N:</b> 156	Treatment	Secondary	
	Age yr. (mean [range]): 34.8	duration: 40 wk.	PEF AM	
	(12-81)	Device: diskhaler	PEF PM	
	Males %: 36	Withdraw LOE:	<ul> <li>pre-dose</li> </ul>	
	FEV <sub>1</sub> % predicted	NR	FEV <sub>1</sub>	
	(mean±SD): 79±114.9		SFD	
	Mean PEF AM (mean±SD):	GROUP 3	RFD	
	409±167.4	Drug mcg/day:	SFD	
	Duration of asthma: > 3 mo	FP Class 1: PLA;		
	Smoking status: NR	Class 2: 200;		
	C	Class 3: 500;	<ul> <li>SABA use</li> </ul>	
	GROUP 3	Class 4: 1000		
	<b>N</b> : 154	Dosing: variable		
	Age yr. (mean [range]): 33.2	Treatment		
	(12-72)	duration: 40 wk.		
	Males %: 49	Device: diskhaler		
	FEV <sub>1</sub> % predicted	Withdraw LOE:		
	(mean±SD): 79±119.1	NR		
	Mean PEF AM (mean±SD):			
	407±161.3	Reliever Tx:		
	Duration of asthma: > 3 mo	albuterol		
	Smoking status: NR	Run-in Tx:		
		continued		
		treatment with		
		SABA,		
		anticholinergic, or		
		ICS		
		Run-in duration:		
		2 wk.		

		Treatment	Clinical	
Study	Participant characteristics			Notes
Study Author Year: Koopmans JG 2006 <sup>78</sup> Pub status: Journal article No. countries: 1 (The Netherlands) No. centers: 1 Design: randomized, parallel, double blind Funding: Industry: GlaxoSmithKline	Participant characteristics Randomized: 54 Analyzed: 50 Withdrawals: 4 ITT analysis: no Asthma stage and severity: symptomatic, mild-moderate Baseline ICS use: non-naïve GROUP 1 N: 27 Age yr. (median [range]): 32 (21-59) Males %: 37 FEV <sub>1</sub> % predicted (mean±SD): 92.6±16 Mean PEF AM (mean±SD): 418±102 Duration of asthma: NR Smoking status: all non- smoking GROUP 2 N: 23 Age yr. (median [range]): 32 (19-57) Males %: 30 FEV <sub>1</sub> % predicted (mean±SD): 93.1±16.1 Mean PEF AM (mean±SD): 422±102 Duration of asthma: NA Smoking status: all non- smoking	Treatment characteristics GROUP 1 Drug mcg/day: SAL/FP 100/500 Dosing: fixed Treatment duration: 52 wk. Device: Diskus <sup>®</sup> Withdraw LOE: 0 GROUP 2 Drug mcg/day: FP 500 Dosing: fixed Treatment duration: 52 wk. Device: Diskus <sup>®</sup> Withdraw LOE: 1/4 Reliever Tx: salbutamol Run-in Tx: P1: 2 wk. steroid washout; P2: 4 wk. FP 250 mcg bid Run-in duration: 6 wk.	outcomes reported Definition of exacerbation: NR List of clinical outcomes reported: Primary • No primary clinical outcomes Secondary • PEF PM • FEV1 % predicted • DTS • NTS	Notes Study objective: To investigate over a 1 year treatment period whether the improved clinical outcomes resulting from adding SAL to FP are accompanied by an additional effect on bronchial inflammation.

		-	Clinical	
Otraska.	Deutiein ent ek ene stenisties	Treatment	outcomes	Natas
Study	Participant characteristics	characteristics	reported	Notes
Author Year: Kuna P 2007 <sup>129</sup>	Randomized: 3,335	GROUP 1	Definition of	Study objective:
	Analyzed: 3,321	Drug mcg/day:	exacerbation:	To compare
Pub status:	Withdrawals: 149	FORM/BUD	Severe –	BUD/FORM for
Journal article		12/400	deterioration in	maintenance and
	ITT analysis: no	Dosing: variable	asthma resulting in	relief with SAL/FP
No. countries:	Asthma stage and severity:	Treatment	hospitalization or	and a fixed
16	symptomatic, intermittent to	duration: 26 wk.	ER treatment, or	maintenance dose
No. centers:	moderate	Device:	the need for oral	of BUD/FORM, both
235	Baseline ICS use: non-naïve	Turbuhaler <sup>®</sup>	steroids ≥3 days	with terbutaline for
Design:		Withdraw LOE:	(as judged by the	relief
randomized,	GROUP 1	NR	investigator). Mild	
parallel, double	<b>N:</b> 1,103		<ul> <li>two consecutive</li> </ul>	Additional Details:
blind	Age yr. (mean±SD): 38±17	GROUP 2	mild exacerbation	SMART <sup>®</sup> study
	Males %: 43	Drug mcg/day:	days. Mild	
Funding:	FEV <sub>1</sub> % predicted (mean±SD):	FORM/BUD	exacerbation day –	
Industry:	72±14	24/800	a day with any one	
AstraZeneca	Mean PEF AM (mean): 337	Dosing: fixed	of the following:	
	Duration of asthma: NR	Treatment	morning PEF	
	Smoking status –	duration: 26 wk.	≥20% below	
	never/prev/current (n):	Device:	baseline, daily as-	
	873/178/56	Turbuhaler®	needed medication	
	013/110/30	Withdraw LOE:	use ≥2 inhalations	
	GROUP 2	NR	above baseline or	
	N: 1,099		a night with an	
	Age yr. (mean±SD): 38±17	GROUP 3	asthma-related	
	Males %: 41	Drug mcg/day:		
	FEV <sub>1</sub> % predicted (mean $\pm$ SD):	SAL/FP 100/500	awakening.	
	73±14	Dosing: fixed	List of clinical	
	Mean PEF AM (mean): 335	Treatment	outcomes	
	Duration of asthma: NR	duration; 26 wk.	reported:	
	Smoking status –	Device: MDI	Primary	
	never/prev/current (n):	Withdraw LOE:	<ul> <li>time to first</li> </ul>	
	865/169/71	NR	severe	
			exacerbation	
	GROUP 3	Reliever Tx:		
	<b>N:</b> 1,119	terbutaline prn	Secondary	
	Age yr. (mean±SD): 38±17	Run-in Tx:	<ul> <li>PEF PM</li> </ul>	
	Males %: 43	regular ICS and	<ul> <li>FEV1</li> </ul>	
	FEV <sub>1</sub> % predicted (mean±SD):	terbutaline	<ul> <li>total no.</li> </ul>	
	73±14	Run-in duration:	severe	
	Mean PEF AM (mean): 338	2 wk.	exacerbations	
	Duration of asthma: NR		<ul> <li>total no. mild</li> </ul>	
	Smoking status –		exacerbations	
	never/prev/current (n):			
	904/165/54		<ul> <li>symptom</li> </ul>	
			score	
			SABA use	
			• NTA	
			<ul> <li>SFD</li> </ul>	
			<ul> <li>RFD</li> </ul>	

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year:	Randomized: 617	GROUP 1	Definition of	Study objective:
Kuna P 2006 <sup>45</sup>	Analyzed: 616	Drug mcg/day:	exacerbation: NR	To compare the
Pub status:	Withdrawals: 61	FORM/BUD		efficacy and safety
Journal article		12/200	List of clinical	of a low dose of
	ITT analysis: yes	Dosing: fixed	outcomes	BUD/FORM (80/4.5
No. countries:	Asthma stage and severity:	Treatment	reported:	mcg, 2 inhalations)
8	symptomatic, mild, moderate	duration: 12 wk.	Primary	administered once
No. centers: 61	Baseline ICS use: non-naïve	Device:	• PEF AM	daily with that of
Design:	Dasenne ICS use. non-naive	Turbuhaler <sup>®</sup>		twice-daily
randomized,	GROUP 1	Withdraw LOE:	Secondary	BUD/FORM (80/4.5
	N: 202	10	Secondary	
parallel, double		10	PEF PM	mcg, 1 inhalation
blind	Age yr. (mean [range]): 45.8		<ul> <li>FEV<sub>1</sub></li> </ul>	administered in the
-	(18-80)	GROUP 2	<ul> <li>symptoms</li> </ul>	morning and the
Funding:	Males %: 41	Drug mcg/day:	score 0-3	evening) and a
Industry:	FEV <sub>1</sub> % predicted (mean	FORM/BUD	<ul> <li>% medication</li> </ul>	corresponding
AstraZeneca	[range]): 79.3 (37-115)	12/200	free days	once-daily dose of
	PEF AM (mean [range]): 356	Dosing: fixed	• NTA	BUD (200 mcg, 1
	(115-648)	Treatment	<ul> <li>asthma-</li> </ul>	inhalation in the
	Duration of asthma (mean	duration: 12 wk.	control days	evening) in patients
	[range]): 11.5 (1-63)	Device:	control dayo	with mild to
	Smoking status: <10pack-yr	Turbuhaler®		moderate asthma.
		Withdraw LOE: 5		
	GROUP 2			
	N: 207	GROUP 3		
	Age yr. (mean [range]): 43.9	Drug mcg/day:		
	(19-80)	BUD 200		
	Males %: 38	Dosing: fixed		
	FEV <sub>1</sub> % predicted (mean	Treatment		
	[range]): 77.9 (23-123)	duration: 12 wk.		
	PEF AM (mean [range]): 351	Device:		
	(173-692)	Turbuhaler®		
	Duration of asthma (mean	Withdraw LOE:		
	[range]): 12.2 (0-50)	11		
	Smoking status: ≤10 pack-yr			
		Reliever Tx:		
	GROUP 3	terbutaline sulfate		
	N: 207	or another		
	Age yr. (mean (range)): 45.1	preferred SABA		
	(18-78)	preiened SABA		
	(10-70) Males %: 44	Run-in Tx: BUD		
	FEV <sub>1</sub> % predicted (mean	200 mcg/day		
	[range]): 78.3 (38-119)	Run-in duration:		
		2 wk.		
	<b>PEF AM (mean [range]):</b> 368	∠ WK.		
	(200-500)			
	Duration of asthma (mean			
	[range]): 10.6 (1-58) Smoking status: ≤10pack-yr			

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 467	GROUP 1	Definition of	Study objective: to
Lalloo UG	Analyzed: 467	Drug mcg/day:	exacerbation:	evaluate the efficacy
2003 <sup>113</sup>	Withdrawals: 37	FORM/BUD	Mild = two	and safety of low-dose
Pub status:		12/200	consecutive mild	budesonide/formoterol,
Journal article	ITT analysis: yes	Dosing: fixed	exacerbation days	80/4.5 mcg bid in a
	Asthma stage and severity:	Treatment	(of the dame	single inhaler
No. countries:	intermittent-moderate	duration: 12 wk.	criterion). Severe	compared with an
7	Baseline ICS use: non-naïve	Device:	= nighttime	increased dose of
No. centers:		Turbuhaler®	awakening due to	budesonide, 200 mcg
51	GROUP 1	Withdraw LOE:	asthma, a 20%	bid, in adult patients
Design:	N: 230	NR	decrease in PEF	with mild-to-moderate
randomized.	Age yr. (mean [range]): 42		from baseline, or	asthma not fully
parallel, double	(18-77)	GROUP 2	more than four	controlled on low
blind	Males %: 44	Drug mcg/day:	inhalations of	doses of ICS.
	FEV <sub>1</sub> % predicted (mean	BUD 400	reliever	
Funding:	[range]): 82 (38-117)	Dosing: fixed	medication over a	
Industry:	<b>PEF AM (mean [range]):</b> 362	Treatment	24-hr period.	
AstraZeneca	(153-665)	duration: 12 wk.		
/ loti uzeneou	Duration of asthma ((mean	Device: NR		
	[range]): 12 yr. (0-47)	Withdraw LOE:	List of clinical	
	Smoking status: < 10		outcomes	
	pack/years-yr	Reliever Tx:	reported:	
		terbutaline or	Primary	
	GROUP 2	salbutamol	<ul> <li>mean change</li> </ul>	
	N: 237	(patient	PEF AM	
	Age yr. (mean [range]): 40	preference)		
	(18-78)	Run-in Tx: BUD	<ul> <li>mean change PEF PM</li> </ul>	
	Males %: 41	100 mcg bid		
	FEV <sub>1</sub> % predicted (mean	Run-in duration:	Casandami	
	[range]): 81 (42-137)	2 wk.	Secondary	
	PEF AM (mean [range]): 362	2 WK.	<ul> <li>mean change in FEV<sub>1</sub></li> </ul>	
	(109-643)		<ul> <li>mean change</li> </ul>	
	Duration of asthma (mean		in FEV₁ %	
	[range]): 11 yr. (0-53)		predicted	
	Smoking status: < 10 pack-yr		DTS	
			NTS	
			<ul> <li>asthma</li> </ul>	
			aggravation	
			Reliever use	
			<ul> <li>nightime</li> <li>awakaninga</li> </ul>	
			awakenings	
			FVC	

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Langton Hewer S 1995 <sup>83</sup> Pub status:	Randomized: 23 Analyzed: 23 Withdrawals: 2	GROUP 1 Drug mcg/day: SAL/ICS 200/(ND) high	Definition of exacerbation: NR List of clinical	Study objective: To evaluate the efficacy and safety of SAL 100 mcg bid
Journal article <b>No. countries:</b> 1 (United Kingdom) <b>No. centers:</b> 1 <b>Design:</b> randomized,	ITT analysis: yes Asthma stage and severity: symptomatic, severe Baseline ICS use: non-naïve GROUP 1 N: 11 Age yr. (mean [range]): 15	dose Dosing: fixed Treatment duration: 8 wk. Device: diskhaler Withdraw LOE: 0 GROUP 2	outcomes reported: Primary • PEF AM • PEF AM % predicted • PEF PM • PEF PM %	in a group of children considered to have chronic severe asthma.
parallel, double blind <b>Funding:</b> Institution	(12-17) Males %: 55 FEV <sub>1</sub> % predicted: NR PEF AM (mean±SD): NR Duration of asthma: 13 Smoking status: NR GROUP 2	Drug mcg/day: ICS (ND) high dose Dosing: fixed Treatment duration: 8 wk. Device: diskhaler Withdraw LOE: 0	<ul> <li>FEF FM 78 predicted</li> <li>Secondary</li> <li>FEV1</li> <li>FEV1 % predicted AM</li> <li>nighttime symptom</li> </ul>	
	N: 12 Age yr. (mean [range]): 14 (12-16) Males %: 83 FEV <sub>1</sub> % predicted: Fig 1 PEF AM (mean±SD): NR Duration of asthma: NR Smoking status: NR	Reliever Tx: NR Run-in Tx: current dose ICS (ND) Run-in duration: 2 wk.	score exacerbations SFD SFN	

			Clinical	
•		Treatment	outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 167	GROUP 1	Definition of	Study objective:
Lemanske RF	Analyzed: 167	Drug mcg/day:	exacerbation:	To determine
2001 <sup>79</sup>	Withdrawals: 23	SAL/TAA 100/800	NR	whether ICS
Pub status:		Dosing: fixed		therapy can be
Journal article	ITT analysis: yes	Treatment	List of clinical	reduced or
	Asthma stage and severity:	duration: 24 wk.	outcomes	eliminated in
No. countries:	mixed asymptomatic and	Device: MDI	reported:	patients with
1 (United	symptomatic, mild	Withdraw LOE: 4	Primary	persistent asthma
States)	Baseline ICS use: non-naïve		<ul> <li>Time to</li> </ul>	after adding a long-
No. centers: 6		GROUP 2	treatment	acting β <sub>2</sub> -agonist to
Design:	GROUP 1	Drug mcg/day:	failure	their treatment
randomized,	N: 74	SAL/TAA 100/400		regimen.
parallel, triple	Age yr. (mean±SD):	Dosing: fixed	Secondary	
blind, double	35.7±12.25	Treatment	PEF PM	Additional Details:
dummy	Males %: 53	duration: 24 wk.	<ul> <li>FEV1</li> </ul>	Triamcinolone
aanniy	FEV <sub>1</sub> % predicted (mean±SD):	Device: MDI		reduction phase
Funding:	73.81±(10.43)	Withdraw LOE:	DTS	weeks 3-10,
Government	PEF AM (mean±SD):	12	NTS	triamcinolone
and Industry	445.6±124.2	12	<ul> <li>PC<sub>20</sub></li> </ul>	elimination phase
(various)	Duration of asthma: NR	GROUP 3		weeks 11-18.
(various)				weeks 11-18.
	Smoking status: <10 pack-yr	Drug mcg/day:		
	and no smoking in past year	TAA 400		
		Dosing: fixed		
	GROUP 2	Treatment		
	N: 74	duration: 24 wk.		
	Age yr. (mean±SD):	Device: MDI		
	34.23±10.8	Withdraw LOE:		
	Males %: 47	1		
	FEV <sub>1</sub> % predicted (mean±SD):			
	73.78±11.24	Reliever Tx:		
	PEF AM (mean±SD):	albuterol		
	425.3±125.3	Run-in Tx: TAA		
	Duration of asthma: NR	400 mcg bid and		
	Smoking status: <10 pack/yr.	albuterol prn		
	and no smoking in past year	Run-in duration:		
		6 wk.		
	GROUP 3			
	<b>N:</b> 19			
	Age yr. (mean±SD):			
	35.58±14.39			
	Males %: 42			
	FEV <sub>1</sub> % predicted (mean±SD):			
	72.47±12.50			
	PEF AM (mean±SD):			
	398.4±110.3			
	Duration of asthma: NR			
	Smoking status: <10 pack-yr.			
	and no smoking in past year			

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Leuppi JD 2003 <sup>189</sup> Pub status: Journal article No. countries: 1 (Switzerland) No. centers: 32 Design: randomized, parallel, open label Funding: Industry: AstraZeneca	Randomized: 142 Analyzed: 127 Withdrawals: 2 ITT analysis: no Asthma stage and severity: mixed asymptomatic and symptomatic, intermittent to severe Baseline ICS use: non-naïve GROUP 1 N: 58 Age yr. (mean/median [range]): 47.6/47.7 (12-78) Males %: 58.6 FEV <sub>1</sub> % predicted (mean±SD): 80.3±19.4 PEF AM (mean±SD): NR Duration of asthma: >6months Smoking status: NR GROUP 2 N: 69 Age yr. (mean/median [range]): 44.7/41.6 (13-74) Males %: 40.6 FEV <sub>1</sub> % predicted (mean±SD): 78.4±17.1 PEF AM (mean±SD): NR Duration of asthma: >6months Smoking status: NR	GROUP 1 Drug mcg/day: FORM/BUD 24/800 Dosing: fixed Treatment duration: 12 wk. Device: Turbuhaler <sup>®</sup> Withdraw LOE: 1 GROUP 2 Drug mcg/day: FORM/BUD, 12- 48 /400-1600 Dosing: variable Treatment duration: 12 wk. Device: Turbuhaler <sup>®</sup> Withdraw LOE: 0 Reliever Tx: terbutaline Run-in Tx: FORM/BUD 24/800 daily + terbutaline prn Run-in duration: 4 wk.	Definition of exacerbation: worsening asthma requiring OCS List of clinical outcomes reported: Primary • no. treatment successes • no. treatment failures Secondary • FEV <sub>1</sub> • PEF AM • PEF PM • asthma symptoms • mini - AQLQ • SABA use • NTA • change in variable dose • asthma severity	Study objective: To compare self-guided adjustable maintenance dosing with budesonide/formoterol in a single inhaler with fixed dosing. Additional Details: NA

			Clinical	
		Treatment	outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year: Li	Randomized: 50	GROUP 1	Definition of	Study objective:
X 1999 <sup>86</sup>	Analyzed: 45	Drug mcg/day:	exacerbation: NR	To determine the
Pub status:	Withdrawals: 5	SAL/BUD/BDP		effects of 12-wk
Journal article		200-500/	List of clinical	treatment with SAL
	ITT analysis: no	100/100-500	outcomes	on "allergic"
No. countries:	Asthma stage and severity:	Dosing: fixed	reported:	inflammation of the
1 (Australia)	symptomatic, mild-moderate	Treatment	Primary	airways, as well as
No. centers:	Baseline ICS use: non-naïve	duration: 12 wk.	<ul> <li>bronchial</li> </ul>	clinical status, in a
NR		Device: diskhaler	biopsy results	clinically relevant
Design:	GROUP 1	Withdraw LOE: 2	biopoy reduito	group.
randomized,	<b>N</b> : 13		Secondary	group.
parallel, double	Age yr. (mean [range]): 38	GROUP 2	<ul> <li>exacerbation</li> </ul>	
blind	(20-70)	Drug mcg/day:	leading to	
biind	Males %: 61.5	FP/BUD/BDP	withdrawal	
Funding:	FEV <sub>1</sub> % predicted (median	200-500/200/100-		
Industry:	[range]): 84 (63-106)	500	• PD <sub>20</sub>	
GlaxoSmithKline	<b>PEF AM (mean [range]):</b> 474	Dosing: fixed		
	(301-625)	Treatment		
	Duration of asthma: NR	duration: 12 wk.		
	Smoking status: all	<b>Device:</b> diskhaler		
	nonsmokers	Withdraw LOE: 0		
	Honsmokers			
	GROUP 2	GROUP 3		
	<b>N</b> : 16	Drug mcg/day:		
	Age yr. (mean [range]): 42	ICS 100-500		
	(22-63)	Dosing: fixed		
	Males %: 68.8	Treatment		
	FEV <sub>1</sub> % predicted (median	duration; 12 wk.		
	[range]): 80 (61-102)	<b>Device:</b> diskhaler		
	<b>PEF AM (mean [range]):</b> 420	Withdraw LOE:		
		1		
	(341-531) Duration of asthma: NR	I		
		Poliovor Ty:		
	Smoking status: all nonsmokers	Reliever Tx:		
	HUNSHIUKEIS	albuterol prn		
		Run-in Tx: ICS at		
	GROUP 3	pre-study dose up		
	N: 16	to 500 mcg BDP		
	Age yr. (mean [range]): 33	or BUD +		
	(22-68)	albuterol 200 mcg		
	Males %: 43.8	prn		
	FEV <sub>1</sub> % predicted (median	Run-in duration:		
	[range]): 83 (61-109)	2-6 wk.		
	PEF AM (mean [range]): 404			
	(280-623)			
	•			
	nonsmokers			
	Duration of asthma: NR Smoking status: all			

Study Author Year: Lundbäck B 2006 <sup>84</sup> Pub status: Journal article	Participant characteristics Randomized: 282 Analyzed: 282	Treatment characteristics GROUP 1	outcomes reported	Notes
Author Year: Lundbäck B 2006 <sup>84</sup> Pub status:	Randomized: 282 Analyzed: 282			
Lundbäck B 2006 <sup>84</sup> <b>Pub status:</b>	Analyzed: 282	GROUP 1	Description of the second s	
2006 <sup>84</sup> Pub status:	-		Definition of	Study objective:
Pub status:		Drug mcg/day:	exacerbation: any	To assess asthma
	Withdrawals: 19	SAL/FP 100/500	deterioration in	control using
Journal article		Dosing: fixed	asthma that	salmeterol plus FP
	ITT analysis: no	Treatment	required an	in combination
Ne equatrica.	Asthma stage and severity:	duration: 52 wk.	increase in rescue	(SFC) versus
No. countries:	symptomatic, mild-moderate Baseline ICS use: naïve &	Device: diskhaler Withdraw LOE: 0	medication use	salmeterol or FP as
1 (Sweden) No. centers: 3	non-naïve		(beta-agonist) over that used during	monotherapy in patients with mild to
Design:	non-naive	GROUP 2	the run-in period of	moderate asthma.
randomized,	GROUP 1	Drug mcg/day:	>6 puffs/day for ≥2	moderate astima.
parallel, double	N: 95	FP 500	consecutive days,	
blind	Age yr. (mean±SD): 39.9±11.9	Dosing: fixed	or and increase of	
	Males %: 34	Treatment	≥2 doses/day in	
Funding:	FEV <sub>1</sub> % predicted (mean):	duration: 52 wk.	regular inhaled	
Industry:	92.1	Device: diskhaler	medication (study	
GlaxoSmithKline	PEF AM (mean±SD): NR	Withdraw LOE: 0	medication or	
	Duration of asthma: NR		additional ICS) for	
	Smoking status (% current):	GROUP 3	≥2 days by the	
	14	Drug mcg/day:	patient's own	
		SAL 100	decision, or ≥2	
	GROUP 2	Dosing: fixed	days when asthma	
	<b>N</b> : 92	Treatment	symptoms	
	Age yr. (mean±SD): 39.1±12.0	duration; 52 wk.	prevented the	
	Males %: 42	Device: diskhaler	patient's work or	
	FEV <sub>1</sub> % predicted (mean): 93	Withdraw LOE:	normal activities.	
	PEF AM (mean±SD): NR Duration of asthma: NR	0	List of alimical	
	Smoking status (% current):	Reliever Tx:	List of clinical outcomes	
	12	salbutamol dry	reported:	
	12	powder (0.2 mg)	Primary	
	GROUP 3	or salbutamol	% pts required	
	N: 95	aerosol (0.1 mg)	increase in	
	Age yr. (mean±SD): 40.7±12.3	Run-in Tx: P1:	study	
	Males %: 37	previous therapy;	medication	
	FEV <sub>1</sub> % predicted (mean):	P2: ICS reduced		
	94.9	to BUD 400 mcg	Secondary	
	PEF AM (mean±SD): NR	Run-in duration:	PEF AM	
	Duration of asthma: NR	8 wk.	PEF diurnal	
	Smoking status (% current):		variation	
	17		<ul> <li>FEV<sub>1</sub></li> </ul>	
			• FVC	
			<ul> <li>no. pts with ≥</li> </ul>	
			2	
			exacerbations	
			SFN	
			SFD	
			<ul> <li>PC<sub>20</sub></li> </ul>	
			RFD	
			RFN	

2006 <sup>100 -</sup> Withdrawals: 61       FORWEUD 6/200       One or serveral of and cost-effectiveness of and cost-effectivenes of and cost-effectivenes of and cost-effe				Clinical	
Author Year: Lundborg M 2006 <sup>100</sup> Randomized: 491 Analyzed: 489       GROUP 1       Definition of exacerbation: Dosing: variable (also relief med)       Definition of exacerbation: Dosing: variable (also relief med)       Study objectiv row evaluate effinition of exacerbation: Dosing: variable (also relief med)       Definition of exacerbation: To evaluate effinition of exacerbation: Dosing: variable (also relief med)       Study objectiv row evaluate effinition of exacerbation: Dosing: variable (also relief med)       Definition of exacerbation: To evaluate effinition of exacerbation: Dosing: variable (also relief med)       Study objectiv row exacerbation: To evaluate effinition of exacerbation: Dosing: variable (also relief med)       Study objectiv row exacerbation: Treatment         No. centries: Parallel open label       ITT analysis: no symptomatic (75% stable, intermittent, moderate Baseline ICS use: non-naive Baseline ICS use: 10 pack-yr       Drug mcg/day: FORM/BUD With Dosing: variable (also relief med)       Drug mcg/day: the study because of need of added outcomes reported: PEF AM (meantSD): NR Borustion of asthma (meantSD): NR Smoking status: ≤ 10 pack-yr       Trethubale <sup>®</sup> Withdraw LCE: NR       List of clinical outcomes reported: PEF AM (meantSD): NR Borustion of asthma (meantSD): NR Smoking status: ≤ 10 pack-yr       NR       List of clinical outcomes reported: PEF AM (meantSD): NR Smoking status: ≤ 10 pack-yr       NR       List of clinical outcomes reported: PEF AM (meantSD): NR Smoking status: ≤ 10 pack-yr       NR       List of clinical outcomes rep					
Lundborg M 2006 <sup>100</sup> Withdrawals: 61 Pub status: Journal article Journal article Journ					
2006 <sup>190</sup> Withdrawals: 61       FORM/BUD 6/200       One or serveral of additional discrete with adsymptomatic and symptomatic and symptomatic and symptomatic (75% stable, intermittent, moderate besign: intermittent, moderate baseline (C5% stable, intermittent, moderate barallel, open label       FORM/BUD additional additional dose 1.2 x daily plus additional dose 1.2 x daily plus additional dose 3.2 x daily plus additional dose 3.8 needed core of the following: an and cost-effectiveness of additional dose 1.2 x daily plus additional dose 3.8 needed core dose					
Pub status:       Journal article       ITT analysis: no       Dosing: variable       the following: an asthma-related asymptomatic and mixed, symptomatic and systable, symptomatic 75% stable, symptomatic 75% stable, symptomatic 75% stable, intermittent, moderate       Desig: variable       the following: an asthma-related asymptomatic and mixed, symptomatic 75% stable, bavies:       the following: an asthma-related asymptomatic and mixed, symptomatic 75% stable, bavies:       the following: an asthma-related asymptomatic and mixed, symptomatic 75% stable, bavies:       the following: an asthma-related asymptomatic and mixed asymptom asymptom asymptom asymptom asymptom asymptom asymptom asymptom and asymptom asymptom and asymptom asymptom asymptom and asymptom a	Lundborg M	-			To evaluate efficacy
Journal article Journal articl		Withdrawals: 61			
Asthma stage and severity:     Treatment     serious adverse     maintenance (o event, treatment at medical care       No. countries:     symptomatic (75% stable, symptomatic (75% stable, intermittent, moderate     Device:     a medical care     a medical care       randomized, parallel, open label     Baseline ICS use: non-naïve     Turbuhaler <sup>®</sup> methiled     compared with bronchodilators, use of ICS or OCS     compared with higher fixed dos       Funding:     Age yr. (mean±SD): 39.7±19.6     GROUP 2     Drug mcg/day: for RN/BUD 9t/do     of a sathma outration of asthma (mean±SD): NR     GROUP 3     For RM/BUD 9t/do     of a sathma bronchodilators, withdrawal from withdrawal from     For RM/BUD 9t/do       NR     Beseline ICS use: non-naïve     For RM/BUD 9t/do     of a sathma and/or withdrawal from     For RM/BUD 9t/do       Industry:     Males %: 43     For RM/BUD 9t/do     of a sathma and/or withdrawal from     for a dded asthma       Smoking status: ≤ 10 pack-yr     N: NR     GROUP 3     Primary     For RM/BUD       NR     Age yr. (mean±SD): NR     Daviso: 96.5±15.2     Daviso: 96.5±15.2     Picter Tx: mo.     mo.       Smoking status: ≤ 10 pack-yr     For RM/BUD     Reliver T X: mo.     mo.     score       Males %: :49     For M/Meantso     Parenteral or nebulised     score       FU, % predicted (mean±SD):     NR     Reliver T X: mo.     mo. <td></td> <td></td> <td></td> <td></td> <td></td>					
No. countries: 1 (Sweden)       mixed asymptomatic (75% stable, symptomatic (75% stable, intermittent, moderate Baseline ICS use: non-naïve label       duration: 24 wk. Device: Turbuhaler®       event, treatment at a medical care centre with parallel, open label       dose 1-2x daily moderate Baseline ICS use: non-naïve Baseline ICS use: non-naïve Baseline ICS use: non-naïve label       duration: 24 wk. Device: Turbuhaler®       event, treatment at a medical care bronchodilators, use of ICS or OCS Drug mcg/day: FORM/BUD 9400 Dosing: variable maintenance free/twithdraw LOE: NR       mebulised bronchodilators, use of ICS or OCS Drug mcg/day: FORM/BUD 9400 Dosing: variable maintenance free/twithdrawal from the study because of need of added astma maintenance free/twither withdrawal from the study because free/twither withdrawal from the study because free/twither maintenance free/twither withdrawal Criment duration: 24 wk. Device: Turbuhaler®       event, treatment at a medical care centre with parenteral or ast need for extra maintenance free/twither withdrawal from the study because free/twither withdrawal Criment duration: 24 wk. Device: NR       event, treatment at a medical care centre with a mebulised bronchodilators, use of ICS Run-in duration: free/twither withdraw LOE: NR       withdrawal from the study because free/twither withdraw LOE: NR       control vexcerbation free/tree therapy.         N: NR Age yr. (mean±SD): NR Smoking status: ≤ 10 pack-yr       Reliver Tx: PEF AM (mean±SD): NR Smoking status: ≤ 10 pack-yr       Reliver Tx: Parenteral or nebulised bronchodilators of extra exacerbation for extra exacerbation for extra exacerbation for extra exacerbation for extra exacerbation for extra exacerbation for extra	Journal article				
1 (Sweden)       symptomatic (75% stable, symptomatic (75% stable, intermittent, moderate       Device:       a medical care centre with doses as needed (SMART <sup>®</sup> )         Pesign:       intermittent, moderate       Baseline ICS use: non-naive       Turbuhaler <sup>®</sup> centre with doses as needed (SMART <sup>®</sup> )         parallel, open       GROUP 1       NR       nebulised       compared with - higher fixed dos         label       GROUP 1       N: NR       GROUP 2       use of ICS or OCS       FORM/BUD 9400         Industry:       Age yr. (mean±SD): 39.7±19.6       Drug mcg/day:       for ed of addded asthma and/or need of addded asthm	N				
No. centers: 53 Design: randomized, parallel, open label Baseline ICS use: non-naive Baseline ICS use: non-inhalations of extra Baseline ICS use: non-inhalations of extra Baseline ICS use: non-inhalations of extra Baseline ICS user Baseline ICS user Baseli				,	3,
Design: randomized, parallel, open label       intermittent, moderate Baseline ICS use: non-naïve       Withdraw LOE: NR       parallel, open label       parallel, open label       GROUP 1 N: NR       parallel, open label       GROUP 2 N: NR       parallel, open label       GROUP 2 N: NR       use of ICS or OCS PCRM/BUD 940 due to worsening of asthma and/or withdrawal from the study because of need of added attraal courcomes of need of added attraal cources       GROUP 2 N: NR       Doring: variable duration of asthma (mean±SD): NR       Doring: variable patients with persistent asthma       maintenance therapy.         GROUP 2 N: NR       GROUP 2 N: NR       GROUP 3 PEF AM (mean±SD): 38.2±20.6 Males %: 49       Dosing: fixed Treatment duration of asthma (mean±SD): NR       List of clinical outcomes         GROUP 3 N: NR       GROUP 3 PEF AM (mean±SD): NR       Dosing: fixed Treatment duration of asthma (mean±SD): NR       Dosing: fixed Treatment duration of asthma (mean±SD): NR       PEF AM (mean±SD): NR         GROUP 3 N: NR       Duration of asthma (mean±SD): NR       Device: Secondary       Secondary         GROUP 3 N: NR       Duration of asthma (mean±SD): NR       Device: NR       Secondary         GROUP 3 N: NR       PEF AM (mean±SD): Males %: 49       Reliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations       Secondary         NR       Secondary       - time to first with duration of asthma (mean±SD): NR       Sing of CS NR       Symptom score       - no. inhalations of e					
randomized, parallel, open label       Baseline ICS use: non-naïve       NR       nebulised bronchodilators, use of ICS or OCS       compared with i higher fixed dos bronchodilators, use of ICS or OCS         Funding: Industry: AstraZeneca       Males %: 43       GROUP 1       GROUP 2       use of ICS or OCS       CRM/BUD with ingler fixed dos bronchodilators, use of ICS or OCS         StraZeneca       FEV, % predicted (mean±SD): 95.7±13.7       FEV, % predicted (mean±SD): 95.7±13.7       GROUP 2       GROUP 2       Freatment duration: 24 wk.       astima and/or withdrawal from the study because of need of added astima         GROUP 2       GROUP 2       Turbuhaler <sup>®</sup> Turbuhaler <sup>®</sup> maintenance therapy.         Males %: 49       mean±SD): NR       NR       List of clinical outcomes         Males %: 49       Brey fixed dos       FORM/BUD       Preference         Stratis 210 pack-yr       NR       List of clinical outcomes       outcomes         GROUP 3       NR       PEF AM (mean±SD): NR       Dosing: fixed treatment       Control         GROUP 3       N: NR       Reliver Tx: Parenteral or nebulised       Secondary       • time to first exacerbation rate over 6         Males %: 49       PEF AM (mean±SD): NR       Parenteral or nebulised       . symptom score       . symptom score         96.5±15.2       PEF AM (mean±SD): NR       Soriniued with					
parallel, open labelGROUP 1 N: NRGROUP 2 Drug mcg/day: FCPM/BUD 9/400 Dosing: variable Males %: 43bigher fixed dos FORM/BUD 9/400 Dosing: variable duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrbrochodilators, PEF AM (mean±SD): NRbrochodilators, due to worsening of asthma and/or the study because of asthma maintenance therapy.higher fixed dos FORM/BUD 9/400 of asthma and/or the study because of added asthma maintenance therapy.RCUP 2 N: NR GROUP 2 N: NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrBRUP 3 Duration of asthma (mean±SD): NR 96.2±14.7Discretion field Dosing: fixed Treatment duration: 24 wk.List of clinical outcomes reported: Primary PrimaryGROUP 2 N: NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrReliever Tx: Parenteral or nebulised Dosing: fixedSecondary the to first exacerbation scoreGROUP 3 N: NR Age yr, (mean±SD): NR Smoking status: ≤ 10 pack-yrReliever Tx: Parenteral or nebulised Docistions or OCS to treat exacerbationSecondary the to first exacerbation scoreRdie wr 6 mo. mate over 6 mo. (Group C) Astma Treatment Control divers or Do in the duration: 2 with Age or (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrReliever Tx: Parenteral or no. inhalations of extra exacerbation scoreRun-in duration: 2 withPEF AM (mean±SD): Age or (Croup C)Reliever Tx: Parenteral or no. inhalations of extra PCRM/BUD (Group C)PEF AM (					
labelGROUP 1 N: NRGROUP 2 Drug mcg/day: fuel to worsening of asthma and/or withdrawal from the study because of need of added asthma (meantSD): NR Smoking status: ≤ 10 pack-yrGROUP 2 Treatment duration of asthma (meantSD): NR Smoking status: ≤ 10 pack-yrGROUP 2 NR Turbuhaler®GROUP 2 NR TurbuhalerGROUP 3 NR TurbuhalerSecondary of set of asthma duration 24 wk.Secondary matter on need of added asthma duration 24 wk.Secondary matter of need of added asthma duration 24 wk.Secondary matter on need new of need of asthma duration 24 wk.SecondaryGROUP 2 N: NR Age yr. (meantSD): NR Definition of asthma (meantSD): NR Smoking status: ≤ 10 pack-yrGROUP 3 N: NRGROUP 3 N: NRSecondary• exacerbation reported: PEF AM (meantSD): NR Dosing: fixed Dosing: fixed NR kSecondaryReliever Tx: PEF AM (meantSD): NR Smoking status: ≤ 10 pack-yrReliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbation for MBUD• imact sore sore of exacerbation of extra preorMBUD (Group C) Astma Treatment dose of ICS Run-in duration: 2 w/rSecondary mater and for withdraw LOE:	,	Baseline ICS use: non-naive	NR		
Funding: Industry: AstraZeneca       N: NR Age yr. (mean±SD): 39.7±19.6 Age yr. (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yr       Drug mcg/day: FORM/BUD 9/400 Dosing: variable (also relief med)       due to worsening of asthma and/or withdrawal from the study because of need of added asthma maintenance       FORM as needu for asthma and/or withdrawal from the study because of need of added         ROUP 2       N: NR Smoking status: ≤ 10 pack-yr       Treatment       of need of added         N: NR Age yr. (mean±SD): NR Smoking status: ≤ 10 pack-yr       Turbuhaler®       List of clinical outcomes         PEF AM (mean±SD): NR Males %: 49       Drug mcg/day: FORM/BUD       Primary         96.2±14.7       PEF AM (mean±SD): NR Duration of asthma (mean±SD): NR       Drug mcg/day: FORM/BUD       Primary         96.2±14.7       PEF AM (mean±SD): NR Duration of asthma (mean±SD): NR       Dosing: fixed Treatment       Control Questionnaire         GROUP 3 N: NR Age yr. (mean±SD): NR Smoking status: ≤ 10 pack-yr       NR       Secondary       • time to first exacerbation rate over 6 mo.         Males %: 49 FEV, % predicted (mean±SD): 96.5±15.2       Reliever Tx: Parenteral or nebulised mean±SD): NR Smoking status: ≤ 10 pack-yr       Reliever Tx: Parenteral or nebulised monchodilators or OCS to treat exacerbations of extra FORM/BUD       • symptom score         9 or FORM B) or FORM       B) or FORM B) or FORM       B) or FORM					
Funding: Industry: AstraZeneca       Age yr. (mean±SD): 39.7±19.6 Males %: 43       FORM/BUD 9/400 Dosing: variable (also relief med)       of asthma and/or withdrawal from the study because of need of added asthma maintenance therapy.       patients with persistent asthm         AstraZeneca       95.7±13.7 PEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yr       FORM/BUD 9/400 Dosing: variable (also relief med)       of asthma and/or withdrawal from the study because of need of added asthma maintenance therapy.       patients with persistent asthm         GROUP 2 N: NR Age yr. (mean±SD): 38.2±20.6 Males %: 49 FEV1 % predicted (mean±SD): 96.2±14.7       GROUP 3 N: NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yr       GROUP 3 N: NR Age yr. (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yr       GROUP 3 N: NR Age yr. (mean±SD): 40.8±19.9 Males %: 49 FEV1 % predicted (mean±SD): 96.5±15.2       NR Pierertarial or nebulised bronchodilators or OCS to treat exacerbation mater adver 6 mo. NR NR       • Escondary • time to first exacerbation rate over 6 mo. • symptom score • no. inhalations of extra FORMBUD (Group A & B) or FORM	label				
Industry: AstraZenecaMales %: 43 FEV, % predicted (mean±SD): 95.7±13.7 PEF AM (mean±SD): NR Uration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrDosing: variable (also relief med) Treatment duration: 24 wk. Device: Turbuhaler® Withdraw LOE: NRwithdrawal from the study because of need of added asthma maintenance therapy.GROUP 2 N: NR Age yr. (mean±SD): 38.2±20.6 Males %: 49 FEV, % predicted (mean±SD): 96.2±14.7GROUP 3 N: NR Age yr. (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrGROUP 3 N: NR Age yr. (mean±SD): 40.8±19.9 Males %: 49Fever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbation scoreSecondary • time to first exacerbation scoreGROUP 3 N: NR Age yr. (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrReliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations fetvi % predicted (mean±SD): NRReliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations fetvi % predicted (mean±SD): NRReliever Tx: Parenteral or no. inhalations of extra exacerbation score• symptom score • no. inhalations of extra B) or FORM B) or FORM (Group C) Astima Treatment	Funding			5	
AstraZeneca       FEV, % predicted (mean±SD): 95.7±13.7       (also relief med) 95.7±13.7       the study because of need of added of need of added autation: 24 wk. Device: Turbuhale®         PEF AM (mean±SD): NR Smoking status: ≤ 10 pack-yr       Treatment duration: 24 wk. Device: NR       the study because of need of added autation: 24 wk. Device: NR         GROUP 2 N: NR Age yr. (mean±SD): 38.2±20.6 Males %: 49       GROUP 3 Drug mcg/day: FORM/BUD       Tist of clinical outcomes reported: Primary         96.2±14.7       GROUP 3 N: NR Duration of asthma (mean±SD): NR Duration of asthma (mean±SD): NR       GROUP 3 Device: Turbuhaler®       PEF AM (mean±SD): NR Duration of asthma (mean±SD): 40.8±19.9 Males %: 49       Device: Turbuhaler®       PEF AM (mean±SD): 40.8±19.9 Males %: 49         Reliever Tx: Parenteral or peEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yr       NR       Secondary time to first exacerbation OCS to treat exacerbations for extra FORM/BUD       • time to first exacerbation of extra FORM/BUD         PEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yr       NR       • time to first exacerbations of extra FORM/BUD         Run-in Tx: Continued with previous daily dose of ICS Run-in duration:       • of PCM (Groups A & B) or FORM (Group C) Astima Treatment					
95.7±13.7 PEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yr R GROUP 2 N: NR Age yr. (mean±SD): 38.2±20.6 Males %: 49 FEV1 % predicted (mean±SD): 96.2±14.7 PEF AM (mean±SD): NR Duration of asthma (mean±SD): NR GROUP 3 N: NR Age yr. (mean±SD): 40.8±19.9 Males %: 49 R GROUP 3 N: NR Age yr. (mean±SD): 40.8±19.9 Males %: 49 R Buration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yr Males %: 49 R Buration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yr Males %: 49 R Buration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yr Males %: 49 R Buration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yr Males %: 49 Smoking status: ≤ 10 pack-yr Males %: 49 Smoking status: ≤ 10 pack-yr Males %: 49 FEV1 % predicted (mean±SD): 96.5±15.2 PEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Buration of asthma (mean±SD): NR Buration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yr Males %: 49 FEV1 % predicted (mean±SD): 96.5±15.2 PEF AM (mean±SD): NR Buration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yr Males %: 40 FEV1 % predicted (mean±SD): 96.5±15.2 PEF AM (mean±SD): NR Buration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yr Smoking status: ≤ 10 pack-yr Males %: 40 FEV1 % predicted (mean±SD): 96.5±15.2 PEF AM (mean±SD): NR Buration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yr Males %: 40 FEV1 % predicted (mean±SD): Males %: 40 FEV1 % predicted (mean±SD): Males %: 40 FEV1 % predicted (mean±SD): Males %: 40 FEV1 % predicted (mean±SD): PEF AM (mean±SD): NR Buration fasthma (mean±SD): NR B) or FORM (Groups A & B) or FORM (Groups A & B) or FORM (Groups A & B) or FORM			•		persistent astrind.
PEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrduration: 24 wk. Device: Turbuhaler®asthma maintenance therapy.GROUP 2 N: NR Age yr. (mean±SD): 38.2±20.6 Males %: 49GROUP 3 PEF AM (mean±SD): 96.2±14.7List of clinical outcomesFEV: % predicted (mean±SD): 96.2±14.7GROUP 3 PEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrGROUP 3 N: NR NR Males %: 49List of clinical outcomesGROUP 3 N: NR N: NR N: NR N: NR Males %: 49GROUP 3 N: NR NRNRList of clinical outcomesGROUP 3 N: NR Males %: 49Treatment Uuration of asthma (mean±SD): VR Smoking status: ≤ 10 pack-yrDate outcomes PEF AM (mean±SD): NR NRList of clinical outcomesGROUP 3 N: NR Males %: 49NRSecondary Trubuhaler® Withdraw LOE:Immonian Control QuestionnaireGROUP 3 N: NR Males %: 49NRSecondary Trubuhaler® Withdraw LOE:Immonian exacerbationFEV, % predicted (mean±SD): 96.5±15.2PEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrNRsecretations Run-in Tx: continued with previous daily dose of ICS Run-in duration: 2wk. no. inhalations of extra B) or FORM (Group C)					
Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrDevice: Turbuhaler®maintenance therapy.GROUP 2 N: NR Age yr. (mean±SD): 38.2±20.6 Males %: 49GROUP 3 Drug mcg/day: FEV1 % predicted (mean±SD): 18/800List of clinical outcomesFEV1 % predicted (mean±SD): 96.2±14.7GROUP 3 Drug mcg/day: FORM/BUDPEF AM ControlPEFF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrGROUP 3 Treatment duration: 24 wk.PEr AM Obsing: fixed Dosing: fix					
(mean±SD): NR Smoking status: ≤ 10 pack-yrTurbuhaler® Withdraw LOE: NRtherapy.GROUP 2 N: NR Age yr. (mean±SD): 38.2±20.6 Males %: 49Turbuhaler® Withdraw LOE: NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrGROUP 3 Dosing: fixed Treatment duration: 24 wk.List of clinical outcomes reported: Primary • PEF AM QuestionnaireGROUP 3 NE: NR GROUP 3 N: NR Age yr. (mean±SD): A0.8±19.9 Males %: 49 FEV_1 % predicted (mean±SD): NR N: NR Age yr. (mean±SD): 40.8±19.9 Males %: 49Greiver Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations Run-in Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations Run-in Tx: Control ControlSecondary • time to first exacerbation rate over 6 mo.Reliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations Run-in Tx: Continued with previous daily dose of ICS Run-in duration: 2.withTurbuhaler® Withdraw LOE: NR• time to first exacerbation rate over 6 mo.PEF AM (mean±SD): NR Smoking status: ≤ 10 pack-yrReliever Tx: Parenteral or no. inhalations of extra FORM/BUD (Groups A & B) or FORM (Group C) • Asthma Treatment					
Smoking status: ≤ 10 pack-yrWithdraw LOE: NRGROUP 2 N: NR Age yr. (mean±SD): 38.2±20.6 Males %: 49GROUP 3 Drug mcg/day: FORM/BUDList of clinical outcomesFEV, % predicted (mean±SD): 96.2±14.7GROUP 3 Treatment duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrGROUP 3 18/800PEF AM ControlGROUP 3 N: NR Age yr. (mean±SD): 40.8±19.9 FEV, % predicted (mean±SD): 96.5±15.2Treatment duration of asthma (mean±SD): 40.8±19.9 PEF AM (mean±SD): NR Smoking status: ≤ 10 pack-yrReliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations Run-in Tx: continued with previous daily dose of ICS Run-in duration: 2. wtWithdraw LOE: NRList of clinical outcomes reported: PEF AM Questionnaire Questionnaire QuestionnaireGROUP 3 N: NR Age yr. (mean±SD): 40.8±19.9 FEV, % predicted (mean±SD): 96.5±15.2Reliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations Run-in duration: 2. wtSecondary time to first mo.PEF AM (mean±SD): NR Smoking status: ≤ 10 pack-yrReliever Tx: continued with previous daily dose of ICS Run-in duration: Treatment- symptom score FORM/BUD (Groups A & Astima Treatment					
GROUP 2NRList of clinical outcomesN: NRGROUP 3reported:Age yr. (mean±SD): 38.2±20.6Drug mcg/day: FEV, % predicted (mean±SD):Primary96.2±14.7Dosing: fixed Treatment• PEF AMDuration of asthma (mean±SD): NRTreatment duration: 24 wk.• Control QuestionnaireDuration of asthma (mean±SD): NRTreatment duration: 24 wk.• time to first exacerbationGROUP 3 N: NRNR• time to first exacerbationN: NRNR• exacerbation rate over 6 mo.Age yr. (mean±SD): 40.8±19.9 96.5±15.2Reliever Tx: Parenteral or nebulised• symptom score9EF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrReliever Tx: Parenteral or no.• symptom score9EF AM (mean±SD): NR Smoking status: ≤ 10 pack-yrRun-in Tx: corivid daily dose of ICS Run-in duration: 2 wt• Control control• Simptom score90Status: ≤ 10 pack-yrGroup C) dose of ICS Run-in duration: 2 wt• Asthma Treatment				alorapy.	
N: NRGROUP 3reported: PrimaryAge yr. (mean±SD): 38.2±20.6Drug mcg/day: FORM/BUDPEF AMFEV1 % predicted (mean±SD): 96.2±14.7Dosing: fixed Treatment duration of asthma (mean±SD): NR• PEF AM Control QuestionnairePEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrDevice: Turbuhale®SecondaryGROUP 3 N: NR Age yr. (mean±SD): 40.8±19.9 96.5±15.2NRSecondaryFEV4, % predicted (mean±SD): 96.5±15.2Reliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations Run-in Tx:symptom scorePEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrReliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations Run-in Tx: Continued with previous daily dose of ICS Run-in duration: 2 wthFORM/BUD (Group C)		<b>3 1 1 1 1 1 1</b>		List of clinical	
Age yr. (mean±SD): 38.2±20.6 Males %: 49Drug mcg/day: FORM/BUDPrimaryFEV, % predicted (mean±SD): 96.2±14.718/800• Asthma ControlPEF AM (mean±SD): NR Duration of asthma (mean±SD): NRDosing: fixed Treatment• Asthma ControlDuration of asthma (mean±SD): NR N: NR Age yr. (mean±SD): 40.8±19.9 96.5±15.2Device: Turbuhaler® Withdraw LOE: NRSecondary • time to first exacerbation rate over 6 mo.GROUP 3 N: NR Age yr. (mean±SD): 40.8±19.9 96.5±15.2NR Parenteral or nebulised bronchodilators or OCS to treat exacerbations• time to first exacerbation rate over 6 mo.PEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrReliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations Run-in Tx: continued with previous daily dose of ICS Run-in duration:no. inhalations of extra FORM/BUD (Group C)Mates %: 49 FEV1 % predicted (mean±SD):Parenteral or nebulised bronchodilators or OCS to treat exacerbations• no. inhalations of extra FORM/BUD (Group C)90.5±15.2 90.5±15.2Run-in Tx: (Groups A & B) or FORM (Group C)• no. inhalations of extra FORM B) or FORM (Group C)		GROUP 2		outcomes	
Males %: 49FORM/BUDPEF AMFEV1 % predicted (mean±SD):96.2±14.7Dosing: fixedAsthma96.2±14.7Dosing: fixedControlQuestionnairePEF AM (mean±SD): NRDevice:SecondaryUration of asthmaJuration of asthmaDosk-yrTurbuhaler®• time to firstGROUP 3N: NRNRexacerbationN: NRAge yr. (mean±SD): 40.8±19.9NR• time to firstMales %: 49PEF AM (mean±SD): NRParenteral or nebulised• symptom scorePEF AM (mean±SD): NRDorice:symptom score• symptom scoreDuration of asthma (mean±SD): NRRun-in Tx: continued with previous daily dose of ICS Run-in duration:• for Asthma continued with previous daily dose of ICS Asthma• Asthma ControlMales %: 49FORM/BUD• symptom score• symptom scoreFEV1 % predicted (mean±SD):NR• symptom score• symptom scorePEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yr• for Asthma rratment• for Asthma Group C)ParkSmoking status: ≤ 10 pack-yr• for Asthma rreatment• for Asthma Treatment		N: NR	GROUP 3	reported:	
FEV1 % predicted (mean±SD):18/800Asthma Control96.2±14.7Dosing: fixedControlPEF AM (mean±SD): NRDevice:QuestionnaireDuration of asthmaduration: 24 wk.Device:GROUP 3Turbuhaler®withdraw LOE:time to first exacerbationN: NRNRNRexacerbationAge yr. (mean±SD): 40.8±19.9Reliever Tx: Parenteral or nebulisedmo.96.5±15.2PEF AM (mean±SD): NR Duration of asthma (mean±SD): NRReliever Tx: Parenteral or nebulisedsymptom score0CS to treat (mean±SD): NR Smoking status: ≤ 10 pack-yrRun-in Tx: continued with previous daily dose of ICS Run-in duration:symptom score0Status: ≤ 10 pack-yrRun-in duration: 2w/kAsthma Control		Age yr. (mean±SD): 38.2±20.6	Drug mcg/day:		
96.2±14.7Dosing: fixed Treatment duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrDosing: fixed Treatment duration: 24 wk.Control QuestionnaireGROUP 3 N: NR Age yr. (mean±SD): 40.8±19.9 96.5±15.2Dosing: fixed Treatment duration: 24 wk.SecondaryReliever Tx: Parenteral or nebulised bronchodilators or (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrNRSecondary96.5±15.2 PEF AM (mean±SD): NR Smoking status: ≤ 10 pack-yrReliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations Run-in Tx: continued with previous daily dose of ICS Run-in duration: 2 w/kControl Questionnaire96.5±15.2 PEF AM (mean±SD): NR Smoking status: ≤ 10 pack-yrReliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations Run-in duration: 2 w/kControl Questionnaire96.5±15.2 PEF AM (mean±SD): NR Smoking status: ≤ 10 pack-yrReliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations.97.5 PUTNR PUTPUT.98.6 PUT99.7 PUT99.7 PUT99.7 PUT99.7 PUT90.7 PUT90.7 PUT90.7 PUT90.7 PUT90.7 PUT90.7 PUT90.7 PUT <td< td=""><td></td><td>Males %: 49</td><td>FORM/BUD</td><td>PEF AM</td><td></td></td<>		Males %: 49	FORM/BUD	PEF AM	
PEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrTreatment duration: 24 wk.QuestionnaireGROUP 3 N: NR Age yr. (mean±SD): 40.8±19.9 Males %: 49Turbuhaler® Withdraw LOE: NR• time to first exacerbation rate over 6 mo.FEV1 % predicted (mean±SD): 96.5±15.2Reliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations molined• time to first exacerbation rate over 6 mo.PEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrReliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations Run-in Tx: continued with previous daily dose of ICS Run-in duration: 2 w/k. time to first exacerbation mol score • no. inhalations of extra FORM/BUD (Groups A & B) or FORM (Group C)		FEV <sub>1</sub> % predicted (mean±SD):	18/800	<ul> <li>Asthma</li> </ul>	
Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrduration: 24 wk. Device: Turbuhaler® Withdraw LOE: NRSecondaryGROUP 3 N: NR Age yr. (mean±SD): 40.8±19.9 Males %: 49 FEV1 % predicted (mean±SD): 96.5±15.2NRSecondaryMales %: 49 FEV1 % predicted (mean±SD): 96.5±15.2Reliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbationssymptom scorePEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrReliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbationssymptom scoreRun-in Tx: continued with previous daily dose of ICS Run-in duration: 2 w/kSecondary			Dosing: fixed	Control	
(mean±SD): NR Smoking status: ≤ 10 pack-yrDevice: Turbuhaler® Withdraw LOE:SecondaryGROUP 3 N: NR Age yr. (mean±SD): 40.8±19.9 Males %: 49 FEV1 % predicted (mean±SD): 96.5±15.2NR• time to first exacerbation rate over 6 mo.Perenteral or nebulised bronchodilators or OCS to treat exacerbations• symptom scorePEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrReliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations• symptom scoreRun-in Tx: continued with previous daily dose of ICS Run-in duration: 2 w/kMevice: Turbuhaler® Withdraw LOE: NR• time to first exacerbation mate over 6 mo.				Questionnaire	
Smoking status: ≤ 10 pack-yrTurbuhaler® Withdraw LOE: NRtime to first exacerbation rate over 6 mo.Age yr. (mean±SD): 40.8±19.9 Males %: 49 FEV1 % predicted (mean±SD): 96.5±15.2Reliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbations Run-in Tx: continued with previous daily dose of ICS Run-in duration: 2.w/ktime to first exacerbation rate over 6 mo.Smoking status: ≤ 10 pack-yrTurbuhaler® Withdraw LOE: NRtime to first exacerbation rate over 6 mo.Reliever Tx: Parenteral or nebulised bronchodilators or (Groups A & B) or FORM (Group C)no. inhalations of extra FORM/BUD (Groups A & B) or FORM (Group C)					
GROUP 3 N: NRWithdraw LOE: exacerbation rate over 6Age yr. (mean±SD): 40.8±19.9 Males %: 49Reliever Tx: Parenteral or nebulisedmo.FEV1 % predicted (mean±SD): 96.5±15.2Reliever Tx: Parenteral or nebulisedsymptom scorePEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrOCS to treat exacerbationsno. inhalations of extra FORM/BUD (Groups A & B) or FORM (Group C)Males %: 49 FEV1 % predicted (mean±SD): 96.5±15.2Run-in Tx: cortinued with previous daily dose of ICSmo.				Secondary	
GROUP 3 N: NRNRexacerbation rate over 6 mo.Age yr. (mean±SD): 40.8±19.9 Males %: 49Reliever Tx: Parenteral or nebulisedmo.FEV1 % predicted (mean±SD): 96.5±15.2Parenteral or nebulisedsymptom scorePEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrOCS to treat exacerbationsno. inhalations of extra FORM/BUD (Groups A & B) or FORM (Group C)Barbon Duration of asthma (mean±SD): NR (mean±SD): NR (Group S A & Continued with previous daily dose of ICS (Group C)no. inhalations of extra FORM/BUD (Group C)NR (Bub (Group C)NR (Group C)NR (Group C)		Smoking status: ≤ 10 pack-yr			
N: NRReliever Tx: rate over 6 mo.Age yr. (mean±SD): 40.8±19.9 Males %: 49Reliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbationssymptom score96.5±15.2 PEF AM (mean±SD): NR (mean±SD): NR (mean±SD): NR Smoking status: ≤ 10 pack-yrReliever Tx: Parenteral or nebulised bronchodilators or OCS to treat exacerbationssymptom score0CS to treat exacerbationson . inhalations of extra FORM/BUD (Groups A & B) or FORM (Group C)0CS to treat exacerbationsprevious daily dose of ICS Run-in duration: 2 w/k				exacerbation	
Age yr. (mean±SD): 40.8±19.9 Males %: 49Reliever Tx: Parenteral or nebulisedmo.FEV1 % predicted (mean±SD): 96.5±15.2Parenteral or nebulisedsymptom scorePEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yrOCS to treat exacerbationsof extra FORM/BUD (Groups A & B) or FORM (Group C)NR Smoking status: ≤ 10 pack-yrRun-in Tx: continued with previous daily dose of ICS Run-in duration: 2.w/kStatus and the over of mo.			NR		
Males %: 49Parenteral or nebulisedsymptom scoreFEV1 % predicted (mean±SD): 96.5±15.2Parenteral or nebulisedsymptom scorePEF AM (mean±SD): NR (mean±SD): NR (mean±SD): NR Smoking status: ≤ 10 pack-yrParenteral or nebulised bronchodilators or OCS to treat exacerbationssymptom scoreMales %: 49 (mean±SD): (mean±SD): NR (mean±SD): NR (mean±SD): NR Smoking status: ≤ 10 pack-yrParenteral or nebulised bronchodilators or OCS to treat exacerbationssymptom scoreNR (Groups A & B) or FORM (Group C)NR (Group C)NR (Group C)NR (Druct and the previous daily dose of ICSAsthma Treatment			Dellever Tw	rate over 6	
FEV1 % predicted (mean±SD):nebulisedscore96.5±15.2bronchodilators oroc. inhalations9EF AM (mean±SD): NROCS to treatof extraDuration of asthmaexacerbationsFORM/BUD(mean±SD): NRRun-in Tx:(Groups A &Smoking status: ≤ 10 pack-yrcontinued withB) or FORMSmoking status: ≤ 10 pack-yrRun-in duration:AsthmaContinued withFORMCroups A &Duration of asthmacontinued withB) or FORMContinued withprevious dailyCroup C)Continued withContinued withAsthmaContinued withCroup C)Croup C)Continued withCroup C)<				mo.	
96.5±15.2 PEF AM (mean±SD): NR Duration of asthma (mean±SD): NR Smoking status: ≤ 10 pack-yr Marking Status: ≤ 10 pack-y				<ul> <li>symptom</li> </ul>	
PEF AM (mean±SD): NR       OCS to treat       of extra         Duration of asthma       exacerbations       FORM/BUD         (mean±SD): NR       Run-in Tx:       (Groups A &         Smoking status: ≤ 10 pack-yr       continued with       B) or FORM         Variation of usthma       previous daily       (Group C)         Asthma       Treatment					
Duration of asthma (mean±SD): NRexacerbations Run-in Tx: continued with previous daily dose of ICS Run-in duration: 2 w/rFORM/BUD (Groups A & B) or FORM (Group C) Asthma Treatment					
(mean±SD): NRRun-in Tx: continued with previous daily dose of ICS Run-in duration:(Groups A & B) or FORM (Group C)***********************************					
Smoking status: ≤ 10 pack-yr       continued with previous daily dose of ICS       B) or FORM (Group C)         Run-in duration:       2 w/r					
previous daily dose of ICS Run-in duration: 2 w/r					
dose of ICS • Asthma <b>Run-in duration:</b> Treatment					
Run-in duration: • Asuma Treatment				,	
			2 wk.	Questionnaire	
Westormare     Store as the second seco					
• // astinia controlled					
days					
uuyo				aayo	

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year:	Randomized: 203	GROUP 1	Definition of	Study objective:
Mitchell C	Analyzed: 201	Drug mcg/day:	exacerbation:	To compare the
2003 <sup>115</sup>	Withdrawals: 19	FORM/BDP	Mild = asthma	effect of the
Pub status:		24/1000	symptom score of	addition of the
Journal article	ITT analysis: yes	Dosing: fixed	3 and increased	LABA formoterol to
	Asthma stage and severity:	Treatment	use of rescue	medium-high doses
No. countries:	symptomatic, intermittent to	duration: 12 wk.	medication.	of ICS with that of
1 (Australia)	severe	Device: Aerolizer	Moderate =	doubling the dose
No. centers: 16	Baseline ICS use: non-naïve	Withdraw LOE:	treatment with a	of ICS, in patients
Design:		NR	course or oral	with poorly-
randomized,	GROUP 1		corticosteroids	controlled,
parallel, double	<b>N:</b> 100	GROUP 2	and/or nebulised	moderate-to-severe
blind, double	Age yr. (mean±SD): 43.9±14.9	Drug mcg/day:	β2-andrenoceptor	asthma.
dummy	Males %: 45.1	BDP 2000	agonists. Severe =	
	FEV <sub>1</sub> % predicted (mean±SD):	Dosing: fixed	hospitalization	Additional Details:
Funding:	71.83±11.56	Treatment	caused by an	NA
Industry:	PEF AM (mean±SD):	duration: 12 wk.	asthma	
Novartis	352.2±119.8	Device: Aerolizer	exacerbation if the	
	Duration of asthma yr.	Withdraw LOE:	adverse event was	
	(mean <b>±SD):</b> 26.5±15.9	NR	considered to be	
	Smoking status: G1 (current		related to the study	
	and previous smokers %):	Reliever Tx:	medication.	
	51.9	salbutamol		
		Run-in Tx: BDP	List of clinical	
	GROUP 2	500 mcg bid +	outcomes	
	<b>N:</b> 101	salbutamol prn	reported:	
	Age yr. (mean±SD):	Run-in duration:		
	43.86±15.4	2-4 wk.	Primary	
	Males %: 43.6		<ul> <li>PEF AM</li> </ul>	
	FEV <sub>1</sub> % predicted (mean±SD):			
	72.37±11.16		Secondary	
	PEF AM (mean±SD):		<ul> <li>FEV1</li> </ul>	
	349.7±103.0		• DTS	
	Duration of asthma yr.		NTS	
	(mean±SD): 29.4±14.7		• % pts	
	Smoking status (current and		symptomatic	
	previous smokers %): 46.5		<ul> <li>daytime SABA</li> </ul>	
			use	

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year: Molimard M 2001 <sup>85</sup> Pub status: Journal article No. countries: 1 (France) No. centers: multicenter (ND) Design: randomized, parallel, open label Funding: Industry: Novartis	Randomized: 259 Analyzed: 229 Withdrawals: 30 ITT analysis: yes Asthma stage and severity: symptomatic, moderate Baseline ICS use: non-naïve GROUP 1 N: 118 Age yr. (mean±SD): 38.5±14.9 Males %: 42 FEV <sub>1</sub> % predicted (mean±SD): 72.7±10.0 PEF AM (mean±SD): 387.4±108.2 Duration of asthma (mean±SD): 15.1 yr. ±11.5 Smoking status - never/past/current (n(%)): 91(70)/20(15)/19(15) GROUP 2 N: 111 Age yr. (mean±SD): 39.5±15.0 Males %: 45 FEV <sub>1</sub> % predicted (mean±SD): 73.7±9.4 PEF AM (mean±SD): 396.2±85.0 Duration of asthma (mean±SD): NA Smoking status - never/past/current (n(%)): 88(68)/23(18)/18(14)	GROUP 1 Drug mcg/day: FORM/BDP, BUD, FP 24/medium dose Dosing: fixed Treatment duration: 12 wk. Device: DPI Withdraw LOE: 0 GROUP 2 Drug mcg/day: ICS Dosing: variable Treatment duration: 12 wk. Device: MDI Withdraw LOE: 3 Reliever Tx: salbutamol prn. In case of asthma exacerbation, a transient increase in the daily dose of the ICS, a course of OCS or a symptomatic $\beta_2$ -agonist nebulization therapy were allowed. Run-in Tx: salbutamol as needed Run-in duration: 2-3 wk.	Definition of exacerbation: NR List of clinical outcomes reported: Primary • PEF AM Secondary • PEF PM • FEV1 • DTS • NTS • SFD • SFN • SGRQ • daytime SABA use • nighttime SABA use	Study objective: To compare the efficacy of FORM dry-powder capsule 12 mcg b.i.d. and on-demand salbutamol in patients with moderate persistent asthma treated with ICS, in the conditions of real practice.

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 680	GROUP 1	Definition of	Study objective:
Morice AH	Analyzed: 668	Drug mcg/day:	exacerbation: NR	To compare the
2007 <sup>96</sup>	Withdrawals: 79	FORM/BUD		efficacy and safety
Pub status:		18/800	List of clinical	of a novel
Journal article	ITT analysis: yes	Dosing: fixed	outcomes	hydrofluoroalkane
No. countries:	Asthma stage and severity: symptomatic, moderate-severe	Treatment duration: 12 wk.	reported:	(HFA) pressurized metered-dose
8	Baseline ICS use: non-naïve	Device:	<ul><li>Primary</li><li>PEF AM</li></ul>	inhaler (pMDI)
No. centers: 62	Baseline ics use. non-naive	Turbuhaler®		formulation of
Design:	GROUP 1	Withdraw LOE: 2	Secondary	BUD/FORM with
randomized,	N: 223		PEF PM	that of budesonide
parallel, double	Age yr. (mean [range]): 39	GROUP 2		pMDI and
blind, double	(11-78)	Drug mcg/day:	• FEV <sub>1</sub>	philbrana
dummy	Males %: 38.9	FORM/BUD	symptom	Additional Details:
aanniy	FEV <sub>1</sub> % predicted (mean	18/800	score	Comparing HFA
Funding:	[range]): 69 (50-90)	Dosing: fixed	SABA use	pressurized MDI
Industry:	<b>PEF AM (mean [range]):</b> 321	Treatment	• NTA	with a DPI
AstraZeneca	(93-668)	duration: 12 wk.	SFD	
/ loti allonood	Duration of asthma (mean	Device: MDI	RFD	
	[range]): 9 yr. (1-63)	Withdraw LOE:	<ul> <li>asthma</li> </ul>	
	Smoking status – current (n	11	control days	
	<b>(%)):</b> 11 (5)		<ul> <li>AQLQ</li> </ul>	
	(,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	GROUP 3		
	GROUP 2	Drug mcg/day:		
	N: 229	BUD 800		
	Age yr. (mean [range]): 40	Dosing: fixed		
	(12-78)	Treatment		
	Males %: 40.2	duration; 12 wk.		
	FEV <sub>1</sub> % predicted (mean	Device: MDI		
	[range]): 71 (39-92)	Withdraw LOE:		
	PEF AM (mean [range]): 326	15		
	(89-715)			
	Duration of asthma (mean	Reliever Tx:		
	[range]): 8 yr. (1-58)	terbutaline prn		
	Smoking status – current (n	Run-in Tx:		
	<b>(%)):</b> 13 (6)	current ICS;		
		stopped previous		
	GROUP 3	LABA use		
	<b>N:</b> 216	Run-in duration:		
	Age yr. (mean [range]): 40	2 wk.		
	(12-79)			
	Males %: 31.3			
	FEV <sub>1</sub> % predicted (mean			
	[range]): 71 (45-91)			
	PEF AM (mean [range]): 318			
	(109-638)			
	Duration of asthma (mean			
	[range]): 10 yr. (0-70)			
	Smoking status – current (n			
	<b>(%)):</b> 14 (6)			

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 514	GROUP 1	Definition of	Study objective:
Murray JJ	Analyzed: 514	Drug mcg/day:	exacerbation:	To determine
1999 <sup>117</sup>	Withdrawals: 107	SAL/BDP	events requiring	whether the
Pub status:		100/400	treatment with any	addition of
Journal article	ITT analysis: yes	Dosing: fixed	asthma medication	salmeterol to
	Asthma stage and severity:	Treatment	excluded during	existing ICS therapy
No. countries:	symptomatic, moderate-severe	duration: 24 wk.	study participation,	provides greater
1 (United	Baseline ICS use: non-naïve	Device: MDI	including oral and	therapeutic benefit
States)		Withdraw LOE: 5	parenteral	than doubling the
No. centers: 35	GROUP 1		corticosteroids.	dose of inhaled
Design:	N: 260	GROUP 2		corticosteroids in
randomized,	Age yr. (mean±SD): 42.2±12.9	Drug mcg/day:		symptomatic
parallel, double	Males %: 41	BDP 800	List of clinical	patients with
blind, double	FEV <sub>1</sub> % predicted (mean±SD):	Dosing: fixed	outcomes	asthma.
dummy	65.2±10.5	Treatment	reported:	
-	PEF AM (mean±SD):	duration: 24 wk.	Primary	
Funding:	390.2±95.1	Device: MDI	PEF AM	
Industry:	Duration of asthma: NR	Withdraw LOE: 5	<ul> <li>FEV<sub>1</sub></li> </ul>	
GlaxoSmithKline	Smoking status: NR		·	
		Reliever Tx:	Secondary	
	GROUP 2	albuterol prn	PEF PM	
	N: 254	Run-in Tx: BDP	<ul> <li>total</li> </ul>	
	Age yr. (mean±SD): 41.9±14.3	200 mcg bid +	exacerbations	
	Males %: 45	albuterol prn	<ul> <li>exacerbation</li> </ul>	
	FEV <sub>1</sub> % predicted (mean±SD):	Run-in duration:	leading to	
	64.0±10.8	2 wk.	hospitalization	
	PEF AM (mean±SD):		<ul> <li>asthma</li> </ul>	
	381.6±95.6		symptom	
	Duration of asthma: NR		score	
	Smoking status: NR		SFD	
			<ul> <li>SABA use</li> </ul>	
			diurnal	
			varation PEF	
			AM	
			diurnal	
			variation PEF	
			PM	
			RFD	

StudyParticipant characteristicsreportedNotesAuthor Year. Author Year.Randomized: 267 Mitray JaGROUP 1 Drug mcg/day: SAL/FP 100/200Definition of exacerbation: NRStudy objective: To compare the efficacy and safety Dosing: fixed Duration of astima: 26 mo Smoking status: <10 pack-yrDefinition of study objective: Dosing: fixed Dosing: fixed Drug mcg/day: Device: DiskusStudy objective: To compare the efficacy and safety outcomes1 (United States randomized, N: 88 parallel, double blindIT analysis: yes symptomatic mild-severe Baseline ICS use: naïveGROUP 2 GROUP 1 Males %: 47GROUP 2 GROUP 2 SAL/TPSecondary single device with administered from a sorre sorre sorreSecondary single device with agents alone.Funding: Industry: GlaxoSmithKineFEV ty predicted (mean): 66 PEF AM (mean±SD): SAL 100GROUP 2 Doration of astima: 26 mo Smoking status: <10 pack-yrGROUP 3 Run-in Tx: albuterol Age yr. (mean [range]): 32 fixed Age yr. (mean [range]): 32 Age yr. (mean [range]): 32 titter albuterol RCOUP 3 Reviewed frequenciesGROUP 3 Run-in Tx: albuterol Run-in tration: 12 wk. SAL 1000Males %: 40 FEV, % predicted (mean): 66 PEF AM (mean±SD): SO Somoking status: <10 pack-yrReliever Tx: albuterol Run-in tration: 12 wk. SAL 1000Males %: 40 FEV, % predicted (mean): 66 PEF AM (mean±SD): 349497.7 Duration of astima: >6 mo Smoking status: <10 pack-yrReliever Tx: albuterol Run-in duration: 2 wk.0Males %: 40 FEV, % predicted (mean): 66 PEF AM (mean±SD): 349
Author Year: Murray JJ 2004Randomized: 267 Analyzed: 267GROUP 1 Drug mcg/day: SAL/FP 100/200Definition of exacerbation: NRStudy objective: To compare the efficacy and safety of initiating maintenance therapy with an inhaled, LABA and administered from a single device with agents alone.Study objective: To compare the efficacy and safety of initiating reported: therapy with an inhaled, LABA and administered from a single device with agents alone.Study objective: To compare the efficacy and safety of initiating rotations in table therapy with an inhaled, LABA and administered from a single device with agents alone.Study objective: To compare the efficacy and safety of initiating rotation of administered from a single device with agents alone.Study objective: To compare the efficacy and safety of initiating therapy with an inhaled, LABA and administered from a single device with agents alone.No. centers: 33 Design: randomized, parallel, double blindIf Reg (12-75) Males %: 47GROUP 2 Drug mcg/day: SAL 100 Dosing: fixed Dosing: fixed Dosing: fixed Dosing: fixed Dosing: fixed Dosing: fixed Treatment duration; 12 wk. Device: Diskus®Definition of exacerbation: NR to the individual agents alone.GROUP 2 N: 89 Duration of asthma: 26 mo Smoking status: <10 pack-yr N: 90GROUP 3 Run-in Tx: albuterol Run-in duration: 2 wk.Definition of accord and file program Primary the individual socoreSFNGROUP 3 N: 90 Males %: 51Run-in Tx: albuterolRun-in Tx: albuterolN: 90 Ma

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 365	GROUP 1	Definition of	Study objective: To
Nathan RA 200694	Analyzed: 365	Drug mcg/day:	exacerbation: NR	compare the efficacy
Pub status:	Withdrawals: 122	SAL/FP 100/500		and tolerability of the
Journal article		Dosing: fixed	List of clinical	combination of FP and
	ITT analysis: yes	Treatment	outcomes reported:	SAL delivered via a
No. countries: 1	Asthma stage and severity:	duration: 12 wk.	Primary	single HFA MDI with
(United States)	symptomatic, intermittent to severe	Device: MDI	<ul> <li>PEF AM AUC</li> </ul>	those of its 2
No. centers: 45	Baseline ICS use: non-naïve	Withdraw LOE: 7	<b>.</b> .	components alone
Design:		GROUP 2	Secondary	delivered via a CFC
randomized,	GROUP 1		PEF PM	MDI and placebo
parallel, double blind	N: 94 Age yr. (mean [range]): 38.8 (13-	Drug mcg/day: FP 500	<ul> <li>daily symptom</li> </ul>	delivered via HFA MDI
Dilliu	69)	Dosing: fixed	score	in adolescent and
Funding:	Males %: 39	Treatment	SABA use	adult patients with persistent asthma that
Industry:	FEV <sub>1</sub> % predicted (mean±SD):	duration: 12 wk.	NTA	were not controlled by
GlaxoSmithKline	68.3±11.6	Device: MDI	SFN	medium doses
	PEF AM (mean±SD): 342.6±93.1	Withdraw LOE: 11	<ul> <li>SFD</li> </ul>	(equivalent to FP 500-
	Duration of asthma: NR			800 mcg/day) of ICS
	Smoking status: no pts smoked in	GROUP 3		
	last year and <10 pack-yr.	Drug mcg/day:		Additional Details:
		SAL 100		Compares HFA to
	GROUP 2	Dosing: fixed		CFC propellant
	<b>N:</b> 91	Treatment		
	Age yr. (mean [range]): 39.1 (12-	duration: 12 wk.		
	82)	Device: MDI		
	Males %: 37	Withdraw LOE: 23		
	FEV <sub>1</sub> % predicted (mean±SD):			
	69.0±10.5	GROUP 4		
	<b>PEF AM (mean±SD):</b> 344.4±91.6	Drug mcg/day:		
	Duration of asthma: NR	PLA Descharge finned		
	Smoking status: no pts smoked in	Dosing: fixed		
	last year and <10 pack-yr.	Treatment duration: 12 wk.		
	GROUP 3	Device: single		
	N: 91	drugs		
	Age yr. (mean [range]): 37.5 (12-	Withdraw LOE: 48		
	73)			
	Males %: 38	Reliever Tx:		
	FEV <sub>1</sub> % predicted (mean±SD):	albutarol prn		
	68.5±11.4	Run-in Tx: current		
	PEF AM (mean±SD): 344.3±88.7	ICS therapy and		
	Duration of asthma: NR	albuterol as needed		
	Smoking status: no pts smoked in	Run-in duration: 2		
	last year and <10 pack-yr.	wk.		
	GROUP 4			
	N: 89			
	Age yr. (mean [range]): 41.1 (12-			
	76)			
	Males %: 44			
	FEV <sub>1</sub> % predicted (mean±SD):			
	67.5±12.3			
	<b>PEF AM (mean±SD):</b> 347.4±93.4			
	Duration of asthma: NR			
	Smoking status: no pts smoked in			
	last year and <10 pack-yr.			

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year: Nelson HS 2003 <sup>57</sup>	Randomized: 283 Analyzed: 283 Withdrawals: 26	GROUP 1 Drug mcg/day: SAL/FP 100/200	Definition of exacerbation: NR	<b>Study objective:</b> To compare the efficacy and safety
Pub status: Journal article No. countries:	ITT analysis: no Asthma stage and severity: symptomatic, intermittent-	Dosing: fixed Treatment duration: 12 wk. Device: MDI	List of clinical outcomes reported: Primary	of twice-daily FP 100 mcg and SAL 50 mcg combined in a CFC-free MDI
1 (United States) <b>No. centers:</b> 33	severe Baseline ICS use: naïve	Withdraw LOE: 1 GROUP 2	• FEV <sub>1</sub> AUC • Secondary	with the individual agents alone, each delivered through
<b>Design:</b> randomized, parallel, double blind	GROUP 1 N: 95 Age yr. (mean [range]): 29.2 (12-77)	Drug mcg/day: FP 200 Dosing: fixed Treatment	<ul> <li>PEF PM</li> <li>FEV<sub>1</sub></li> <li>daily symptom score (scale</li> </ul>	an MDI containing CFC propellants, in patients with persistent asthma
Funding: Industry: GlaxoSmithKline	Males %: 52 FEV <sub>1</sub> % predicted: 67.2 PEF AM (mean±SD): 356.4±88.0 Duration of asthma: >6 mo.	duration: 12 wk. Device: MDI Withdraw LOE: 3 GROUP 3	0-5) • SABA use • SFD • RFD	previously uncontrolled with as-needed SABA alone.
	Smoking status: NR	Drug mcg/day: SAL 100 Dosing: fixed	<ul> <li>nights with no awakenings</li> </ul>	Additional Details: SAL/FP (CFC-free) compared to
	N: 97 Age yr. (mean [range]): 33.6 (12-76) Males %: 53 FEV <sub>1</sub> % predicted: 64.7	Treatment duration: 12 wk. Device: MDI Withdraw LOE: 7		individual agents through MDI containing CFC propellants.
	PEF AM (mean±SD): 361.4±87.5 Duration of asthma: >6 mo. Smoking status: NR	<b>Reliever Tx:</b> albuterol prn <b>Run-in Tx:</b> PLA MDI + albuterol		
	GROUP 3 N: 91 Age yr. (mean [range]): 34.3	prn <b>Run-in duration:</b> 2 wk.		
	(12-67) Males %: 53 FEV <sub>1</sub> % predicted: 66.0 PEF AM (mean±SD): 363.8±86.0 Duration of asthma: >6 mo.			
	Smoking status: NR			

			Clinical	
		Treatment	outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 34	GROUP 1	Definition of	Study objective:
Nielsen LP	Analyzed: NR	Drug mcg/day:	exacerbation: NR	To determine
1999 <sup>139</sup>	Withdrawals: NR	SAL/BDP		whether SAL had
Pub status:		100/800-1,600	List of clinical	steroid-sparing
Journal article	ITT analysis: yes	Dosing: variable	outcomes	properties in stable
	Asthma stage and severity:		reported:	asthma patients
No. countries:	asymptomatic, mild-moderate	Treatment	Primary	already receiving
1 (Denmark)	Baseline ICS use: non-naïve	duration: NR	PEF AM	maintenance ICS
No. centers:		Device:	PEF PM	
multicenter (ND)	GROUP 1	Diskhaler <sup>®</sup>	<ul> <li>FEV<sub>1</sub></li> </ul>	Additional Details:
Design:	N: NR	Withdraw LOE:	,	Assessment of
randomized,	Age yr. (mean): 45	NR	Secondary	MAD (defined as
parallel, double	Males %: 33		<ul> <li>symptom</li> </ul>	the dose one step
blind	FEV <sub>1</sub> % predicted (mean):	GROUP 2	score	above the dose
	86.1	Drug mcg/day:	• DTS	resulting in unstable
Funding:	PEF AM (mean±SD): NR	BDP 800-1,600 +	<ul> <li>NTS</li> </ul>	asthma).
Industry:	Duration of asthma yr.	PLA	SFD	
GlaxoSmithKline	(mean): 15.4	Dosing: variable	<ul> <li>SABA use</li> </ul>	
	Smoking status (current n	Treatment	<ul> <li>MAD</li> </ul>	
	<b>[%]):</b> 5 (33)	duration: NR		
		Device:		
	GROUP 2	Diskhaler <sup>®</sup>		
	N: NR	Withdraw LOE:		
	Age yr. (mean): 43	NR		
	Males %: 53			
	FEV <sub>1</sub> % predicted (mean):	Reliever Tx:		
	86.7	salbutamol prn		
	PEF AM (mean±SD): NR	Run-in Tx: P1:		
	Duration of asthma yr.	switched to BDP		
	<b>(mean):</b> 12.9	at doses		
	Smoking status (current n	equivalent to		
	<b>[%)]:</b> 9 (47.4)	current tx. P2: If		
		stable then BDP		
		decreased 200 µg		
		/ wk until unstable		
		(MAD). P3: given		
		3 times MAD		
		dose up to		
		3000µg/d x 2 wks.		
		If stable then		
		randomized		
		Run-in duration:		
		2 wk.		

		The states of	Clinical	
Study	Derticipent characteristics	Treatment	outcomes	Notoo
Study	Participant characteristics	characteristics	reported	Notes
Author Year: Noonan M	Randomized: 596	GROUP 1	Definition of exacerbation: NR	Study objective: To compare the
2006 <sup>92</sup>	Analyzed: 585 Withdrawals: 225	Drug mcg/day: FORM/BUD		
Pub status:		18/800	List of clinical	efficacy and safety of FORM/BUD
Journal article	ITT analysis: yes	Dosing: fixed	outcomes	pressurized MDI
	Asthma stage and severity:	Treatment	reported:	with BUD pMDI,
No. countries:	NR, moderate, severe	duration: 12 wk.	Primary	FORM DPI, BUD
1 (United	Baseline ICS use: non-naïve	Device: MDI	● FEV <sub>1</sub> 12-hr	plus FORM in
States)	Dasenne 105 use. non-naive	Withdraw LOE:	post dose	separate inhalers
No. centers: 84	GROUP 1	NR	<ul> <li>FEV<sub>1</sub> 12-hr</li> </ul>	(BUD pMDI +
Design:	N: 121		• FEV112-III predose	FORM DPI) and
randomized,	Age yr. (mean±SD): 41.8±15.5	GROUP 2	•	PLA
parallel, double	Males %: 35.5	Drug mcg/day:	Secondary	
blind, double	FEV <sub>1</sub> % predicted (mean±SD):	FORM/BUD	PM PEF	Additional Details:
dummy	67.5±11.5	18/800	exacerbations	Comparing pMDI
aanniy	PEF AM (mean): 341	Dosing: fixed	<ul> <li>DTS (4-pt</li> </ul>	and DPI inhalers
Funding:	Duration of asthma	Treatment	score)	
Industry:	(mean±SD): 23.1±15.1	duration: 12 wk.	• NTS	
AstraZeneca	Smoking status: ≤10 pack-yr	Device: DPI	<ul> <li>NTA</li> </ul>	
/ loti uzeneou	history	Withdraw LOE:		
	hiotory	NR		
	GROUP 2			
	N: 113	GROUP 3		
	Age yr. (mean±SD): 40.3±14.7	Drug mcg/day:		
	Males %: 43.5	BUD 800 + PLA		
	FEV <sub>1</sub> % predicted (mean±SD):	Dosing: fixed		
	66.9±10.9	Treatment		
	<b>PEF AM (mean):</b> 338	duration; 12 wk.		
	Duration of asthma	Device: MDI		
	(mean±SD): 21.7±13.4	Withdraw LOE:		
	Smoking status: ≤10 pack-yr.	NR		
	GROUP 3	GROUP 4		
	N: 109	Drug mcg/day: FORM 18 + PLA		
	Age yr. (mean±SD): 40.7±14.2 Males %: 34.9			
		Dosing: fixed		
	FEV <sub>1</sub> % predicted (mean±SD):	Treatment		
	$70.0\pm10.5$	duration: 12 wk.		
	PEF AM (mean): 342 Duration of asthma	Device: separate		
	(mean±SD): 23.2±16.0	drug Withdraw LOE:		
	Smoking status: ≤10 pack-yr.	NR		
	Smoking status. 210 pack-yr.			
	GROUP 4	Reliever Tx:		
	<b>N:</b> 118	salbutamol prn		
	Age yr. (mean±SD): 40.0±16.4	Run-in Tx: single		
	Males %: 35.0	blind BUD (pMDI)		
	FEV <sub>1</sub> % predicted (mean±SD):	320 mcg/day.		
	67.5±11.5	Rescue		
	Mean PEF AM (mean): 339	salbutamol as		
	Duration of asthma	needed.		
	(mean±SD): 21.7±15.3	Run-in duration:		
	Smoking status: ≤10 pack-yr.	2 wk.		

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year:	Randomized: 2,760	GROUP 1	Definition of	Study objective: To
O'Byrne PM	Analyzed: 2,760 (ITT)	Drug mcg/day:	exacerbation:	determine if
2005 <sup>105</sup>	Withdrawals: 83	FORM/BUD,	Severe = deterioration in	FORM/BUD used for
Pub status:		12/200	asthma resulting in	regular maintenance
Journal article	ITT analysis: yes	Dosing: variable	hospitalization/emergency	therapy and sympto
	Asthma stage and severity:	Treatment	room treatment, oral	relief would further
No. countries:	symptomatic, intermittent-severe	duration: 48 wk.	steroid treatment (or an	reduce exacerbation
22	Baseline ICS use: non-naïve	Device:	increase in ICS [via a	and improve overall
No. centers:	Buschine 100 use. Hor harve	Turbuhaler®	separate inhaler] and/or	asthma control
246	GROUP 1	Withdraw LOE:	other additional treatment	compared with
Design:	N: 925	NR	for children aged 4-11	traditional LABA/ICS
randomized,	Age yr. (mean [range]): 35 (4-77)		years), or morning PEF of	therapy.
parallel, double	Males %: 45.5	GROUP 2	70% or less of baseline	uleiapy.
blind				
uinu	FEV <sub>1</sub> % predicted (mean	Drug mcg/day:	on 2 consecutive days.	
Fundin au	[range]): 73 (43-108)	FORM/BUD,	Mild = 2 consecutive days	
Funding:	PEF AM (mean±SD): NR	12/200	with either a morning PEF	
Industry:	Duration of asthma yr. (mean	Dosing: fixed	of 80% or less of	
AstraZeneca	[range]): 9 (0-63)	Treatment	baseline, as-needed use	
	Smoking status: NR	duration: 48 wk.	two or more inhalation per	
		Device:	day above baseline, or	
	GROUP 2	Turbuhaler <sup>®</sup>	awakenings caused by	
	N: 909	Withdraw LOE:	asthma.	
	Age yr. (mean [range]): 36 (4-79)	NR		
	Males %: 43.3		List of clinical	
	FEV <sub>1</sub> % predicted (mean	GROUP 3	outcomes reported:	
	[range]): 73 (46-108)	Drug mcg/day:	Primary	
	PEF AM (mean±SD): NR	BUD 640 mcg	<ul> <li>decrease to ≤ 70%</li> </ul>	
	Duration of asthma yr. (mean	Dosing: fixed	of baseline	
	[range]): 9 (0-65)	Treatment	<ul> <li>time to first</li> </ul>	
	Smoking status: NR	duration: 48 wk.	exacerbation	
	<b>3</b> • • • • •	Device:	no. severe	
	GROUP 3	Turbuhaler®	exacerbations	
	N: 926	Withdraw LOE:	exacerbation	
	Age yr. (mean [range]): 36 (4-79)	NR		
	Males %: 44.9		requiring ED/hospital	
	FEV <sub>1</sub> % predicted (mean	Reliever Tx:	time to second	
	[range]): 73 (49-100)	Group 1:	severe exacerbation	
	PEF AM (mean±SD): NR	FORM/BUD 6/100	<ul> <li>time to third</li> </ul>	
	. ,		exacerbation.	
	Duration of asthma yr. (mean [range]): 9 (0-69)	mcg prn; Group 2:	<ul> <li>Exacerbation</li> </ul>	
		FF/BUD 6/100 mcg	requiring OCS	
	Smoking status: NR	prn, terbutaline 0.4	Secondary	
		mcg prn; Group 3:	PM L/min	
		BUD + terbutaline	• DTS	
		0.4 mcg prn	NTS	
		Run-in Tx: ND	SFD	
		(pre-randomization	control days	
		treatment ICS 400-		
		1,000 ug)	daytime SABA use	
		Run-in duration:	nighttime SABA use	
		>10 d.	<ul> <li>change in ICS dose</li> </ul>	
			RFD	
			• NTA	
			<ul> <li>mild exacerbation</li> </ul>	
			days	

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year:	Randomized: 1,970	GROUP 1	Definition of	Study objective: To
O'Byrne PM	Analyzed: 1,947	Drug mcg/day:	exacerbation:	determine whether
2001 <sup>58</sup>	Withdrawals: 301	FORM/BUD	Severe = need for	regular treatment
Pub status:		12/200	treatment with oral	with low doses of
Journal article	ITT analysis: yes	Dosing: fixed	corticosteroids, as judged	BUD, with or without
	Asthma stage and severity:	Treatment	by the investigator, or	low doses of FORM,
No. countries:	symptomatic, intermittent-mild	duration: 52 wk.	hospital admission or	would reduce severe
17	Baseline ICS use: naïve	Device:		asthma
	Dasenne ICS use. naive	Turbuhaler <sup>®</sup>	emergency treatment for	
No. centers:			worsening asthma, or a	exacerbations and
198	GROUP 1	Withdraw LOE:	decrease in morning PEF	improve asthma
Design:	N: NR	NR	> 25% from baseline (the	control compared
randomized,	Age yr. (mean Stratum A/ mean		mean values during the	with placebo.
parallel, double	Stratum B): 31.2/36.5	GROUP 2	last 14 d. of the run-in) on	
blind	Males %: 36.8/ 44.6	Drug mcg/day:	two consecutive days.	
	FEV <sub>1</sub> % predicted (mean±SE):	FORM/BUD		
Funding:	89.1±0.97/86.4±0.91	12/400		
Industry:	PEF AM (mean±SE):	Dosing: fixed	List of clinical	
AstraZeneca	416±7.5/429±7.1	Treatment	outcomes reported:	
	Duration of asthma: NR	duration: 52 wk.	Primary	
	Smoking status: NR	Device:	<ul> <li>time to first severe</li> </ul>	
	Smoking status. NR	Turbuhaler <sup>®</sup>		
			exacerbation	
	GROUP 2	Withdraw LOE:	<ul> <li>poorly controlled</li> </ul>	
	N: NR	NR	asthma days	
	Age yr. (mean Stratum A/ mean			
	Stratum B): 36.8	GROUP 3	Secondary	
	Males %: 41.0	Drug mcg/day:	PEF AM	
	FEV <sub>1</sub> % predicted (mean±SE):	BUD 200	<ul> <li>FEV<sub>1</sub> % predicted</li> </ul>	
	86.5±0.92	Dosing: fixed	<ul> <li>rate per year of</li> </ul>	
	PEF AM (mean±SE): 412±6.5	Treatment	severe	
	Duration of asthma: NR	duration; 52 wk.		
	Smoking status: NR	Device:	exacerbations	
	emoking status. Art	Turbuhaler®	<ul> <li>rescue inhalations</li> </ul>	
	GROUP 3	Withdraw LOE:	SFD	
			<ul> <li>NTA</li> </ul>	
	N: NR	NR		
	Age yr. (mean Stratum A/ mean			
	Stratum B): 30.6/38.1	GROUP 4		
	Males %: 40.8/ 41.6	Drug mcg/day:		
	FEV <sub>1</sub> % predicted (mean±SE):	BUD 400		
	90.1±0.94/ 86.3±0.94	Dosing: fixed		
	PEF AM (mean±SE):	Treatment		
	421±7.4/419±7.1	duration: 52 wk.		
	Duration of asthma: NR	Device: single		
	Smoking status: NR	drugs		
	e	Withdraw LOE:		
	GROUP 4	NR		
		DITX		
	N: NR	Delleven Ter ND		
	Age yr. (mean Stratum A/ mean	Reliever Tx: NR		
	Stratum B): 37.5	Run-in Tx: PLA		
	Males %: 42.6	(group 1, ICS		
	FEV <sub>1</sub> % predicted (mean±SE):	naïve) or BUD 100		
	87.0±0.93	mcg bid (ICS		
	PEF AM (mean±SE): 416±6.5	maintenance)		
	Duration of asthma: NR	Run-in duration: 4		
	Smoking status: NR	wk.		
	Smoking status. NIX	VVI		

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Overbeek SE 2005 <sup>70</sup> Pub status: Journal article No. countries: 1 (The Netherlands) No. centers: 1 Design: randomized, parallel, double blind Funding: Industry: AstraZeneca	Randomized: 40 Analyzed: 40 Withdrawals: 0 ITT analysis: yes Asthma stage and severity: asymptomatic, intermittent to severe Baseline ICS use: naïve GROUP 1 N: 20 Age yr. (Group 1 & 2 combined) (mean (range)): 28.8 (19-52) Males % (Group 1 & 2 combined): 52.5 FEV <sub>1</sub> % predicted (mean±SD): 81.2±8.0 PEF AM (mean±SD): NR Duration of asthma: NR Smoking status: non-smoking GROUP 2 N: 20 Males %: NR FEV <sub>1</sub> % predicted (mean±SD): 75.1±12.1 PEF AM (mean±SD): NR Duration of asthma: NR Smoking status: non-smoking	GROUP 1 Drug mcg/day: FORM/BUD 24 /200 (8 wks)/ 800 (8 wks) Dosing: fixed Treatment duration: 16 wk. Device: Turbuhaler <sup>®</sup> Withdraw LOE: 0 GROUP 2 Drug mcg/day: BUD 200 (8 wks) + PLA/800 (8 wks) + PLA Dosing: fixed Treatment duration: 16 wk. Device: Turbuhaler <sup>®</sup> Withdraw LOE: 0 Reliever Tx: terbutaline prn Run-in Tx: terbutaline only Run-in duration: 4 wk.	Definition of exacerbation: NR List of clinical outcomes reported: Primary • No primary clinical outcomes of interest Secondary • FEV1 % predicted • PC <sub>20</sub>	Study objective: To determine if adding inhaled LABA to a low dose of ICS resulting in better asthma control than increasing the dose of ICS is due to an additional reduction of airway inflammation Additional Details: Increased dose of BUD by 400 mcg in both groups in weeks 9-16.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Papi A 2007 <sup>132</sup> Pub status: Journal article No. countries: NR No. centers: 13 Design: randomized, parallel, double blind, double dummy Funding: Industry: Chiesi Pharmaceutical	Randomized: 219 Analyzed: 216 Withdrawals: 19 ITT analysis: yes Asthma stage and severity: symptomatic, moderate-severe Baseline ICS use: non-naïve GROUP 1 N: 107 Age yr. (mean±SD): 43.4±12.3 Males %: 42.1 FEV <sub>1</sub> % predicted (mean±SD): 70.5±10.7 PEF AM (mean±SD): 308.9±106.6 Duration of asthma (minimum): 11.8 yr. (9.5) Smoking status: <10 pack-yr GROUP 2 N: 109 Age yr. (mean±SD): 46.0±11.1 Males %: 42.2 FEV <sub>1</sub> % predicted (mean±SD): 69.3±9.7 PEF AM (mean±SD): 305.2±100 Duration of asthma (minimum): 12.4 yr. (10.4) Smoking status: <10 pack-yr	GROUP 1 Drug mcg/day: FORM/BDP 24/400 Dosing: fixed Treatment duration: 12 wk. Device: MDI Withdraw LOE: NR GROUP 2 Drug mcg/day: FORM/BUD 24/800 Dosing: fixed Treatment duration: 12 wk. Device: Turbuhaler <sup>®</sup> Withdraw LOE: NR Reliever Tx: salbutamol Run-in Tx: current ICS only Run-in duration: 2 wk.	Definition of exacerbation: NR List of clinical outcomes reported: Primary • PEF AM Secondary • PEF PM • FEV1 • FVC • no. mild/mod/seve re exacerbations • time to first exacerbation • DTS • NTS • SABA use • SFD • RFN • MEF 50%	Study objective: To compare the fixed combination of BDP and FORM in an HFA MDI (pMDI), with a combination of BUD and FORM administered via a Turbuhaler <sup>®</sup> DPI Additional Details: Comparison of pMDI and DPI inhalers

			Clinical	
<b>0</b> ( )		Treatment	outcomes	Nutri
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 228	GROUP 1	Definition of	Study objective:
Papi A 2007 <sup>134</sup>	Analyzed: 225	Drug mcg/day:	exacerbation:	To compare a new
Pub status:	Withdrawals: 3	FORM/BDP	Mild = ≥2	fixed combination of
Journal article		24/400	consecutive days	extrafine BDP and
	ITT analysis: yes	Dosing: fixed	with: morning PEF	FORM, with the
No. countries:	Asthma stage and severity:	Treatment	more than 20%	fixed combination
NR	symptomatic, moderate-severe	duration: 12 wk.	below the baseline	FP and SAL
No. centers: 12	Baseline ICS use: non-naïve	Device: MDI	value, or use of	
Design:		Withdraw LOE: 0	more than three	
randomized,	GROUP 1		additional	
parallel, double	<b>N:</b> 115	GROUP 2	inhalations of	
blind	Age yr. (mean±SD): 47.3±12.6	Drug mcg/day:	rescue salbutamol	
	Males %: 45.2	SAL/FP 100/500	for a 24 hr period	
Funding:	FEV <sub>1</sub> % predicted (mean±SD):	Dosing: fixed	when compared	
Industry: Chiesi	67.7±9.57	Treatment	with baseline, or a	
Pharmaceutical	PEF AM (mean±SD):	duration: 12 wk.	night-time asthma	
	287.2±99.1	Device: MDI	symptoms score	
	Duration of asthma (median	Withdraw LOE: 0	≥3. Severe =	
	[range]): 10.1 (8.6)		morning PEF more	
	Smoking status: <10 pack-yr.	Reliever Tx: OCS	than 30% below	
	emeking etatue. The pack yr.	in case of	the baseline value	
	GROUP 2	exacerbations;	on ≥2 consecutive	
	<b>N</b> : 113	salbutamol prn	days, or a	
	Age yr. (mean±SD): 49.7±10.2	Run-in Tx:	deterioration in	
	Males %: 42.5	current ICS	asthma requiring	
	FEV <sub>1</sub> % predicted (mean±SD):		administration of	
	66.9±9.59	(≤1,000 mcg/day) <b>Run-in duration:</b>	oral	
	PEF AM (mean±SD): 275.1±92.6	2 wk.	corticosteroids.	
	Duration of asthma (median		List of clinical	
	[range]): 8.7 (7.7)		outcomes	
	Smoking status: <10 pack-yr		reported:	
			Primary	
			PEF AM	
			Secondary	
			mean change	
			in PEF PM	
			mean change	
			in FEV <sub>1</sub>	
			• FVC	
			<ul><li>PVC</li><li>DTS</li></ul>	
			• NTS	
			<ul><li>Reliever use</li><li>SFD</li></ul>	

			Clinical	
		Treatment	outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 852	GROUP 1	Definition of	Study objective:
Pauwels RA	Analyzed: 852	Drug mcg/day:	exacerbation:	To evaluate the
1997 <sup>140</sup>	Withdrawals: 158	FORM/BUD	Severe – requiring	effects of adding
Pub status:		24/200	treatment with oral	inhaled FORM to
Journal article	ITT analysis: yes	Dosing: fixed	glucocorticoids, as	both lower and
	Asthma stage and severity:	Treatment	judged by the	higher doses of
No. countries:	asymptomatic, intermittent to	duration: 52 wk.	investigator or a	BUD.
9	severe	Device:	decrease in the	
No. centers: 71	Baseline ICS use: non-naïve	Turbuhaler®	PEF as measured	
Design:		Withdraw LOE:	in the morning to	
randomized,	GROUP 1	total (across all	more than 30%	
parallel, double	<b>N:</b> 210	groups): 30	below the BL value	
blind	Age yr. (mean [range]): 41		on 2 consecutive	
	(18-68)	GROUP 2	days. Mild – days	
Funding:	Males %: 49.5	Drug mcg/day:	when one of the	
Industry: Astra	FEV <sub>1</sub> % predicted (mean):	BUD 200 + PLA	following occurred:	
Draco	75.7	Dosing: fixed	a PEF ĂM >20%	
	PEF AM (mean): 399	Treatment	below the BL	
	Duration of asthma	duration: 52 wk.	value; the use of	
	(minimum): ≥6 mo.	Device:	>3 additional	
	Smoking status: NR	Turbuhaler <sup>®</sup>	inhalations of	
	5	Withdraw LOE:	terbutaline per 24	
	GROUP 2	NR	hours as	
	N: 213		compared with the	
	Age yr. (mean [range]): 42	GROUP 3	BL period; or	
	(18-70)	Drug mcg/day:	awakening at night	
	Males %: 50.7	FORM/BUD	due to asthma.	
	FEV <sub>1</sub> % predicted (mean):	24/800		
	75.8	Dosing: fixed	List of clinical	
	PEF AM (mean): 397	Treatment	outcomes	
	Duration of asthma	duration; 52 wk.	reported:	
	(minimum): ≥6 mo	Device:	Primary	
	Smoking status: NR	Turbuhaler®	• mild	
	entering etataer int	Withdraw LOE:	exacerbations	
	GROUP 3	NR	<ul> <li>severe</li> </ul>	
	N: 215		<ul> <li>severe exacerbations</li> </ul>	
	Age yr. (mean [range]): 42	GROUP 4	exacerbations	
			0	
	(17-70) Malos %: 47.4	Drug mcg/day: BUD 800 + PLA	Secondary	
	Males %: 47.4	<b>Dosing:</b> fixed	<ul> <li>FEV<sub>1</sub></li> </ul>	
	FEV <sub>1</sub> % predicted (mean):		withdrawals	
	76.3	Treatment	due to	
	PEF AM (mean): 394	duration: 52 wk.	exacerbations	
	Duration of asthma	Device: separate	<ul> <li>pts without</li> </ul>	
	(minimum): ≥6 mo.	drug	severe	
	Smoking status: NR	Withdraw LOE:	exacerbation	
		NR	<ul> <li>DTS</li> </ul>	
	GROUP 4	Della	NTS	
	N: 214	Reliever Tx:	<ul> <li>daytime SABA</li> </ul>	
	Age yr. (mean [range]): 44	terbutaline prn	use	
	(18-70)	Run-in Tx: BUD	<ul> <li>nighttime</li> </ul>	
	Males %: 47.7	800 mcg bid +	SABA use	
	FEV <sub>1</sub> % predicted (mean):	terbutaline prn	<ul> <li>episode-free</li> </ul>	
	75.4	Run-in duration:	days	
	PEF AM (mean): 381	4 wk.	<ul> <li>NTA</li> </ul>	
	Duration of asthma			
	<b>(minimum):</b> ≥6 mo			
	Smoking status: NR			

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Pearlman DS ar 2004 <sup>74</sup> A Pub status: W Journal article II No. countries: A 2 (United sy States, Puerto B Rico) no No. centers: 36 Design: G randomized, N parallel, double A blind (1 Funding: FI Industry: 68 GlaxoSmithKline PI 37 D States Puerto B Rico) no No. centers: 36 Design: G randomized, N parallel, double A blind (1 M Funding: FI Industry: 68 GlaxoSmithKline PI 37 D States Puerto B Rico) no No. centers: 36 Design: G randomized, N parallel, double A blind (1 M Funding: FI Industry: 68 GlaxoSmithKline PI 36 D	<pre>kandomized: 360 (181 CE rms) analyzed: 279 (160 CE arms) Vithdrawals: 81 (21 CE arms) Vithdrawals: 81 (21 CE arms) Vithdrawals: 81 (21 CE arms) IT analysis: no asthma stage and severity: ymptomatic, intermittent-mild aseline ICS use: naïve &amp; on-naïve GROUP 1 I: 85 age yr. (mean [range]): 32.8 12-63) Iales %: 38 EV1 % predicted (mean±SD): 8.1±11.1 PEF AM (mean±SD): 76.1±75.6 Puration of asthma: NR moking status: NR GROUP 2 I: 75 age yr. (mean [range]): 34.7 12-74) Iales %: 42 EV1 % predicted (mean±SD): 7.1±11.3 PEF AM (mean±SD): 69.2±76.2 Puration of asthma: NR moking status: NR</pre>	GROUP 1 Drug mcg/day: SAL/FP 100/200 Dosing: fixed Treatment duration: 12 wk. Device: MDI HFA Withdraw LOE: 14/281 GROUP 2 Drug mcg/day: FP 200 Dosing: fixed Treatment duration: 12 wk. Device: MDI Withdraw LOE: 20/277 Reliever Tx: albuterol Run-in Tx: PLA HFAa propellant in MDI and albuterol prn Run-in duration: 2 wk.	Definition of exacerbation: Clinical exacerbation requiring emergency treatment. List of clinical outcomes reported: Primary • % improvement • FEV1 AUC • Secondary • PEF AM • PEF PM • DTS • SFD • NTA • probability of remaining in study	Study objective: To compare the efficacy and safety of FP/SAL (44/21 mcg) delivered as two inhalations twice daily via a single hydrofluoroalkane (HFA 134a) MDI (FSC) with that of placebo HFA 134a (PLA), FP (44 mcg CFC) alone and SAL (21 mcg CFC) alone (S) in patients with persistent asthma previously treated with $\beta_2$ - agonists (short- or long-acting) or ICS. Additional Details: Comparing HFA and CFC propellants

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Peters SP 2007 <sup>123</sup> Pub status: Journal article No. countries: 1 ? No. centers: 19 Design: randomized, parallel, double blind Funding: Industry: GlaxoSmithKline	Randomized: 500 Analyzed: 495 Withdrawals: 49 ITT analysis: no Asthma stage and severity: asymptomatic, mild Baseline ICS use: non-naïve GROUP 1 N: 162 Age yr. (mean±SD): 30.8±14.4 Males %: 37.6 FEV <sub>1</sub> % predicted (mean±SD): 92.4±15.3 PEF AM (mean±SD): NR Duration of asthma (mo.): age at onset 16.2±22.2 Smoking status – prev (n (%)): 30 (18.2) GROUP 2 N: 168 Age yr. (mean±SD): 29.3±14.6 Males %: 39.1 FEV <sub>1</sub> % predicted (mean±SD): 92.8±10.4 PEF AM (mean±SD): NR Duration of asthma: NR Smoking status – prev (n (%)): 17 (10.1)	GROUP 1 Drug mcg/day: SAL/FP 50/100 Dosing: fixed Treatment duration: 16 wk. Device: diskhaler Withdraw LOE: 4 GROUP 2 Drug mcg/day: FP 200 Dosing: fixed Treatment duration: 16 wk. Device: diskhaler Withdraw LOE: 3 Reliever Tx: NR Run-in Tx: open label FP 100µg bid Run-in duration: 16 wk.	Definition of exacerbation: NR List of clinical outcomes reported: Primary • time to Tx failure • tx failure rate Secondary • mean change in PEF % predicted • mean change in FEV1 % predicted • % SFD • ACQ • ASUI • Mini-AQLQ • reliever use • % predicted FVC • % RFD • >1 night awakening % pts	Study objective: To describe the effect of stepping down therapy to either therapy with the leukotriene modifier montelukast or with once-daily fluticasone plus salmeterol in patients with mild asthma that was well controlled with the use of twice- daily fluticasone. Additional Details: Use of montelukast or a combination of fluticasone and salmeterol as step- down therapy.

		Treatment	Clinical outcomes	
Study	Participant charactoristics			Notos
Study Author Year: Peters 2008 <sup>101</sup> Pub status: Industry report No. countries: 1 (United States) No. centers: 77 Design: randomized, parallel, double blind Funding: Industry: AstraZeneca	Participant characteristics Randomized: 708 Analyzed: 708 Withdrawals: 129 ITT analysis: yes Asthma stage and severity: asymptomatic, moderate, severe Baseline ICS use: non-naïve GROUP 1 N: 132 Age yr (mean±SD): 38.6±16.15 Males %: 40.9 FEV <sub>1</sub> % predicted (mean±SD): 72.1±13.59 PEF AM L/min (mean±SD): NR Duration of asthma (mean±SD): 22.6 yr. ±15.19 Smoking status: NR GROUP 2 N: 443 Age yr (mean±SD): 41±16.61 Males %: 37 FEV <sub>1</sub> % predicted (mean±SD): 74.8±14.46 PEF AM L/min (mean±SD): NR Duration of asthma (mean±SD): 22.3 yr. ±15.34 Smoking status: NR GROUP 3 N: 133 Age yr (mean±SD): 39.8±15.61 Males %: 31.6 FEV <sub>1</sub> % predicted (mean±SD): 72.7±13.59 PEF AM L/min (mean±SD): NR Duration of asthma (mean±SD): 24.4 yr. ±15.48	TreatmentcharacteristicsGROUP 1Drug mcg/day:FORM/BUD18/800Dosing: fixedTreatmentduration: 52 wk.Device: MDIWithdraw LOE:NRGROUP 2Drug mcg/day:FORM/BUD36/1600Dosing: fixedTreatmentduration: 52 wk.Device: MDIWithdraw LOE:NRGROUP 3Drug mcg/day:BUD 1600Dosing: fixedTreatmentduration: 52 wk.Device: MDIWithdraw LOE:NRReliever Tx:albuterol prnRun-in Tx: BUD800 mcg (singleblind); albuterolprnRun-in duration:2 wk.	reported         Definition of         exacerbation:         worsening asthma         requiring use of         OCS or         hospitalization or         ED visit         List of clinical         outcomes         reported:         Primary         • No variable         described as         primary         clinical         outcome         Secondary         • FEV1         • no. pts with ≥1         exacerbation         • DTS         • SFD         • asthma         control days         • RFD         • Use of other         asthma tx         • missed         work/school         due to asthma	Notes Study objective: To examine long- term safety of BUD/FORM via pMDI in pts with moderate to severe asthma.

			Clinical	
04	Deuticia autoricano eteriotica	Treatment	outcomes	Natas
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 133	GROUP 1	Definition of	Study objective: To
Pohl WR 2006 <sup>141</sup>	Analyzed: 126	Drug mcg/day:	exacerbation:	examine the effects of
	Withdrawals: 24	FORM/BUD, 18	Severe = requiring	adjustable
Pub status:	ITT analysia, year all nationta	(wk 1-4), 9-18	one or more of:	maintenance dosing
Journal article	ITT analysis: yes – all patients	(wk 5-8), 6-18	hospitalization;	with
No countricou	with efficacy measurement on	(wk 9-20)	nebulized β <sub>2</sub> -	budesonide/formoterol
No. countries:	treatment (n=126)	mcg/640 (wk 1-	agonits; oral	(160/4.5 mcg) or
1 No contoro:	Asthma stage and severity: intermittent to severe	4), 320-640 (wk 5-8), 200-640	steroids; or	higher-dose budesonide (320 mcg);
No. centers: 16	Baseline ICS use: naïve &	(wk 9-20) mcg	withdrawal owing	the ICS dose per
			to lack of efficacy or a life-	•
Design:	non-naïve	<b>Dosing:</b> fixed	•••••	inhalation was 2-fold
randomized,		(wk fixed-4),	threatening/fatal condition.	higher in patients
parallel, double blind	GROUP 1 N: 65	variable (wk 5-	condition.	treated with budesonide than in
DIITU		variable0)	List of alinical	
Funding	<b>Age yr. (mean (range))</b> : 45	Treatment duration: 20 wk.	List of clinical outcomes	those treated with
Funding:	(20-80) <b>Males %:</b> 59	Device:		budesonide/formoterol.
Industry:			reported:	Additional Dataila
AstraZeneca	FEV <sub>1</sub> % predicted (mean	Turbuhaler® Withdraw LOE:	Primary	Additional Details:
	(range)): 65 (39-85)	Withdraw LOE:	Composite:	Fixed dosing weeks 1- 4, adjustable dosing
	PEF AM (mean±SD): NR Duration of asthma yr. (mean	GROUP 2	no. patients	
			experiencing	regimen (2-4
	(range)): 10 (0-35)	Drug mcg/day:	treatment	inhalations/dy) weeks
	Smoking status –	BUD, 1280 (wk	failure	4-8, adjustable dosing
	documented smoking habit	1-4), 640-1280	(treatment	regimen (1-4
	<b>n(%):</b> 24 (38)	(wk 5-8), 320-	failure	inhalations/dy) from
		1280 (wk 9-20)	defined as (a)	week 8.
	GROUP 2 N: 68	mcg	hospitalizatio	
		<b>Dosing:</b> fixed	n; (b)	
	<b>Age yr. (mean (range))</b> : 45	(wk fixed-4),	nebulized	
	(20-82) <b>Males %:</b> 48	variable (wk 5-	beta2-	
		variable0) <b>Treatment</b>	agonists; (c)	
	FEV <sub>1</sub> % predicted (mean		oral steroids;	
	(range)): 67 (35-88) PEF AM (mean±SD): NR	duration: 20 wk. Device:	(d) withdrawal	
		Turbuhaler®	due to no	
	Duration of asthma yr. (mean (range)): 4.5 (0-30)	Withdraw LOE:	efficacy or	
		Withuraw LOE.	fatal	
	Smoking status –	Reliever Tx:	condition.)	
	documented smoking habit		0	
	<b>n(%):</b> 21 (33)	Terbutaline prn	Secondary	
		Run-in Tx: no	mean change	
		run-in <b>Run-in duration:</b>	in PEF PM	
		20 wk.	mean change	
		20 WK.	in FEV <sub>1</sub>	
			<ul> <li>% days pts</li> </ul>	
			required use	
			<ul> <li>treatment</li> </ul>	
			satisfaction	
			<ul> <li>dose of</li> </ul>	
			medication	

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year:	Randomized: 663	GROUP 1 (Part 1)	Definition of	Study objective: To
Price D 2002 <sup>91</sup>	Analyzed: 663	Drug mcg/day:	exacerbation: Any	determine the effect of
Pub status:	Withdrawals: 37	FORM/BUD 18/800	combination of the	adding formoterol to a
Journal article		Dosing: fixed	following for 2	lower dose
	ITT analysis: yes	Treatment	consecutive days:	budedsonide (400 mcg
No. countries: 2	Asthma stage and severity:	duration: 4 wk.	PEF <80% baseline,	gd) on the time to first
United Kingdom,	asymptomatic, mild	Device: Turbohaler	SABA use 4	mild asthma
reland)	Baseline ICS use: naïve	Withdraw LOE: NR	inhalations above	exacerbation (Part 2).
No. centers: 152	Baseline 100 ase. haive		baseline post-Part 1,	
Design:	GROUP 1 (Part 1)	GROUP 2 (Part 1)	night awakening due	Additional details:
randomized,	N: 332	Drug mcg/day:	to asthma	Study consisted o
parallel, double	Age yr. (mean±SD): 38.9±16.7	BUD 800 + PLA	to astrina	,
,	Males %: 41		List of clinical	two randomization
blind		Dosing: fixed	List of clinical	periods: Part 1 to
<b>F</b>	FEV <sub>1</sub> % predicted: NR	Treatment	outcomes reported:	determine effect of
Funding:	PEF AM L/min (mean±SD):	duration: 4 wk.	Bailes and	adding formoterol to a
Industry:	402.2±94.8	Device:	Primary	moderate dose of
AstraZeneca	Duration of asthma: <1yr - >5yrs	Turbuhaler®	time until 3	budesonide (400 mcg
	Smoking status: NR	Withdraw LOE: NR	consecutive days	bid) on length of time to
			with symptom score	achieve asthma
	GROUP 2 (Part 1)	GROUP 1 (Part 2)	of 0 (Part 1)	control. Treatment
	N: 331	Drug mcg/day:	time to first mild	period lasted 4 wk. Par
	Age yr. (mean±SD): 37.7±16.1	FORM/BUD 18/400	exacerbation (Part 2)	2 described above.
	Males %: 43	Dosing: fixed	, , , , , , , , , , , , , , , , , , ,	Patients achieving
	FEV <sub>1</sub> % predicted: NR	Treatment	Secondary	asthma control by end
	PEF AM L/min (mean±SD):	duration; 26 wk.	time to first	of Part 1 re-randomized
	404.1±93.5	Device:	severe exacerbation	to Part 2 treatment.
	Duration of asthma: <1yr - >5yrs	Turbuhaler®	frequency of	
	Smoking status: NR	Withdraw LOE: NR	mild and severe	
	emening etataer nit			
	GROUP 1 (Part 2)	GROUP 2 (Part 2)	exacerbations	
	N: 250	Drug mcg/day:	% of pts free of	
	Age yr. (mean±SD): 37.2±16.0	BUD 400 + PLA	exacerbations during	
	Males %: 39		6 mo. treatment	
		Dosing: fixed Treatment	time to first	
	FEV1 % predicted: NR		poorly controlled day	
	PEF AM L/min (mean±SD):	duration: 26 wk.	frequency of	
	441.2±106.7	Device:	poorly controlled	
	Duration of asthma: <1yr - >5yrs	Turbohaler®	days	
	Smoking status: NR	Withdraw LOE: NR	5	
	GROUP 2 (Part 2)	Reliever Tx: SABA		
	N: 255	as needed		
	Age yr. (mean±SD): 38.3±16.7	<b>Run-in Tx:</b> <400		
	Males %: 42	mcg/d BUD or BDP		
	FEV <sub>1</sub> % predicted: NR	via MDI or <200		
	PEF AM L/min (mean±SD): 439.6	mcg/d via		
	±101.7	Turbuhaler®		
	Duration of asthma: <1yr - >5yrs Smoking status: NR	Run-in duration: 7- 14 d		

			Clinical	
		Treatment	outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 697	GROUP 1	Definition of	Study objective: To
Rabe KF	Analyzed: 696	Drug mcg/day:	exacerbation:	compare the efficacy
2006 <sup>122</sup>	Withdrawals: 58	FF/BUD 9/160	hospitalization/ED	and safety of
Pub status:		Dosing: fixed	treatment due to	FORM/BUD for both
Journal article	ITT analysis: all randomized (1	Treatment	asthma worsening,	maintenance and
	pt lost)	duration: 26 wk.	need for OCS,	symptom relief with
No. countries:	Asthma stage and severity:	Device: DPI	≥30% decrease	that of double the
9	symptomatic, mild to moderate	Withdraw LOE:	from baseline PEF	dose of BUD (320
No. centers: 77	Baseline ICS use: non-naïve	NR	AM for 2	mcg) and terbutaline
Design:			consecutive days.	over 6 mo.
randomized,	GROUP 1	GROUP 2		
parallel, double	N: 354	Drug mcg/day:	List of clinical	
blind	Age yr. (mean±SD): 38±16.75	BUD 320	outcomes	
Funding an	Males %: 41	Dosing: fixed	reported:	
Funding:	FEV <sub>1</sub> % predicted (mean±SD):	Treatment duration: 26 wk.	Primary	
Industry: AstraZeneca	75±18 PEF AM L/min (mean±SD):	Device: DPI	PEF AM	
Asliazeneca	345±142.5	Withdraw LOE:		
	Duration of asthma, yr.	NR	PEF PM	
	(mean±SD): 10±17.25		Secondary	
	Smoking status %	Reliever Tx:	FEV <sub>1</sub> %	
	(never/occasional/habitual):	Terbutaline as	predicted	
	93/3/4	needed	total daily	
		Run-in Tx: BUD	asthma symptom	
	GROUP 2	100 mcg bid +	score (scale 0-3)	
	N: 342	terbutaline as	RFD	
	Age yr. (mean±SD): 38±16.75	needed	SFD	
	Males %: 36	Run-in duration:	NTA	
	FEV <sub>1</sub> % predicted (mean±SD):	14-18 d	asthma	
	75±14.25		control days	
	PEF AM L/min (mean±SD):		(combined SFD	
	335 <b>±</b> 151.75		and RFD)	
	Duration of asthma, yr.			
	(mean±SD): 10±15			
	Smoking status %			
	(never/occasional/habitual):			
	92/4/4			

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Ringdal N 2002 <sup>130</sup> Pub status: Journal article No. countries: 11 No. centers: NR	Randomized: 428 Analyzed: 379 Withdrawals: 49 ITT analysis: yes Asthma stage and severity: symptomatic, moderate to severe Baseline ICS use: non-naïve	GROUP 1 Drug mcg/day: SAL/FP 100/500 + 2 placebo Turbuhalers <sup>®</sup> Dosing: fixed Treatment duration: 12 wk. Device: Diskus <sup>®r</sup> Withdraw LOE:	Definition of exacerbation: severe = deterioration in asthma requiring emergency hospital treatment List of clinical outcomes	Study objective: To demonstrate similar efficacy between SAL/FP 100/500 in one Diskus vs. FORM/BUD 24/1600 in two Turbuhalers <sup>®</sup>
Design: randomized, parallel, double blind, double dummy	GROUP 1 N: 189 Age yr. (mean±SD): 46.5±14 Males %: 40 FEV <sub>1</sub> % predicted (mean±SD):	2 GROUP 2 Drug mcg/day: FORM/BUD,	reported: Primary PEF AM	
Funding: Industry: GlaxoSmithKline	69.2±10.7) PEF AM L/min (mean±SD): 349±101 Duration of asthma: Smoking status: <10 pack-yr.	24/1600 + PLA Diskus Dosing: fixed Treatment duration: 12 wk. Device:	Secondary PEF PM PEF PM % diurnal variation FEV <sub>1</sub> exacerbation	
	GROUP 2 N: 190 Age yr. (mean±SD): 48.1±13.9 Males %: 49 FEV <sub>1</sub> % predicted: 69±10.1 PEF AM L/min (mean±SD): 348±101 Duration of asthma: Smoking status: <10 pack-yr.	Turbuhaler <sup>®</sup> Withdraw LOE: 4 Reliever Tx: salbutamol Run-in Tx: pre- study ICS Run-in duration:	rate DTS score NTS score salbutamol use night time awakening withdrawals	

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Rojas RA 2007 <sup>60</sup> Pub status: Journal article No. countries: 9 No. centers: 52 Design: randomized, parallel, double blind Funding: Industry: GlaxoSmithKline	Randomized: 362 Analyzed: 362 Withdrawals: 12 ITT analysis: yes Asthma stage and severity: symptomatic, moderate Baseline ICS use: naïve GROUP 1 N: 180 Age yr (mean [range]): 40 (15-78) Males %: 43 FEV <sub>1</sub> % predicted (mean±SD): 72.6±7.2 PEF AM L/min (mean±SD): 337±102 Duration of asthma yr.: <5: 30%; 5-10: 18%; 10-<20: 26; ≥20: 26% Smoking status: <10 pack-yr. GROUP 2 N: 182 Age yr (mean [range]): 41 (12-74) Males %: 42 FEV <sub>1</sub> % predicted(mean±SD): 71.9±5.9 PEF AM L/min (mean±SD): 335±106 Duration of asthma yr.: <5: 28%; 5-10: 24%; 10-<20: 27; ≥20: 21% Smoking status: <10 pack-yr.	GROUP 1 Drug mcg/day: SAL/FP 100/500 Dosing: fixed Treatment duration: 12 wk. Device: diskhaler Withdraw LOE: NR GROUP 2 Drug mcg/day: FP 500 Dosing: fixed Treatment duration: 12 wk. Device: diskhaler Withdraw LOE: NR Reliever Tx: salbutamol prn Run-in Tx: NR Run-in duration: 2 wk.	Definition of exacerbation: Deterioration in asthma that required OCS. List of clinical outcomes reported: Primary PEF AM Secondary exacerbation rate SFD SFN % pts who achieved well- controlled asthma	Study objective: To investigate whether the use of SAL/FP 50 mcg/250 mcg combination bid as initial maintenance therapy in patients with moderate asthma and treated with SABA only offered superior efficacy to FP 250 mcg bid

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year:	Randomized: 61	GROUP 1	Definition of	Study objective: To
SAM30007	Analyzed: 61	Drug mcg/day:	exacerbation: NR	determine whether
2005 <sup>146</sup>	Withdrawals: 6	SAL/FP NR/1000,		FP in combination
Pub status:		500, 200; 100	List of clinical	with SAL allowed
Industry report	ITT analysis: yes	(dose-scaling)	outcomes	dose-titration to a
	Asthma stage and severity:	Dosing: fixed	reported:	lower ICS dose than
No. countries:	asymptomatic, moderate	Treatment		FP alone while
1 (Denmark)	Baseline ICS use: non-naïve	duration: 24	Primary	maintaining asthma
No. centers: 5		Device: NR	minimum	control.
Design:	GROUP 1	Withdraw LOE:	acceptable dose	
randomized,	N: 29	0	time to	Additional details:
parallel, double	Age yr (mean±SD): 38.2±11.4		uncontrolled	Dose reduction
blind	Males %: 52	GROUP 2	asthma	design: Initial Tx
	FEV <sub>1</sub> % predicted (mean±SD):	Drug mcg/day:		dose was
Funding:	NR	FP 1000 500,	Secondary	administered for 6
Industry:	PEF AM L/min (mean±SD):	200; 100 (dose-	PEF AM	wk. After each 6-wk.
GlaxoSmithKline	470.4±121.7	scaling)	PEF PM	period, subjects
	Duration of asthma: NR	Dosing: fixed	FEV <sub>1</sub> AM	whose asthma was
	Smoking status: NR	Treatment	DTS score	controlled were
		duration: 24 wk.	NTS score	given the next dose
	GROUP 2	Device: NR	reliever use (#	down for a further 6
	N: 32	Withdraw LOE:	days with no relief	wk. and so on until
	Age yr (mean±SD): 36.2±11.8	0	medication)	subjects were no
	Males %: 53		medication	longer receiving
	FEV <sub>1</sub> % predicted (mean±SD):	Reliever Tx: NR		study medication.
	NR	Run-in Tx: BUD		
	PEF AM L/min (mean±SD):	1500-2000 mcg		
	469±119.5	or equivalent		
	Duration of asthma: NR	Run-in duration:		
	Smoking status: NR	2 wk.		

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year:	Randomized: 237	GROUP 1	Definition of	Study objective: To
SAM30013	Analyzed: 237	Drug mcg/day:	exacerbation: NA	compare the efficacy
2005 <sup>126</sup>	Withdrawals: 11	SAL/FP 100/200		of SAL/FP 50/100
Pub status:		Dosing: fixed	List of clinical	mcg bid with FP 250
Industry report	ITT analysis: yes	Treatment	outcomes	mcg bid in the
	Asthma stage and severity:	duration: 12 wk.	reported:	treatment of mild to
No. countries:	symptomatic, mild, moderate	Device: MDI	Primary	moderate asthmatics
1 (Canada)	Baseline ICS use: non-naïve	Withdraw LOE:	PEF AM	who remain
No. centers: 40		0		uncontrolled on FP
Design:	GROUP 1		Secondary	100 bid.
randomized,	<b>N:</b> 121	GROUP 2	PEF PM	
parallel, double	Age yr (mean±SD): 37.7±14.1	Drug mcg/day:	FEV <sub>1</sub>	
blind	Males %: 30	FP 500		
	FEV <sub>1</sub> % predicted (mean±SD):	Dosing: fixed		
Funding:	NR	Treatment		
Industry:	PEF AM L/min (mean±SD):	duration: 12 wk.		
GlaxoSmithKline	335.6±105.2	Device: MDI		
	Duration of asthma: NR	Withdraw LOE:		
	Smoking status: NR	0		
	GROUP 2	Reliever Tx: NR		
	<b>N:</b> 116	Run-in Tx: Open		
	Age yr (mean±SD): 36.4±14.9	label FP 200		
	Males %: 40	mcg/d		
	FEV <sub>1</sub> % predicted (mean±SD):	Run-in duration:		
	NR	6 wk.		
	PEF AM L/min (mean±SD):			
	349.1±98.0			
	Duration of asthma: NR			
	Smoking status: NR			

Author Year: SAM40008Randomized: 186GROUP 1SAM40008Analyzed: 186Drug mcg/da2004 <sup>145</sup> Withdrawals: 172SAL/FPPub status:100/1000, 500Industry reportITT analysis: yes200, no drugAsthma stage and severity:Dosing: fixedNo. countries:asymptomatic, severeTreatment10Baseline ICS use: non-naïveduration: 24 yNo. centers: 34Device: diskhDesign:GROUP 1Withdraw LOrandomized,N: 9367/93parallel, doubleAge yr (mean±SD): 48.4±15.1GROUP 2	ability of SAL/FP to allow tapering of the outcomes ICS dose in subjects reported: currently taking BUD Primary 1,500-2,000 mcg;
Funding:FEV1 % predicted (mean±SD):Drug mcg/daIndustry:PEF AM L/min (mean±SD):200, no drugGlaxoSmithKline386Dosing: fixedDuration of asthma: NRTreatmentSmoking status: NRduration: 24 %Device: diskhGROUP 2N: 9374/93Age yr (mean±SD): 50.9±16.1Reliever Tx: 1Males %: 43Reliever Tx: NRFEV1 % predicted (mean±SD):Run-in duratiNRPEF AM L/min (mean±SD):NR90339Duration of asthma: NR	naler DE:acceptable dose % pts with acceptable control time to treatment failurecontrol can be maintained with a lower mcg of SAL/FP than FP alone.ay: O,Secondary PEF AM PEF PM 

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAM40010 2004 <sup>136</sup> Pub status: Industry report No. countries: 6 No. centers: 50	Randomized: 373 Analyzed: 373 Withdrawals: 11 ITT analysis: yes Asthma stage and severity: symptomatic, mild-severe Baseline ICS use: non-naïve	GROUP 1 Drug mcg/day: FORM/BUD 9/400 Dosing: fixed Treatment duration: 12 wk. Device: 6 Withdraw LOE:	Definition of exacerbation: NR List of clinical outcomes reported: Primary PEF AM	Study objective: To compare the efficacy of SAL/FP 50/100 mcg bid vs FORM/BUD 4.5/200 bid in subjects whose asthma is poorly controlled by low-dose ICS.
Design: randomized, parallel, double blind, double dummy Funding: Industry: GlaxoSmithKline	GROUP 1 N: 183 Age yr (mean $\pm$ SD): 41.9 $\pm$ 15.4 Males %: 44 FEV <sub>1</sub> % predicted (mean $\pm$ SD): NR PEF AM L/min (mean $\pm$ SD): 353 $\pm$ 90 Duration of asthma: $\geq$ 6 mo () Smoking status: NR GROUP 2 N: 190 Age yr (mean $\pm$ SD): 42.9 $\pm$ 16.2 Males %: 37 FEV <sub>1</sub> % predicted (mean $\pm$ SD): NR PEF AM L/min (mean $\pm$ SD): 346 $\pm$ 89 Duration of asthma: $\geq$ 6 mo. Smoking status: NR	GROUP 2 Drug mcg/day: SAL/FP 100/200 Dosing: fixed Treatment duration: 12 wk. Device: diskhaler Withdraw LOE: 0/183 Reliever Tx: NR Run-in Tx: current asthma therapy Run-in duration: 4 wk.	Secondary PEF PM PEF diurnal variation PEF AM % predicted FEV <sub>1</sub> no. pts with exacerbations 24-hr. periods with symptom score $\geq 2$ 24-hr. periods with no relief medication SFD SFN	

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAM40034 2004 <sup>66</sup> Pub status: Industry report No. countries:	Randomized: 154 Analyzed: 154 Withdrawals: 9 ITT analysis: yes Asthma stage and severity: symptomatic, mild-severe	GROUP 1 Drug mcg/day: SAL/FP 100/200 Dosing: fixed Treatment duration: 12 wk. Device: diskhaler	Definition of exacerbation: NR List of clinical outcomes reported: Primary	Study objective: To compare efficacy and safety of SAL/FP 50/100 mcg bid in patients who were taking SABA only but required
3 No. centers: 27	Baseline ICS use: naïve	Withdraw LOE: 0/75	PEF AM	further management.
Design: randomized, parallel, double blind Funding: Industry: GlaxoSmithKline	GROUP 1 N: 75 Age yr (mean±SD): 36.8±11.6 Males %: 36 FEV <sub>1</sub> % predicted (mean±SD): NR PEF AM L/min (mean±SD): 430±73.6 Duration of asthma: NR Smoking status: NR GROUP 2 N: 79 Age yr (mean±SD): 37.4±11.0 Males %: 42 FEV <sub>1</sub> % predicted (mean±SD): NR PEF AM L/min (mean±SD): 453±74.7 Duration of asthma: NR Smoking status: NR	GROUP 2 Drug mcg/day: FP, 500 Dosing: fixed Treatment duration: 12 wk. Device: diskhaler Withdraw LOE: 0/79 Reliever Tx: salbutamol prn Run-in Tx: salbutamol 200 mcg as needed Run-in duration: 2 wk.	Secondary PEF PM time to 3 d. consecutive of PEF higher than at randomization FEV <sub>1</sub> % asthma control days % pts with asthma control time to 1st treatment wk with asthma control	

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year:	Randomized: 577	GROUP 1	Definition of	Study objective: To
SAM40036	Analyzed: 577	Drug/mcg/day:	exacerbation: NR	demonstrate that
2004 <sup>65</sup>	Withdrawals: 34	SAL/FP 50/100		once daily treatment
Pub status:		Dosing: fixed	List of clinical	with SAL/FP 50/100
Industry report	ITT analysis: yes	Treatment	outcomes	mcg at night is at
	Asthma stage and severity:	duration: 12 wk.	reported:	least as effective as
No. countries:	asymptomatic, mild-moderate	Device: diskhaler		BUD 400 mcg at
9	Baseline ICS use: naïve	Withdraw LOE:	Primary	night over 12-wk.
No. centers: 74		0	PEF AM	period.
Design:	GROUP 1			
randomized,	N: 288	GROUP 2	Secondary	
parallel, double	Age yr (mean±SD): 37.2±15.6	Drug/mcg/day:	PEF PM	
blind, double	Males %: 40.3	BUD 400	FEV <sub>1</sub>	
dummy	FEV <sub>1</sub> % predicted (mean±SD):	Dosing: fixed	FEF <sub>25-75</sub>	
	NR	Treatment	DTS	
Funding:	PEF AM L/min (mean±SD):	duration: 12 wk.	NTS	
Industry:	381±97.1	Device: 6	Reliever use	
GlaxoSmithKline	Duration of asthma: NR	Withdraw LOE:	(daytime and	
	Smoking status: NR	0	nighttime)	
	GROUP 2	Reliever Tx:		
	N: 289	salbutamol prn		
	Age yr (mean±SD): 36.0±15.7	Run-in Tx:		
	Males %: 45.7	salbutamol prn		
	FEV <sub>1</sub> % predicted (mean±SD):	Run-in duration:		
	NR	2 wk.		
	PEF AM L/min (mean±SD):			
	388±92.9			
	Duration of asthma: NR			
	Smoking status: NR			

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAM40048 2005 <sup>135</sup> Pub status: Industry report No. countries: 1 No. centers: 27	Randomized: 248 Analyzed: 248 Withdrawals: 13 ITT analysis: yes Asthma stage and severity: symptomatic, moderate Baseline ICS use: non-naïve	GROUP 1 Drug mcg/day: SAL/FP 100/500 Dosing: fixed Treatment duration: 12 wk. Device: diskhaler Withdraw LOE: 0	Definition of exacerbation: NR List of clinical outcomes reported: Primary FEV <sub>1</sub> % predicted	<b>Study objective:</b> To determine if SAL/FP 50/250 is superior to FORM/BUD 6/200 in efficacy and tolerability over 12 wk.
No. centers: 27Design: randomized, parallel, double dummyGROUL N: 121 Age yr Males 64.83±Funding: Industry: GlaxoSmithKlinePEF All Duratic Smoking	GROUP 1 N: 121 Age yr (mean±SD): 47±13 Males %: 38 FEV <sub>1</sub> % predicted (mean±SD): 64.83±8.96 PEF AM L/min (mean±SD): 317.9±117.07 Duration of asthma: NR Smoking status: NR GROUP 2 N: 127	GROUP 2 Drug mcg/day: FORM/BUD 12/400 Dosing: fixed Treatment duration: 12 wk. Device: Turbuhaler Withdraw LOE: 0	Secondary PEF AM PEF PM FEV1 DTS NTS % RFD % SFD	
	Age yr (mean±SD): 49±14 Males %: 47 FEV <sub>1</sub> % predicted (mean±SD): 65.6±7.94 PEF AM L/min (mean±SD): 301.33±103.94 Duration of asthma: NR Smoking status: NR	Reliever Tx: NR Run-in Tx: NR Run-in duration: 2 wk.		

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 449	GROUP 1	Definition of	Study objective: To
SAM40065	Analyzed: 449	Drug mcg/day:	exacerbation: NR	determine whether
2007 <sup>99</sup>	Withdrawals: 127	SAL/FP 100/200-		asthma control and
Pub status:		1000	List of clinical	reduced bronchiol
Industry report	ITT analysis: yes	Dosing: fixed	outcomes	hyperresponsivenes
	Asthma stage and severity:	Treatment	reported:	could be achieved
No. countries:	asymptomatic, mild-severe	duration: 40 wk.	Primary	and maintained at a
3	Baseline ICS use: naïve &	Device: diskhaler	mean ICS	lower dose of ICS
No. centers: 51	non-naïve	Withdraw LOE:	dose	with SAL/FP
Design:		2		Diskus™ or FP
randomized,	GROUP 1		Secondary	Diskus™ in adult an
parallel, double	<b>N:</b> 150	GROUP 2	PEF AM	adolescent subjects
blind, double	Age yr (mean±SD): 34.6±15.2	Drug mcg/day:	FEV <sub>1</sub>	with persistent
dummy	Males %: 35.3	FP (BHR) 200-	reliever use	asthma.
	FEV <sub>1</sub> % predicted	1000 + PLA	SFD	
Funding:	(mean±SD): 83.1	Dosing: fixed	OLD	
Industry:	PEF AM L/min (mean±SD):	Treatment		
GlaxoSmithKline	373.3±219.2	duration: 40 wk.		
		Device: diskhaler		
	Duration of asthma: ≥3 mo	Withdraw LOE:		
	Smoking status: NR	2		
	GROUP 2	GROUP 3		
	<b>N:</b> 150	Drug mcg/day:		
	Age yr (mean±SD): 34.2±13.9	FP 200-1000 +		
	Males %: 37.3	PLA		
	FEV <sub>1</sub> % predicted	Dosing: fixed		
	(mean±SD): 80.6	Treatment		
	PEF AM L/min (mean±SD):	duration: 40 wk.		
	403.3±214.1	Device: diskhaler		
	Duration of asthma: ≥3 mo	Withdraw LOE:		
	Smoking status: NR	1		
	GROUP 3	Reliever Tx: NR		
	<b>N:</b> 149	Run-in Tx: Usual		
	Age yr (mean±SD): 33.5±13.3	pre-study tx		
	Males %: 38.3	Run-in duration:		
	FEV <sub>1</sub> % predicted	2 wk.		
	(mean±SD): NR			
	PEF AM L/min (mean±SD):			
	378.6±17.2			
	Duration of asthma: ≥3 mo			
	Smoking status: NR			

		Treatment	Clinical outcomes	
Study	Participant charactoristics	characteristics		Notes
Study Author Year: SAM40090 2005 <sup>144</sup> Pub status: Industry report No. countries: 1 (Canada) No. centers: 79 Design: randomized, parallel, double blind Funding: Industry: GlaxoSmithKline	Participant characteristics Randomized: 483 Analyzed: 483 Withdrawals: 84 ITT analysis: yes Asthma stage and severity: asymptomatic, mild-severe Baseline ICS use: non-naïve GROUP 1 N: 242 Age yr (mean±SD): 38.2±14.9 Males %: 40 FEV <sub>1</sub> % predicted (mean±SD): NR PEF AM L/min (mean±SD): 404.2±117.93 Duration of asthma: ≥ 3 mo. Smoking status: NR	GROUP 1 Drug mcg/day: SAL/FP 100/200 Dosing: fixed Treatment duration: 12 wk. Device: diskhaler Withdraw LOE: 0/242 GROUP 2 Drug mcg/day: FP 500 Dosing: fixed Treatment duration: 12 wk. Device: diskhaler Withdraw LOE: 1/241	reported Definition of exacerbation: NR List of clinical outcomes reported: Primary PEF AM Secondary PEF PM reliever use SFD nighttime awakenings	Study objective: To determine if SAL/FP 50/100 mcg bid can be used to reduce the ICS dose while maintaining asthma control for subjects currently controlled on a medium dose ICS (FP 250 mcg bid).
	GROUP 2 N: 241 Age yr (mean±SD): 40.0±15.0 Males %: 43 FEV <sub>1</sub> % predicted (mean±SD): NR PEF AM L/min (mean±SD): 397.4±114.26 Duration of asthma: ≥ 3 mo. Smoking status: NR	Reliever Tx: salbutamol prn Run-in Tx: open label FP 500 mcg/day Run-in duration: 2 wk.		

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAM40120 2005 <sup>53</sup> Pub status: Industry report No. countries: 1 No. centers: 10 Design: randomized, parallel, double blind	Randomized: 18 Analyzed: 18 Withdrawals: 3 ITT analysis: yes Asthma stage and severity: symptomatic, mild-severe Baseline ICS use: non-naïve GROUP 1 N: 8 Age yr (mean±SD): 52±10 Males %: 50 FEV <sub>1</sub> % predicted (mean±SD):	GROUP 1 Drug mcg/day: SAL/FP 100/200 Dosing: fixed Treatment duration: 12 wk. Device: Evohaler™ Withdraw LOE: 0/8 GROUP 2 Drug mcg/day: FP 500	Definition of exacerbation: NR List of clinical outcomes reported: Primary PEF AM Secondary PEF PM EQ5D % RFD % RFN	Study objective: To compare the effectiveness of SAL/FP in asthmatics with significant smoking history. Additional details: Study population included only those ≥30 yrs. Due to recruitment
Funding: Industry: GlaxoSmithKline	NR PEF AM L/min (mean±SD): 309±46 Duration of asthma: NR Smoking status (pack-yr± SD): 42±24	Dosing: fixed Treatment duration: 12 wk. Device: Evohaler™ Withdraw LOE: 0/8	% SFD mini-AQLQ	problems the study was terminated after 18 subjects recruited. Only primary endpoint analyzed.
	GROUP 2 N: 10 Age yr (mean±SD): 59±10 Males %: 60 FEV <sub>1</sub> % predicted (mean±SD): NR PEF AM L/min (mean±SD): 282±79 Duration of asthma: NR Smoking status (pack-yr± SD): 35±18	Reliever Tx: SABA (ND) Run-in Tx: FP 200-400 or equivalent Run-in duration: ≥1 wk.		

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAS30002 2008 <sup>124</sup> Pub status: Industry report No. countries: 6 No. centers: 25 Design: randomized, parallel, double blind Funding: Industry: GlaxoSmithKline	Randomized: 300 Analyzed: 300 Withdrawals: 41 ITT analysis: yes Asthma stage and severity: symptomatic, moderate Baseline ICS use: naïve & non-naïve GROUP 1 N: 148 Age yr (mean±SD): 38±14 Males %: 35.8 FEV <sub>1</sub> % predicted (mean±SD): 70.7±13.5 PEF AM L/min (mean±SD): 317.8±87.0 Duration of asthma: NR Smoking status: NR GROUP 2 N: 152 Age yr (mean±SD): 37±14 Males %: 40.8 FEV <sub>1</sub> % predicted (mean±SD): 71.9±12.4 PEF AM L/min (mean±SD): 323.6±88.6 Duration of asthma: NR Smoking status: NR	GROUP 1 Drug mcg/day: SAL/FP, 100/200 + PLA Dosing: fixed Treatment duration: 12 wk. Device: Withdraw LOE: NR GROUP 2 Drug mcg/day: BUD + PLA 800 Dosing: fixed Treatment duration: 12 wk. Device: DPI Withdraw LOE: NR Reliever Tx: salbutamol prn Run-in Tx: Usual ICS (up to daily dose of 500 BDP/ BUD or 250 FP) Run-in duration: 2 wk.	Definition of exacerbation: NR List of clinical outcomes reported: Primary PEF AM Secondary PEF AM (24 hrs., wk 1, wk4) time to loss of control % pts with loss of control % pts with asthma exacerbation RFD RFN SFD SFN	Study objective: To compare the effectiveness of SAL/FP 50/100 mcg bid administered via a single inhaler with BUD 400 mcg bid in steroid experienced subjects Additional details: Steroid-naïve subjects were permitted subsequent to protocol amendment.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAS30015 2004 <sup>68</sup> Pub status: Industry report No. countries: 1 (UK) No. centers: 37 Design: randomized, parallel, double blind Funding: Industry: GlaxoSmithKline	Randomized: 156 Analyzed: 156 Withdrawals: 26 ITT analysis: yes Asthma stage and severity: symptomatic, mild-severe Baseline ICS use: naïve GROUP 1 N: 78 Age yr (mean±SD): 34.4±14.1 Males %: 54 FEV <sub>1</sub> % predicted (mean±SD): NR PEF AM L/min (mean±SD): 364±84.1 Duration of asthma: NR Smoking status: NR GROUP 2 N: 78 Age yr (mean±SD): 36.2±15.6 Males %: 55 FEV <sub>1</sub> % predicted (mean±SD): NR PEF AM L/min (mean±SD): 365.7±84.8 Duration of asthma: NR Smoking status: NR	GROUP 1 Drug mcg/day: SAL/FP 100/200 Dosing: fixed Treatment duration: 12 wk. Device: MDI Withdraw LOE: 0 GROUP 2 Drug mcg/day: BDP 400 Dosing: fixed Treatment duration: 12 wk. Device: MDI Withdraw LOE: 1 Reliever Tx: salbutamol prn Run-in Tx: salbutamol prn Run-in duration: 2 wk.	Definition of exacerbation: NR List of clinical outcomes reported: Primary mean change PEF AM Secondary mean change in PEF PM % pts loss of control time to loss of control % pts with exacerbations % SFD % SFN % RFD Composite: time to 1st exacerbation %SABA-free nights	Study objective: To compare the effectiveness of SAL/FP with BDP in patients currently taking SABA only, but who require further asthma management.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAS30039 2005 <sup>67</sup> Pub status: Industry report No. countries: 8 No. centers: 48 Design: randomized, parallel, double blind Funding: Industry: GlaxoSmithKline	Randomized: 362 Analyzed: 362 Withdrawals: 12 ITT analysis: yes Asthma stage and severity: NR, moderate Baseline ICS use: naïve GROUP 1 N: 180 Age yr (mean±SD): 39.9±15.4 Males %: 43 FEV <sub>1</sub> % predicted (mean±SD): NR PEF AM L/min (mean±SD): 337.0±102.4 Duration of asthma: ≥ 6 mo. Smoking status: < 10 pack-yr	GROUP 1 Drug mcg/day: SAL/FP 100/500 Dosing: fixed Treatment duration: 12 wk. Device: diskhaler Withdraw LOE: 0 GROUP 2 Drug mcg/day: FP 500 Dosing: fixed Treatment duration: 12 wk. Device: diskhaler Withdraw LOE: 0	Definition of exacerbation: NR List of clinical outcomes reported: Primary PEF AM Secondary PEF PM DTS NTS DTU nighttime SABA use	Study objective: To compare SAL/FP 50/250 mcg bid to FP 250 mcg bid alone over 12-wk treatment period as initial maintenance therapy in subjects with moderate asthma.
	GROUP 2 N: 182 Age yr (mean±SD): 40.8±14.74 Males %: 42 FEV <sub>1</sub> % predicted (mean±SD): NR PEF AM L/min (mean±SD): 336.2±106.2 Duration of asthma: ≥ 6 mo. Smoking status: < 10 pack-yr	Reliever Tx: salbutamol Run-in Tx: SABA only Run-in duration: >1 wk.		

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAS40026 2006 <sup>49</sup> Pub status: Industry report No. countries: 2 (United States and Canada) No. centers: 76 Design: randomized, parallel, double blind Funding: Industry: GlaxoSmithKline	Randomized: 636 Analyzed: 628 Withdrawals: 76 ITT analysis: yes Asthma stage and severity: asymptomatic, moderate Baseline ICS use: non-naïve GROUP 1 N: 317 Age yr (mean±SD): 39.6±15.1 Males %: 40.5 FEV <sub>1</sub> % predicted (mean±SD): NR PEF AM L/min (mean±SD): 458±122.9 Duration of asthma: >6 mo. Smoking status: ≤10 pack-yr	GROUP 1 Drug mcg/day: SAL/FP 100/200 Dosing: fixed Treatment duration: 12 wk. Device: diskhaler Withdraw LOE: 14 GROUP 2 Drug mcg/day: FP 500 Dosing: fixed Treatment duration: 12 wk. Device: diskhaler Withdraw LOE: 23	Definition of exacerbation: NR List of clinical outcomes reported: Primary asthma stability (% subjects remaining at 12 wk.) Secondary PEF AM FEV <sub>1</sub> % SFD mean SABA use	Study objective: To determine if SAL/FP 50/100 mcg bid could be used to step down the ICS dose for subjects currently controlled on FP 250 mcg bid while maintaining asthma control.
	GROUP 2 N: 311 Age yr (mean±SD): 39.2±14.9 Males %: 34.9 FEV <sub>1</sub> % predicted (mean±SD): NR PEF AM L/min (mean±SD): 437±139.3 Duration of asthma: >6 mo. Smoking status: ≤10 pack-yr	Reliever Tx: NR Run-in Tx: Period 1 (2 wk): FP 220 mcg bid), Period 2 (2 wk): FP 100 mcg bid, Period 3 (4 wk): FP 250 mcg bid Run-in duration: 10 wk (3 periods).		

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year:	Randomized: 483	GROUP 1	Definition of	Study objective: To
SAS40036	Analyzed: 483	Drug mcg/day:	exacerbation: NR	evaluate whether
2005 <sup>102</sup>	Withdrawals: 166	SAL/FP 100/200		study subjects who
Pub status:	withurawais. 100	Dosing: fixed	List of clinical	were stable on
		v		
Industry report	ITT analysis: yes	Treatment	outcomes	SAL/FP could
N	Asthma stage and severity:	duration: 16 wk.	reported:	maintain long-term
No. countries:	asymptomatic, mild-severe	Device: diskhaler	Primary	superior asthma
1	Baseline ICS use: non-naïve	Withdraw LOE:	PEF AM	control when
No. centers: 85		10		continued on
Design:	GROUP 1		Secondary	SAL/FP compared
randomized,	<b>N</b> : 172	GROUP 2	FEV <sub>1</sub>	with "step-down"
parallel, double	Age yr (mean±SD): 40.4±13.4	Drug mcg/day:	% SFD	therapy to FP 100
blind, double	Males %: 39	SAL 100	% RFD	mcg bid, SAL 50
dummy	FEV <sub>1</sub> % predicted (mean±SD):	Dosing: fixed	patient	mcg bid or
	NR	Treatment	satisfaction	monteleukast 10 mg
Funding:	PEF AM L/min (mean±SD):	duration: 16 wk.	00000000	qd.
Industry:	401.5±107.5	Device: diskhaler		
GlaxoSmithKline	Duration of asthma: >6 mo.	Withdraw LOE:		
	Smoking status: NR	34		
	GROUP 2	GROUP 3		
	N: 152	Drug mcg/day:		
	Age yr (mean±SD): 41.7±14.9	FP 200		
	Males %: 38.8	Dosing: fixed		
	FEV <sub>1</sub> % predicted (mean±SD):	Treatment		
	NR	duration; 16 wk.		
	PEF AM L/min (mean±SD):	Device: diskhaler		
	386.0±106.0	Withdraw LOE:		
	Duration of asthma: >6 mo.	64		
	Smoking status: NR			
		Reliever Tx:		
	GROUP 3	albuterol prn		
	N: 159	Run-in Tx:		
	Age yr (mean±SD): 42±14.5	Current ICS use		
	Males %: 45.4	(2 wk). If not		
	FEV <sub>1</sub> % predicted (mean±SD):	controlled, then		
	NR	,		
		open label		
	PEF AM L/min (mean±SD):	SAL/FP100/200		
	394.4±104.7	mcg bid until		
	Duration of asthma: >6 mo.	control achieved		
	Smoking status: NR	(4 wk)		
		Run-in duration:		
		6 wk.		

<b>0</b> 1 <b>1</b>	<b>D</b>	Treatment	Clinical outcomes	Neter
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 532	GROUP 1	Definition of	Study objective: To
SAS40068 2005 <sup>69</sup>	Analyzed: 532 Withdrawals: 99	Drug mcg/day: SAL/FP 100/200	exacerbation: NR	evaluate the efficacy of the SAI /FP
Pub status:	withdrawais: 99	Dosing: fixed	List of clinical	Diskus <sup>®</sup> 50/100 mcg
Industry report	ITT analysis: yes	Treatment	outcomes	bid compared with
industry report	Asthma stage and severity:	duration: 24 wk.	reported:	the FP Diskus <sup>®</sup> 100
No. countries:	symptomatic, mild	Device: Diskus <sup>®</sup>	Primary	mcg bid in adult and
1 (Canada)	Baseline ICS use: naïve	Withdraw LOE:	PFF AM	adolescents with
No. centers: 58		1		mild asthma.
Design:	GROUP 1	·	Secondary	
randomized,	N: 262	GROUP 2	FEV₁ AM	
parallel, double	Age yr (mean±SD):	Drug mcg/day:	exacerbation	
blind	34.8±14.27	FP 200	rate	
	Males %: 13.7	Dosing: fixed	% SFD	
Funding:	FEV <sub>1</sub> % predicted (mean±SD):	Treatment	% RFD	
Industry:	NR	duration: 24 wk.		
GlaxoSmithKline	PEF AM L/min (mean±SD):	<b>Device:</b> Diskus <sup>®</sup>		
	395.3±102.3	Withdraw LOE:		
	Duration of asthma: NR	1		
	Smoking status: NR			
		Reliever Tx: NR		
	GROUP 2	Run-in Tx: NR		
	N: 270	Run-in duration:		
	Age yr (mean±SD): 34.3±14.2	NR		
	Males %: 13.3 FEV <sub>1</sub> % predicted (mean±SD):			
	NR			
	PEF AM L/min (mean±SD):			
	392.5±102.9			
	Duration of asthma: NR			
	Smoking status: NR			

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Schermer TR 2007 <sup>142</sup> Pub status: Journal article No. countries: 1 No. centers: 41 Design: randomized, parallel, double blind Funding: Industry: GlaxoSmithKline	Randomized: 137 Analyzed: 130 Withdrawals: 7 ITT analysis: yes Asthma stage and severity: NR Baseline ICS use: non-naïve GROUP 1 N: 64 Age yr (mean±SD): 42.8±14.7 Males %: 45 FEV <sub>1</sub> % predicted (mean±SD): 90.0±15.5 PEF AM L/min (mean±SD): 449±106 Duration of asthma: ≥3 mo. Smoking status (% current): 17 GROUP 2 N: 66 Age yr (mean±SD): 43.5±15.9 Males %: 32 FEV <sub>1</sub> % predicted (mean±SD): 87.6±15.0 PEF AM L/min (mean±SD): 414±98 Duration of asthma: ≥3 mo. Smoking status (% current): 37	GROUP 1 Drug mcg/day: SAL/FP 100/200 or 500 Dosing: fixed Treatment duration: 12 wk. Device: Diskus <sup>™</sup> Withdraw LOE: NR GROUP 2 Drug mcg/day: FP 500 or 1000 Dosing: fixed Treatment duration: 12 wk. Device: Diskus <sup>™</sup> Withdraw LOE: NR Reliever Tx: salbutamol prn Run-in Tx: FP (open-label) via Diskus <sup>™</sup> + salbutamol Run-in duration: 2 wk.	Definition of exacerbation: NR List of clinical outcomes reported: Primary mean change FEV <sub>1</sub> % predicted Secondary PEF AM days with symptoms nights with symptoms symptom score SABA use SFD AQLQ	Study objective: To compare the effects of a lower dose of FP combined with SAL with a higher dose of FP, both supplemented with SABA as needed.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Scicchitano R 2004 <sup>119</sup> Pub status: Journal article No. countries: 18 No. centers: 211 Design: randomized, parallel, double blind, double dummy Funding: Industry: AstraZeneca	Participant cinatcensitiesRandomized: 1,890Analyzed: 1,890Withdrawals: 317ITT analysis: yesAsthma stage and severity: symptomatic, moderate-severeBaseline ICS use: non-naïveGROUP 1N: 942Age yr (mean [range]): 43 (12-79)Males %: 41.5FEV1 % predicted (mean [range]): 70 (46-102)PEF AM L/min (mean [range]): 339.2 (77-670)Duration of asthma (median [range]): 12 yr. (1-65)Smoking status: NRGROUP 2N: 943Age yr (mean [range]): 43 (11-80)Males %: 42.9FEV1 % predicted (mean [range]): 70 (37-95)PEF AM L/min (mean [range]): 335.8 (104-749)Duration of asthma (median [range]): 12 yr. (1-71)Smoking status: NR	GROUP 1 Drug mcg/day: FORM/BUD 12/400 Dosing: fixed Treatment duration: 52 wk. Device: Turbuhaler Withdraw LOE: 28 GROUP 2 Drug mcg/day: BUD 400 Dosing: fixed Treatment duration: 52 wk. Device: Turbuhaler Withdraw LOE: 43 Reliever Tx: tubertaline prn Run-in Tx: Usual ICS (approx. 400- 1600 mcg) + terbutaline Run-in duration: 2 wk.	Definition of         exacerbation:         Severe =         worsening asthma         resulting in         hospitalization or         ED treatment         List of clinical         outcomes         reported:         Primary         time to 1st         severe         exacerbation         Secondary         PEF AM         PEF PM         no. mild         exacerbations         DTS         NTS         nighttime         awakenings         SABA use         change in ICS         dose         RFD         asthma-         control days         treatment         days with OCS	Study objective: To compare SMART <sup>®</sup> (FORM/BUD for maintenance and relief) with a higher maintenance dose of BUD in pts with moderate to severe asthma.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Study Author Year: Self T 1998 <sup>143</sup> Pub status: Journal article No. countries: 1 (United States) No. centers: 2 Design: randomized, parallel, double blind Funding: Industry: GlaxoSmithKline	Randomized: 24 Analyzed: 18 Withdrawals: 22 ITT analysis: yes Asthma stage and severity: asymptomatic, moderate, severe Baseline ICS use: non-naïve GROUP 1 N: 8 Age yr (mean [range]): 39.6 (30-57) Males %: 25 FEV <sub>1</sub> % predicted (mean±SD): NR PEF AM L/min (mean±SD): 386±76 Duration of asthma: 83% childhood onset Smoking status: NR	GROUP 1 Drug mcg/day: SAL/ICS (BDP, FP, or TAA) 200/>500 Dosing: fixed Treatment duration: 52 wk. Device: MDI Withdraw LOE: NR GROUP 2 Drug mcg/day: ICS (BDP, FP, or TAA) >500 + PLA Dosing: fixed Treatment duration: 52 wk. Device: MDI Withdraw LOE: NR	Definition of exacerbation: NR List of clinical outcomes reported: Primary % reduction in ICS dose Secondary PEF FEV1 AQLQ SABA use	Study objective: To determine is SAL facilitates step-down therapy in pts receiving moderate to high dose ICS.
	GROUP 2 N: 10 Age yr (mean [range]): 46.6 (22-68) Males %: 0 FEV <sub>1</sub> % predicted (mean±SD): NR PEF AM L/min (mean±SD): 388±107 Duration of asthma: 67% childhood onset Smoking status: NR	Reliever Tx: albuterol prn Run-in Tx: study therapy (placebo or SAL) + optimized ICS therapy + SABA prn and before exercise Run-in duration: 2 wk.		

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 475	GROUP 1	Definition of	Study objective: To
SFA103153	Analyzed: 475	Drug mcg/day:	exacerbation: NR	demonstrate that
2007 <sup>100</sup>	Withdrawals: 155	SAL/FP 100/200		SAL/FP 50/100 mcg
Pub status:		Dosing: fixed	List of clinical	is superior to FP 100
Industry report	ITT analysis: yes	Treatment	outcomes	in controlling asthma
	Asthma stage and severity:	duration: 52 wk.	reported:	exacerbation rate in
No. countries:	symptomatic, mild-severe	<b>Device:</b> Diskus™	Primary	subjects of African
1 (United	Baseline ICS use: non-naïve	Withdraw LOE:	exacerbation	American descent.
States)		6	rate	
No. centers: 59	GROUP 1			Additional details:
Design:	<b>N:</b> 239	GROUP 2	Secondary	All subjects of
randomized,	Age yr (mean±SD): 31.5±13.5	Drug mcg/day:	PEF AM	African American
parallel, double	Males %: 40.2	FP 200	FEV <sub>1</sub>	descent
blind	FEV <sub>1</sub> % predicted (mean±SD):	Dosing: fixed	SFD	
-	NR	Treatment	RFD	
Funding:	PEF AM L/min (mean±SD):	duration: 52 wk.		
Industry:	342±91.2	Device: Diskus™		
GlaxoSmithKline	Duration of asthma: NR Smoking status: NR	Withdraw LOE: 9		
	GROUP 2	Reliever Tx:		
	N: 236	albuterol		
	Age yr (mean±SD): 32.2±13.6	Run-in Tx: FP		
	Males %: 36.4	250 mcg bid		
	FEV <sub>1</sub> % predicted (mean±SD):	Run-in duration:		
	NR PEF AM L/min (mean±SD):	4 wk.		
	340±99.9			
	Duration of asthma: NR			
	Smoking status: NR			
	Smoking status. NK			

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year:	Randomized: 84	GROUP 1	Definition of	Study objective: To
Shapiro G 2000 <sup>87</sup>	Analyzed: 81	Drug mcg/day:	exacerbation: NR	compare the efficacy
Pub status:	Withdrawals: 13	SAL/FP 100 500		and safety of SAL/FP
Journal article		Dosing: fixed	List of clinical	50/250 mcg in a
	ITT analysis: yes	Treatment	outcomes reported:	combination dry-
No. countries: 1	Asthma stage and severity:	duration: 12 wk.	Primary	powder product
(United States)	asymptomatic, moderate	Device: diskhaler	mean change	administered twice
No. centers: 42	Baseline ICS use: non-naïve	Withdraw LOE: 3	PEF AM	daily through the
Design:			AUC FEV <sub>1</sub> 12 hr	Diskus device with that
randomized,	GROUP 1	GROUP 2	serial relative to day	of FP and SAL alone in
parallel, double	N: 81	Drug mcg/day: FP	1	patients previously
blind	Age (mean [range]): 38 (12-69)	500	probability of pts	treated with low to
	Males (%): 48	Dosing: fixed	remaining in study	medium dose ICS.
Funding:	FEV <sub>1</sub> % predicted: NR	Treatment	0 ,	
Industry:	Mean PEF AM (mean±SD):	duration: 12 wk.	without being	
GlaxoSmithKline	367±99	Device: Diskus®	withdrawn for	
GiaxuSinittintine			worsening asthma	
	Duration of asthma: ≥ 6 mo.	Withdraw LOE: 18	<b>.</b> .	
	Smoking status: none smoked in		Secondary	
	previous year or had history >10	GROUP 3	mean change in	
	pack/year	Drug mcg/day:	PEF PM	
		SAL 100	SABA use	
	GROUP 2	Dosing: fixed	(puffs/day)	
	<b>N:</b> 81	Treatment	nighttime	
	Age (mean [range]): 40 (12-67)	duration: 12 wk.	awakenings requiring	
	Males %: 54	Device: Diskus <sup>®</sup>	SABA	
	FEV <sub>1</sub> % predicted: NR	Withdraw LOE: 32		
	Mean PEF AM (mean±SD):			
	374±75.6	GROUP 4		
	Duration of asthma: ≥ 6 mo.	Drug mcg/day:		
	Smoking status: none smoked in	PLA		
	previous year or had history >10	Dosing: fixed		
	pack/year	Treatment		
		duration: 12 wk.		
	GROUP 3	Device: single		
	<b>N:</b> 84	drugs		
	Age (mean [range]): 39 (12-68)	Withdraw LOE: 56		
	Males %: 49	Dellar Tra		
	FEV <sub>1</sub> % predicted: NR	Reliever Tx:		
	Mean PEF AM (mean±SD):	albuterol prn		
	372±92.6	Run-in Tx: medium		
	Duration of asthma: ≥ 6 mo.	dose of ICS + PLA		
	Smoking status: none smoked in	Run-in duration: 2		
	previous year or had history >10	wk.		
	pack/year			
	GROUP 4			
	N: 90			
	Age (mean [range]): 38 (12-69)			
	Males %: 41			
	FEV <sub>1</sub> % predicted: NR			
	Mean PEF AM (mean±SD):			
	373±99.6			
	Duration of asthma: ≥ 6 mo.			
	Smoking status: none smoked in			
	previous year or had history >10			
	pack-yr.			
	puon yr.			

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SLGA5021 2005 <sup>125</sup> Pub status: Industry report No. countries: 1 (United States) No. centers: 34 Design: randomized, parallel, double blind, double dummy Funding: Industry: GlaxoSmithKline	Randomized: 488 Analyzed: 478 Withdrawals: 66 ITT analysis: yes Asthma stage and severity: symptomatic, intermittent to severe Baseline ICS use: non-naïve GROUP 1 N: 240 Age (mean [range]): 37.9 (12- 78) Males %: 52 FEV <sub>1</sub> % predicted: NR Mean PEF AM (mean±SD): 376.7±110.0 Duration of asthma: >6 mo. Smoking status: NR GROUP 2 N: 238 Age (mean [range]): 37.3 (12- 76) Males %: 51 FEV <sub>1</sub> % predicted: NR Mean PEF AM (mean±SD): 364.6±114.2 Duration of asthma: >6 mo. Smoking status: NR	GROUP 1 Drug mcg/day: SAL/FP 100/200 Dosing: fixed Treatment duration: 24 wk. Device: MDI Withdraw LOE: 0 GROUP 2 Drug mcg/day: FP 500 + PLA Dosing: fixed Treatment duration: 24 wk. Device: MDI Withdraw LOE: 3 Reliever Tx: albuterol prn Run-in Tx: open label FP 88 mcg bid Run-in duration: 2-4 wk.	Definition of exacerbation: NR List of clinical outcomes reported: Primary mean change PEF AM Secondary am/pm variation mean change in PEF PM pre-dose FEV Composite: combined symptom score wheezing score SOB score chest tightness score	Study objective: to compare the efficacy and safety of adding SAL 42 mcg twice daily (bid) to FP 88 mcg bid versus increasing the dose of FP to 220 mcg in subjects not well controlled on FP 88 mcg bid.

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 46	GROUP 1	Definition of	Study objective: To
SLGF75 2005 <sup>103</sup>	Analyzed: 46	Drug mcg/day:	exacerbation: NR	demonstrate a
Pub status:	Withdrawals: 4	SAL/FP 100/200		higher efficacy of
Industry report		Dosing: fixed	List of clinical	two treatments (SAL
	ITT analysis: yes – subjects	Treatment	outcomes	50 mcg + low-dose
No. countries:	randomized and with at least	duration: 3 mo.	reported:	FP or high-dose FP
1 (Italy)	one dose of administered study	Device: diskhaler	Primary	bid) compared with
No. centers: 7	drug. Per-protocol population –	Withdraw LOE:	NR	FP 100 mcg bid in
Design:	all subjects of ITT without any	0		naïve subjects with
randomized,	major protocol violation were		Secondary	mild-moderate
parallel, double	used for secondary efficacy	GROUP 2	PEF AM/PM	asthma
blind	analysis.	Drug mcg/day:	variation	
	Asthma stage and severity:	FP 200	PEF PM	Additional details:
Funding:	NR, intermittent, mild,	Dosing: fixed		No reported data for
Industry:	moderate	Treatment		secondary outcomes
GlaxoSmithKline	Baseline ICS use: non-naïve	duration: 3 mo.		because study was
		Device: diskhaler		interrupted.
	GROUP 1	Withdraw LOE:		
	<b>N:</b> 14	0		
	Age (mean± SD): 41.7±16.3			
	Males %: 36	GROUP 3		
	FEV <sub>1</sub> % predicted: NR	Drug mcg/day:		
	Mean PEF AM (mean±SD):	FP 500		
	NR	Dosing: fixed		
	Duration of asthma: >6 mo.	Treatment		
	Smoking status: NR	duration; 3 mo.		
		Device: diskhaler		
	GROUP 2 N: 17	Withdraw LOE:		
		0		
	Age (mean±SD): 42±10.6 Males %: 71	Reliever Tx:		
	FEV <sub>1</sub> % predicted: NR	salbutamol prn		
	Mean PEF AM (mean±SD):	Run-in Tx: FP		
	NR	100 mcg bid;		
	Duration of asthma: >6 mo.	salbutamol prn		
	Smoking status: NR	Run-in duration:		
	Smoking status. Nit	4 wk.		
	GROUP 3	· ••••.		
	N: 15			
	Age (mean±SD): 32.9±13.1			
	Males %: 60			
	FEV <sub>1</sub> % predicted: NR			
	Mean PEF AM (mean±SD):			
	NR			
	<b>Duration of asthma:</b> >6 mo.			
	Smoking status: NR			

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SLGQ97/SLGB4010 2005 <sup>104</sup> Pub status: Industry report No. countries: 6 No. centers: 99 Design: randomized, parallel, double blind, double dummy Funding: Industry: GlaxoSmithKline	Randomized: 502 Analyzed: 496 Withdrawals: 64 ITT analysis: yes Asthma stage and severity: symptomatic, mild-severe Baseline ICS use: non-naïve GROUP 1 N: 171 Age (mean±SD): 44.8±15.6 Males %: 40.9 FEV <sub>1</sub> % predicted: NR Mean PEF AM (mean±SD): 346.9±92.9 Duration of asthma: NR Smoking status: NR GROUP 2 N: 165 Age (mean±SD): 43.9±14.9 Males %: 49.7 FEV <sub>1</sub> % predicted: NR Mean PEF AM (mean±SD): 357.5±104.1 Duration of asthma: NR Smoking status: NR GROUP 3 N: 160 Age (mean±SD): 45.7±15.2 Males %: 48.8 FEV <sub>1</sub> % predicted: NR Mean PEF AM (mean±SD): 347.0±101.1 Duration of asthma: NR Smoking status: NR	GROUP 1 Drug mcg/day: SAL/FP 100/500 Dosing: fixed Treatment duration: 24 wk. Device: MDI Withdraw LOE: 5 GROUP 2 Drug mcg/day: FP 1000 + PLA Dosing: fixed Treatment duration: 24 wk. Device: MDI Withdraw LOE: 3 GROUP 3 Drug mcg/day: FP 500 + PLA Dosing: fixed Treatment duration; 24 wk. Device: MDI Withdraw LOE: 4 Reliever Tx: NR Run-in Tx: FP 500 mcg Run-in duration: 4 wk.	Definition of exacerbation: NR List of clinical outcomes reported: Primary mean change PEF AM pts with >1 exacerbation Secondary PEF PM FEV1 no. withdrawals due to exacerbation SFD SFN daytime SABA use nighttime SABA use	Study objective: To evaluate the relative clinical benefits (in terms of asthma control) of either increasing the dose of inhaled corticosteroid to FP 500 mcg bid, or combined treatment with FP 250 mcg and SAL 50 mcg bid in asthmatic subjects poorly controlled on existing inhaled corticosteroid therapy.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SMS40012 2006 <sup>147</sup> Pub status: Industry report No. countries: 1 (France) No. centers: 56 Design: randomized, parallel, double blind Funding: Industry: GlaxoSmithKline	uthor Year:       Randomized: 188         MS40012       Analyzed: 168         MS40012       Withdrawals: 31         ub status:       Withdrawals: 31         dustry report       ITT analysis: yes         Asthma stage and severity:       asymptomatic, NR         o. countries:       asymptomatic, NR         (France)       Baseline ICS use: non-naïve         o. centers: 56       GROUP 1         ndomized,       N: 83         arallel, double       Age (mean±SD): 41.1±13.8         ind       Males %: 44.6         FEV1 % predicted (mean±SD):         unding:       91.8±13.5         dustry:       Mean PEF AM (median±SD):	GROUP 1 Drug mcg/day: SAL/ICS 100/500 Dosing: fixed Treatment duration: 36 wk. Device: diskhaler Withdraw LOE: 1 GROUP 2 Drug mcg/day: ICS, 500 + PLA Dosing: fixed Treatment duration: 36 wk. Device: diskhaler Withdraw LOE: 6	Definition of exacerbation: NR List of clinical outcomes reported: Primary PEF AM Secondary PEF PM FEV <sub>1</sub> % predicted SABA use FVC nighttime SABA use (times/night)	Study objective: To evaluate the efficacy of SAL 100 mcg in helping maintenance of asthma control when ICS dosage is halved in subjects who were receiving 1000 mcg of beclometasone or equivalent.
	GROUP 2 N: 85 Age (mean±SD): 39.5±14.9 Males %: 37.6 FEV1 % predicted (mean±SD): 91.6±20.6 Mean PEF AM (median±SD): 442.9±95.8 Duration of asthma: NR Smoking status: NR	Reliever Tx: NR Run-in Tx: NR- assumed current ICS use (BDP 800-1000 mcg) Run-in duration: NR		

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Ställberg B 2003 <sup>191</sup> Pub status: Journal article No. countries: 1 (Sweden)	Randomized: 1,034 Analyzed: 977 Withdrawals: 57 ITT analysis: no Asthma stage and severity: mixed asymptomatic and symptomatic, moderate	GROUP 1 Drug mcg/day: FORM/BUD 18/400 or 800 Dosing: fixed Treatment duration: 24 wk. Device:	Definition of exacerbation: one or more of the following (as judged by the investigator): use of oral corticosteroids for	Study objective: To examine the potential clinical benefits of a guided adjustable-dosing regimen with BUD/FORM in a single inhaler over a
No. centers: 94 Design: randomized, parallel, open label	Baseline ICS use: non-naïve GROUP 1 N: 486 Age (mean±SD): 44±17 Males %: 39	Turbuhaler <sup>®</sup> Withdraw LOE: GROUP 2 Drug mcg/day: FORM/BUD	treatment due to worsening of asthma; treatment at a medical care unit due to worsening of	six-month period based on patient assessment of their asthma, compared with a fixed-dosing regimen.
Funding: Industry: AstraZeneca	FEV <sub>1</sub> % predicted: 95.8±15.2 Mean PEF AM (mean±SD): NR Duration of asthma: NR Smoking status – never/past/current (n [%]): 353 (68)/109 (21)/ 55 (11)	18/200-1600 Dosing: variable Treatment duration: 24 wk. Device: Turbuhaler <sup>®</sup> Withdraw LOE:	asthma; an asthma-related SAE; withdrawal due to a need to use non-study asthma medication	Additional details: Step-up or step- down therapy determined by specific criteria (Table 1)
	GROUP 2 N: 491 Age (mean±SD): 44±16 Males %: 41 FEV <sub>1</sub> % predicted: 95.4±14.5 Mean PEF AM (mean±SD): NR Duration of asthma: NR Smoking status – never/past/current (n [%]): 356 (69)/123 (24)/38 (7)	Reliever Tx: Terbutaline or salbutamol prn Run-in Tx: Fixed doses of FORM/BUD 4.5/80 mcg or 4.5/160 mcg, 2 inhalations bid. Run-in duration: 4 wk.	outcomes reported: Primary symptom score time to 1st exacerbation Secondary asthma free	
	550 (0 <i>3)</i> /125 (24)/50 (7)	<b>→ ₩</b> Λ.	days SABA use nighttime wakenings	

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Study Author Year: Strand AM 2004 <sup>63</sup> Pub status: Journal article No. countries: 1 (Denmark) No. centers: 45 Design: randomized, parallel, double blind Funding: Industry: GlaxoSmithKline	Participant characteristicsRandomized: 150Analyzed: 150Withdrawals: 24ITT analysis: noAsthma stage and severity: symptomatic, mild-severeBaseline ICS use: naïveGROUP 1N: 78Age (mean±SD): 39±15Males %: 49FEV1 % predicted: NRMean PEF AM (mean±SD): 380±117Duration of asthma (n [%] ≥ 10 yrs): 13 (13) Smoking status – never/past/current (n): 42/26/32GROUP 2 N: 72Age (mean±SD): 38±15 Males %: 38FEV1 % predicted: NR Mean PEF AM (mean±SD): 397±109Duration of asthma (n [%] ≥ 10 yr.): 11 (10) Smoking status – never/past/current (n):	characteristics         GROUP 1         Drug mcg/day:         SAL/FP 100/200         Dosing: fixed         Treatment         duration: 24 wk.         Device: Diskus™         Withdraw LOE:         NR         GROUP 2         Drug mcg/day:         FP 200         Dosing: fixed         Treatment         duration: 24 wk.         Device: Diskus™         Withdraw LOE:         NR         Reliever Tx:         salbutamol prn         Run-in Tx: study         drug and         salbutamol prn         Run-in duration:         2 wk.	reported Definition of exacerbation: NR List of clinical outcomes reported: Primary SFD (24-hr period) Secondary PEF PM DTS NTS SFN % RFD %	Notes Study objective: To determine whether initiation of maintenance treatment with SAL/FP combination is more effective than inhaled steroid alone in patients with asthma symptomatic on short-acting bronchodilator alone

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: van der Molen T 1997 <sup>88</sup> Pub status: Journal article No. countries: 2 (The Netherlands and Canada) No. centers: 16 Design: randomized, parallel, double blind Funding: Industry: AstraZeneca	Randomized: 239 Analyzed: 208 Withdrawals: 31 ITT analysis: no Asthma stage and severity: symptomatic, mild-moderate Baseline ICS use: non-naïve GROUP 1 N: 107 Age (mean±SD): 40.5±13.7 Males %: 48.8 FEV <sub>1</sub> % predicted (mean±SD): 68±15 Mean PEF AM (mean±SD): 392±99.3 Duration of asthma: 20.6 Smoking status – current (n[%]): 18 (14.4) GROUP 2 N: 101 Age (mean±SD): 45.4±14.0 Males %: 49.2 FEV <sub>1</sub> % predicted (mean±SD):	GROUP 1 Drug mcg/day: FORM/ICS 48 /range <400 to ≥1600 Dosing: fixed Treatment duration: 24 wk. Device: Turbuhaler <sup>®</sup> Withdraw LOE: 1 GROUP 2 Drug mcg/day: ICS range <400 to ≥1600 + PLA Dosing: fixed Treatment duration: 24 wk. Device: Tubuhaler <sup>®</sup> Withdraw LOE: 6 Reliever Tx: terbutaline prn Run-in Tx:	Definition of exacerbation: NR List of clinical outcomes reported: Primary total asthma score Secondary PEF PM FEV1 exacerbations requiring OCS use SABA use	Study objective: To investigate the efficacy and safety of FORM in asthmatic subjects already using ICS
	66±16 Mean PEF AM (mean±SD): 382±101.4 Duration of asthma: NA Smoking status – current (n[%]): 12 (10.5)	current tx + terbutaline prn. <b>Run-in duration:</b> 4 wk.		

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: van Noord JA 1999 <sup>120</sup> Pub status: Journal article No. countries: 1 (The Netherlands) No. centers: 27 Design: randomized, parallel, double blind Funding: Industry: GlaxoSmithKline	Randomized: 274 Analyzed: 259 Withdrawals: 15 ITT analysis: no Asthma stage and severity: symptomatic, mild-moderate Baseline ICS use: non-naïve GROUP 1 N: 133 Age (mean±SD): 46±15 Males %: 47 FEV <sub>1</sub> % predicted (mean±SD): 71±16 Mean PEF AM (mean±SD): 348±110 Duration of asthma: NR Smoking status: NR GROUP 2 N: 126 Age (mean±SD): 47±14 Males %: 50 FEV <sub>1</sub> % predicted (mean±SD): 73±16 PEF AM (mean±SD): 358±129 Duration of asthma: NR Smoking status: NR	GROUP 1 Drug mcg/day: SAL/FP 100 /200 or 500 Dosing: fixed Treatment duration: 12 wk. Device: diskhaler Withdraw LOE: NR GROUP 2 Drug mcg/day: FP 200 or 500 Dosing: fixed Treatment duration: 12 wk. Device: diskhaler Withdraw LOE: NR Reliever Tx: salbutamol Run-in Tx: Gr 1: FP 200mcg/d; Gr 2: FP 500 mcg/d Run-in duration: 4 wk.	Definition of exacerbation: NR List of clinical outcomes reported: Primary PEF AM PEF PM Secondary PEF diurnal variation FEV1 FVC days with symptoms nights with symptoms days with rescue medication nights with rescue medication	Study objective: to compare the efficacy and safety of the addition of SAL with that of doubling the dose of FP in asthmatic patients not controlled by a low or intermediate dose of ICS

		Tractions and	Clinical	
Study	Participant characteristics	Treatment characteristics	outcomes reported	Notes
Study Author Year:	Participant characteristics Randomized: 509	GROUP 1	Definition of	Study objective: To
van Noord JA	Analyzed: 503	Drug mcg/day:	exacerbation: NR	demonstrate
2001 <sup>97</sup>	Withdrawals: 62	SAL/FP 100/1000	o, a constant of the test	equivalent efficacy
Pub status:		Dosing: fixed	List of clinical	and comparable
Journal article	ITT analysis: yes	Treatment	outcomes	tolerability of two
	Asthma stage and severity:	duration: 12 wk.	reported:	inhaled combined
No. countries:	symptomatic, intermittent to	Device: MDI		formulations of
13	severe	(HFA)	Primary	SAL/FP 50/500 mcg
No. centers: 61 Design:	Baseline ICS use: non-naïve	Withdraw LOE: NR	PEF AM	bid in asthma patients
randomized,	GROUP 1		Secondary	
parallel, double	<b>N</b> : 173	GROUP 2	PEF PM	
blind, double dummy	Age (mean [range]): 48 (12- 82)	Drug mcg/day: SAL/FP 100/1000	PEF PM % predicted	
,	<b>Males %:</b> 40	Dosing: fixed	diurnal	
Funding:	FEV <sub>1</sub> % predicted (mean): 71	Treatment	variation in PEF %	
Industry:	Mean PEF AM (mean): 327	duration: 12 wk.	predicted	
GlaxoSmithKline	Duration of asthma	<b>Device:</b> Diskus™	FEV <sub>1</sub>	
	(mean±SD): 88±50 Smoking	Withdraw LOE:	FEV <sub>1</sub> %	
	status – prev/current (n[%]):	NR	predicted	
	15(9)/ 50(31)		SFD	
	GROUP 2	GROUP 3	SFN	
	N: 159	Drug mcg/day: FP 1000 + PLA	RFD	
	Age (mean [range]): 47 (15- 81)	Dosing: fixed Treatment		
	Males %: 40	duration: 12 wk.		
	FEV <sub>1</sub> % predicted (mean):	Device: MDI		
	73.6	Withdraw LOE:		
	Mean PEF AM (mean): 341 Duration of asthma	NR		
	(mean±SD): 84±52	Reliever Tx:		
	Smoking status –	salbutamol prn		
	prev/current (n[%]): 12(7)/	Run-in Tx: usual		
	54(36)	ICS		
		Run-in duration:		
	GROUP 3	2 wk.		
	<b>N:</b> 171			
	<b>Age (mean [range]):</b> 46 (14- 79)			
	Males %: 42			
	FEV <sub>1</sub> % predicted (mean): 72.5			
	Mean PEF AM (mean): 345 Duration of asthma			
	(mean±SD): 104±60			
	Smoking status –			
	prev/current (n[%]): 12(7)/ 43(27)			

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Vermetten FA 1999 <sup>121</sup> Pub status: Journal article No. countries: 1 (The Netherlands) No. centers: 1 Design: randomized, parallel, double blind Funding: Industry: GlaxoSmithKline	Randomized: 233 Analyzed: NR Withdrawals: 31 ITT analysis: yes Asthma stage and severity: asymptomatic, mild Baseline ICS use: non-naïve GROUP 1 N: NR Age (mean±SD): 42±14 Males %: 53 FEV <sub>1</sub> % predicted: NR Mean PEF AM (mean±SD): 404±105 Duration of asthma: NR Smoking status (n[%]): 37 (33) GROUP 2 N: NR Age (mean±SD): 42±14 Males %: 38 FEV <sub>1</sub> % predicted: NR Mean PEF AM (mean±SD): 390±103 Duration of asthma: NR Smoking status (n[%]): 40 (33)	GROUP 1 Drug mcg/day: SAL/BDP 100/400 Dosing: fixed Treatment duration: 12 wk. Device: diskhaler Withdraw LOE: 6 GROUP 2 Drug mcg/day: BDP 800 Dosing: fixed Treatment duration: 12 wk. Device: diskhaler Withdraw LOE: 10 Reliever Tx: salbutamol 400 mcg (up to max of 8 inhalations daily) Run-in Tx: BDP 100 or 200 mcg bid Run-in duration: 2 wk.	Definition of exacerbation: NR List of clinical outcomes reported: Primary PEF PM % predicted Secondary PEF AM % predicted diurnal variation PEF PEF AM PEF PM QoL score no. blisters (AM, PM)	Study objective: To compare the addition of SAL 50 mcg bid with beclomethasone 200 mcg bid in adult asthmatic patients already using 200- 400 mcg beclomethasone daily

		Treature and	Clinical	
Study	Participant characteristics	Treatment	outcomes reported	Notes
Study	Participant characteristics	characteristics		
Author Year: Vogelmeier C	Randomized: 2,143	GROUP 1	Definition of	Study objective: To
2005 <sup>131</sup>	Analyzed: 2,135 Withdrawals: 269	Drug mcg/day: FORM/BUD	exacerbation:	assess the
Pub status:	Withdrawais: 209	18/800	Severe – a deterioration in	effectiveness of BUD/FORM for
Journal article				
Journal anticle	ITT analysis: yes Asthma stage and severity: ,	Dosing: variable Treatment	asthma, resulting	maintenance plus
No. countries:	Baseline ICS use: non-naïve	duration: 52 wk.	in boonitalization/EP	relief with a control
16	Baseline ICS use. non-maive	Device:	hospitalization/ER treatment, oral	group using SAL/FP for maintenance plus
No. centers:	GROUP 1	Turbuhaler <sup>®</sup>	steroids for ≥3	SABA for relief.
246	N: NR	Withdraw LOE:	days or an	SADA IUI TEIIEI.
Design:	Age (mean [range]): 45 (12-	NR	unscheduled visit	
randomized.	80)	INIX	(i.e. patient	
parallel, open	Males %: 42.3	GROUP 2	initiated) leading to	
label	FEV <sub>1</sub> % predicted (mean	Drug mcg/day:	treatment change.	
	[range]): 73 (39-115)	SAL/FP 100/500	a cathont onango.	
Funding:	Mean PEF AM (mean±SD):	Dosing: fixed	List of clinical	
Industry:	NR	Treatment	outcomes	
AstraZeneca	Duration of asthma (mean	duration: 52 wk.	reported:	
/ loti uzeneou	[range]): 13 yr. (1-75)	Device: Diskus <sup>®</sup>	Primary	
	Smoking status: NR	Withdraw LOE:	time to 1st	
	entening etataer int	NR	severe	
	GROUP 2		exacerbation	
	N: NR	Reliever Tx:	Chaborballon	
	Age (mean [range]): 45 (12-	salbutamol prn	Secondary	
	84)	Run-in Tx: usual	FEV <sub>1</sub> pre-	
	Males %: 39.9	ICS and LABA, if	SABA	
	FEV <sub>1</sub> % predicted (mean	appropriate	FEV <sub>1</sub> post-	
	[range]): 73 (28-100)	Run-in duration:	SABA	
	Mean PEF AM (mean±SD):	2 wk.	no. severe	
	NR		exacerbations	
	Duration of asthma (mean		no. days with	
	[range]): 12 yr. (0-74)		exacerbation	
	Smoking status: NR		days with	
			OCS	
			exacerbations	
			leading to ER/hosp	
			visits	
			exacerbation	
			leading to	
			unscheduled clinic	
			visits	
			ACQ-5 score	
			SABA use	
			daily dose of	
			ICS	
			no. pts ending	
			study on lowest Tx	
			dose	

<b>Study</b>	Deutiein aut els -us -t-uistis	Treatment	Clinical outcomes	Net
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 56	GROUP 1	Definition of	Study objective:
Wallin A 2003 <sup>116</sup>	Analyzed: 46	Drug mcg/day:	exacerbation: NR	To test the
Pub status:	Withdrawals: 10	SAL/FP 100/400		hypothesis that the
Journal article		Dosing: fixed	List of clinical	addition of SAL to a
	ITT analysis: no	Treatment	outcomes	low dose FP has a
No. countries:	Asthma stage and severity:	duration: 12 wk.	reported:	steroid-sparing
1 (Sweden)	symptomatic, moderate-severe	Device:		effect and does not
No. centers: 1	Baseline ICS use: non-naïve	Diskus <sup>®</sup> /Accuhaler <sup>®</sup>	Primary	result in a
Design:		Withdraw LOE: 0	No primary	worsening of
randomized,	GROUP 1		clinical outcomes	bronchial
parallel, double	<b>N:</b> 14	GROUP 2		inflammation
blind	Age (mean±SD): 43±16	Drug mcg/day:	Secondary	compared to
	Males %: 61.1	FP 400	PEF PM	doubling the dose of
Funding:	FEV <sub>1</sub> % predicted	Dosing: fixed	FEV <sub>1</sub>	ICS.
Industry:	(mean±SD): 80±16	Treatment	no. pts	
GlaxoSmithKline	Mean PEF AM (median): 441	duration: 12 wk.	experiencing	
	Duration of asthma (mean	Device:	exacerbation	
	months±SD): 206±130	Diskus <sup>®</sup> /Accuhaler <sup>®</sup>	exacerbations	
	Smoking status: NR	Withdraw LOE: 1	leading to	
			withdrawal	
	GROUP 2	GROUP 3	withurawai	
	<b>N</b> : 16	Drug mcg/day: FP		
	Age (mean±SD): 42±12	1000		
	Males %: 42.1	Dosing: fixed		
	FEV <sub>1</sub> % predicted	Treatment		
	(mean±SD): 91±20	duration; 12 wk.		
	Mean PEF AM (median): NR	Device:		
	Duration of asthma (mean	Diskus <sup>®</sup> /Accuhaler <sup>®</sup>		
	months±SD): 176±169	Withdraw LOE: 1		
	Smoking status: NR			
	Shioking status. NK	Reliever Tx:		
	GROUP 3	salbutamol		
	<b>N</b> : 16	Run-in Tx: BUD		
	Age (mean±SD): 40±15			
	Males %: 47.4	800-1,200/d or FP		
	FEV <sub>1</sub> % predicted	400-500/d or BDP		
		800-1000/d		
	(mean±SD): 92±12	Run-in duration:		
	Mean PEF AM (median): 456	2 <b>-</b> 4 wk.		
	Duration of asthma (mean			
	months±SD): NA			
	Smoking status: NR			

Notes y objective: to bare the efficacy safety of the escription of 50 mcg twice or 100 mcg daily with BDP ncg twice daily 50 and SAL with BDP 1,000 twice daily 1,000) in nts with asthma pontrolled by 500 mcg twice (or the alent).
are the efficacy safety of the escription of 50 mcg twice or 100 mcg daily with BDP ncg twice daily 50 and SAL with BDP 1,000 twice daily 1,000) in nts with asthma ontrolled by 500 mcg twice (or the
afety of the escription of 50 mcg twice or 100 mcg daily with BDP ncg twice daily 50 and SAL with BDP 1,000 twice daily 1,000) in nts with asthma ontrolled by 500 mcg twice (or the
escription of 50 mcg twice or 100 mcg daily with BDP ncg twice daily 50 and SAL with BDP 1,000 twice daily 1,000) in nts with asthma ontrolled by 500 mcg twice (or the
50 mcg twice or 100 mcg daily with BDP ncg twice daily 50 and SAL with BDP 1,000 twice daily 1,000) in nts with asthma ontrolled by 500 mcg twice (or the
or 100 mcg daily with BDP ncg twice daily 50 and SAL with BDP 1,000 twice daily 1,000) in nts with asthma ontrolled by 500 mcg twice (or the
daily with BDP ncg twice daily 50 and SAL with BDP 1,000 twice daily 1,000) in nts with asthma ontrolled by 500 mcg twice (or the
ncg twice daily 50 and SAL with BDP 1,000 twice daily 1,000) in nts with asthma ontrolled by 500 mcg twice (or the
50 and SAL with BDP 1,000 twice daily 1,000) in hts with asthma ontrolled by 500 mcg twice (or the
with BDP 1,000 twice daily 1,000) in nts with asthma ontrolled by 500 mcg twice (or the
twice daily 1,000) in nts with asthma ontrolled by 500 mcg twice (or the
1,000) in hts with asthma ontrolled by 500 mcg twice (or the
nts with asthma ontrolled by 500 mcg twice (or the
ontrolled by 500 mcg twice (or the
500 mcg twice (or the
(or the
alent).

		Treatment	Clinical outcomes	
Study	Participant characteristics	characteristics	reported	Notes
Author Year:	Randomized: 362	GROUP 1	Definition of	Study objective:
Zetterstrom O	Analyzed: 362	Drug mcg/day:	exacerbation: NR	FORM/BUD in a
2001 <sup>89</sup>	Withdrawals: 53	FORM/BUD		single inhaler was
Pub status:		18/800	List of clinical	compared with BUD
Journal article	ITT analysis: yes	Dosing: fixed	outcomes	alone, and with
N	Asthma stage and severity:	Treatment	reported:	concurrent
No. countries:	NR, mild-severe	duration: 12 wk.	Primary	administration of
6 No. contoro: 50	Baseline ICS use: non-naïve	<b>Device:</b> Turbuhaler <sup>®</sup>	PEF AM	BUD and FORM
No. centers: 59	GROUP 1	Withdraw LOE: 5	Cocondon	from separate
Design: randomized,	N: 123		Secondary	inhalers, in patients with asthma, not
parallel, double	Age (mean [range]): 46.5 (18-	GROUP 2	PEF PM	controlled with
blind, double	78)	Drug mcg/day:	FVC	inhaled
dummy	Males %: 53	FORM/BUD	symptom	glucocorticosteroids
aanniy	FEV <sub>1</sub> % predicted: NR	18/800	score (0-6)	alone
Funding:	Mean PEF AM (mean±SD):	Dosing: fixed	NTA SFD	
Industry:	NR	Treatment		Additional details:
AstraZeneca	Duration of asthma (mean):	duration: 12 wk.	RFD	Comparison of the
	19.1 yr.	Device:	SABA use	original Turbuhaler
	Smoking status –	Turbuhaler <sup>®</sup>		(BUD alone)
	never/past/current (n):	Withdraw LOE: 8		measured metered
	72/40/11			dose with the new
		GROUP 3		Turbuhaler <sup>®</sup> (single
	GROUP 2	Drug mcg/day:		inhaler therapy) has
	<b>N:</b> 115	BUD 800		a dose counter, an
	Age (mean [range]): 44.7 (18-	Dosing: fixed		externally tapered
	77)	Treatment		mouthpiece, and
	Males %: 50	duration; 12 wk.		measures dose as
	FEV <sub>1</sub> % predicted: NR	Device:		delivered dose
	Mean PEF AM (mean±SD): NR	Turbuhaler <sup>®</sup> Withdraw LOE:		
	Duration of asthma (mean):	14		
	16.9			
	Smoking status –	Reliever Tx:		
	never/past/current (n):	terbutaline		
	69/33/13	sulphate or		
		salbutamol		
	GROUP 3 N: 124	Run-in Tx: usual		
		Run-in duration:		
	<b>Age (mean [range]):</b> 48.5 (21-78)	2 wk.		
	Males %: 50			
	FEV <sub>1</sub> % predicted: NR			
	Mean PEF AM (mean±SD):			
	NR Duration of acthma (mean):			
	Duration of asthma (mean):			
	17.1 yr. Smoking status –			
	never/past/current (n):			
	79/38/7			

# APPENDIX 7: DETAILED RESULTS OF CLINICAL REVIEW

# **1 CHARACTERISTICS OF INCLUDED TRIALS**

# 1.1.1 Publication

The results of included trials were published or elsewhere reported between 1994 and 2008 (median 2004; IQR: 2001 to 2006). The majority of reports (85; 79.4%) were published as journal articles. The remaining industry-reports (22; 20.6%) were available online (Table 1).

# 1.1.2 Funding

Almost all trials (104; 97.2%) reported funding, with the majority (102; 95.3%) reporting either receiving funding from the pharmaceutical industry or the affiliation with a pharmaceutical manufacturer of at least one author. Companies represented as the sole source of funding in the trial reports were GlaxoSmithKline (61 trials), AstraZeneca (31 trials), Novartis (4 trials), Chiesi Pharmaceuticals (2 trials), and AstraDraco (1 trial). One trial reported being industry funded, but did not specify the company; one trial reported pharmaceutical company funding (GlaxoSmithKline) in addition to government and institutional funding, and one trial reported pharmaceutical-industry funding (not described) in addition to government funding. Two trials reported receiving only institutional funding and three trials did not declare their funding source.

# 1.1.3 Trial characteristics

All studies (107; 100%) were reported as parallel randomized controlled clinical trials The treatment period of the trials ranged from 8 to 52 weeks (median duration 12 wk.; IQR: 12, 24) with the majority of trials (75.7%) lasting less than 26 weeks (6 months). Most studies (90/107; 84%) compared a combination therapy with ICS monotherapy with the remaining studies comparing a combination therapy with another combination therapy.

# a) Populations

The median number of participants randomized in the 107 trials was 429 (IQR: 199, 582). The age of included participants ranged approximately from 4 to 87 years old. Thirty-nine (36.4%) studies contained participants aged  $\geq$ 18 years. Severity ranged from intermittent to severe with most studies including a range of asthma severity. The majority of studies included a mix of non-smokers, past smokers, and current smokers; however, a few trials (4/107; 3.7%) included only non-smokers. One trial<sup>53</sup>was specifically designed to assess the efficacy of SAL/FP in asthmatics with a smoking history of  $\geq$ 10 pack-years.

# b) Assessment of compliance

C)

Compliance in the trials was assessed using patient-reported diaries, internal counters, and inhaler weight. Of the studies that reported the method of compliance (40/107), the majority of studies (38/40; 95%) reported using diaries. Over one-third of the studies (41/107; 38.3%) failed to report assessing compliance.

### Outcomes (lung function, asthma control, quality of life)

Pulmonary function measures were the most frequently reported primary outcome (63% of studies), followed by asthma control (37%). Secondary outcomes were most frequently measures of asthma control

(94% of studies) but pulmonary function measures were reported almost equally frequently (92%). Quality of life measures were the least frequently reported primary and secondary outcomes (4% and 20% respectively).

Table 1: Characteristics of included studies (N=107)				
Characteristic	Studies (n [%])			
Publication				
Journal	85 (79.4)			
Industry report	22 (20.6)			
Size				
Single centre	8 (7.5)			
Multicentre	93 (86.9)			
Not reported	6 (5.6)			
Funding				
Government	2 (1.9) (1 reported government and industry funding)			
Institution	3 (2.8) (1 reported institution and industry funding)			
Industry	102 (95.3)			
Not reported	3 (2.8)			
Trial design				
Parallel	107 (100)			
Double-blind	94 (87.9)			
Double/triple dummy	31/1 (29.0/0.9)			
Open label	12 (11.2)			
Not reported	1 (0.9)			
Comparisons*				
LABA/ICS vs ICS	95			
SAL/FP vs FP	46			
SAL/FP vs BUD	4			
SAL/FP vs BDP	2			
SAL/BDP vs BDP	8			
SAL/TAA vs TAA	2			
SAL/ICS (mixed or ND) vs ICS (mixed or ND)	6			
FORM/BUD vs BUD	21			
FORM/BUD vs FP	1			
FORM/BDP vs BDP	2			
FORM/ICS (mixed or ND) vs ICS (mixed or ND)	3			
LABA/ICS vs LABA/ICS	17			
FORM/BUD vs SAL/FP	10			
FORM/BDP vs FORM/BUD	1			
FORM/BDP vs SAL/FP	1			
FORM/BUD fixed vs FORM/BUD variable only (3	5			
SMART <sup>®</sup> )	5			
Treatment duration				
<6 mo.	81 (75.7)			
6–12 mo.	25 (23.4)			
>12 mo.	0			
Unclear	1 (0.9)			
Participant characteristics	1 (0.7)			
Age yr. (range)	4-87			
Studies with only participants $\geq 18$ yr.	39 (36.4)			
Asthma severity	J7 (J0.7)			
Mild	9 (8.4)			
141110	2 (0.4)			

Table 1: Characteristics of include	ed studies (N=107) (continued)
Moderate	17 (15.9)
Severe	3 (2.8)
Intermittent-mild	3 (2.8)
Intermittent-mild	8 (74.8)
Intermittent-moderate	20 (18.3)
Mild-moderate	17 (15.9)
Mild-severe	
	14 (12.8)
Moderate-severe	15 (14.0)
Not reported	1 (0.9)
Smoking history	
Non-smokers only	4 (3.7)
Mix of non-smokers/past smokers/smokers	70 (65.4)
Smokers only	1 (0.9)
Not reported	32 (29.9)
Baseline ICS use	
Naïve <sup>†</sup>	9 (8.4)
Low	20 (18.7)
Medium	15 (14.0)
High	14 (13.1)
Naïve to low	1 (0.9)
Naïve to medium	1 (0.9)
Naïve to high	1 (0.9)
Low to medium	13 (12.1)
Low to high	10 (9.3)
Medium to high	11 (10.3)
Not reported	12 (11.2)
Compliance	
Diary	38 (35.5)
Internal counter	1 (0.9)
Weight	1 (0.9)
Reported but not described	7 (6.5)
Not reported	41 (38.3)
Outcome measures	41 (50.5)
Reported at least one measure as primary outcome	
Pulmonary function	67 (62 6)
	<u>67 (62.6)</u> 40 (27.4)
Asthma control	40 (37.4)
Health-related quality of life	4 (3.7)
Reported at least one measure as secondary	
outcome	00 (01 ()
Pulmonary function	98 (91.6)
Asthma control	101 (94.4)
Health-related quality of life	21 (19.6)

\*Some studies included more than one relevant comparison <sup>†</sup>Some studies including patients who were not truly naive, i.e., had ICS therapy removed at run-in, reported baseline ICS dose.

# 1.1.4 Quality of included trials

Overall, the methodological quality of all included studies (n = 107) was moderate. The overall scores from the Jadad quality assessment tool ranged from 1-5 with a median score of 4 (IQR: 3, 4) (Table 2). All included studies were randomized controlled trials, however only 37 (34.6%) adequately described their method for randomization and used an appropriate method of randomization. No studies were recorded as having used an inappropriate method of randomization. Double-blinding was reported used in 94 (87.9%) trials, with 60 (56.0%) explicitly describing the methods by which participants and investigators were blinded to the intervention. Almost all trials (103; 96.3%) reported withdrawals or dropouts if any occurred or otherwise accounted for all participants. Allocation concealment was considered adequate in 16 (15%) of studies and unclear in 91 (85%).

Table 2: Methodological quality of all included studies (N = 107)				
Quality Components No. Yes (%)				
Randomization	107 (100)			
Double-blinding	94 (87.9)			
Description of withdrawals/dropouts	103 (96.3)			
Appropriate method of randomization	37 (34.6)			
Appropriate method of double-blinding	60 (56.0)			
Inappropriate method of randomization	0 (0)			
Inappropriate method of double-blinding	0 (0)			
Adequate concealment of treatment allocation	16 (15.0)			
Inadequate concealment of treatment allocation	0 (0)			
Unclear concealment of treatment allocation	91 (85.0)			

# 2 DATA ANALYSIS AND SYNTHESIS

# 2.1.1 Effectiveness of LABA/ICS therapy for steroid naïve adults

Nineteen unique RCTs<sup>29,46,54-70</sup> were identified that assessed the comparative effectiveness of LABA/ICS combination therapy versus ICS monotherapy in steroid naïve participants (those not receiving ICS therapy for  $\geq 1$  mo. prior to the treatment period). Eleven trials<sup>29,56,57,60-64,66,67,69</sup> compared SAL/FP vs FP, three compared FORM/BUD vs BUD,<sup>46,58,70</sup> two compared SAL/BDP vs BDP,<sup>54,59</sup> one compared SAL/FP vs BUD,<sup>65</sup> one compared SAL/FP vs BDP,<sup>69</sup> and one compared SAL/TAA vs TAA.<sup>55</sup> All trials compared fixed dose LABA/ICS with a fixed dose ICS monotherapy.

LABA/ICS was compared with a similar dose of ICS in 15 trials.<sup>29,46,54-61,63,64,67,69,70</sup> The remaining four trials<sup>62,65,66,68</sup> compared LABA/ICS with a higher dose (double or greater) of ICS. The age of included participants was  $\geq$ 18 years in 5 (26.3%) studies.<sup>46,59,63,66,70</sup> In terms of asthma severity, three trials<sup>54,62,69</sup> included only participants with mild asthma, and two<sup>60,67</sup> included only participants with moderate asthma. The remaining trials examined participants covering a range of asthma severity: intermittent to mild (1 trial),<sup>56</sup> intermittent to moderate (1 trial),<sup>59</sup> intermittent to severe (3 trials),<sup>57,61,70</sup> mild to moderate (4 trials),<sup>46,55,58,65</sup> and mild to severe (5 trials).<sup>29,63,64,66,68</sup> Treatment duration also varied across studies: 8 wk (2 trials),<sup>59,70</sup> 12 wk (10 trials),<sup>46,56,57,59,61,64-68</sup> 26 wk (3 trials),<sup>55,63,69</sup> and 52 wk (4 trials).<sup>29,54,58,62</sup> The median treatment duration was 10 wk (IQR: 10, 26).

# a) Methodological quality

Overall, the methodological quality of included trials examining LABA/ICS therapy in steroid naïve participants (n = 19) was moderate (Table 3). The overall scores from the Jadad quality assessment tool ranged from 1-5 with a median score of 4 (IQR: 3 to 4). Three trials<sup>54,55,59</sup> were considered of low quality according to this rating (Jadad score <3). Allocation concealment was considered unclear in all trials.

All included studies were randomized controlled trials; however, only 5 (26.3%) described the randomization method and were judged to have employed randomization procedures. Doubleblinding was reported in 17 (89.5%) trials with 6 (31.5%) trials explicitly describing the methods by which investigator and participants were blinded to the intervention. Withdrawals or dropouts, if any occurred, and the accounting of all participants was reported in 17 (89.5%) trials. Due to the relatively high scores (Jadad score  $\geq$ 3) of almost all studies, no sensitivity analyses were conducted.

Table 3: Methodological quality of steroid naïve participants					
Quality Components No. Yes (%)					
Randomization	19 (100)				
Double-blinding	17 (89.5)				
Description of withdrawals/dropouts	17 (89.5)				
Appropriate method of randomization	5 (26.3)				
Appropriate method of double-blinding	6 (31.5)				
Inappropriate method of randomization	0 (0)				
Inappropriate method of double-blinding	0 (0)				
Adequate concealment of treatment allocation	0 (0)				
Inadequate concealment of treatment allocation	0 (0)				
Unclear concealment of treatment allocation	19 (100)				

# b) Pulmonary function measures

**PEF** AM: Fifteen trials<sup>39,46,56-58,60-69</sup> involving 7,056 participants (LABA/ICS = 3,517, ICS = 3,539) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on PEF AM (L/min) (Figure 1). The combined result indicated a statistically significant difference favouring LABA/ICS (WMD = 20.78 L/min; 95% CI: 14.03 to 27.53;  $I^2 = 91\%$ ) which was considered to be clinically significant (MCID=18.79 L/min).

		BA/ICS		-	CS			Mean Difference	Mean Difference
Study or Subgroup	Mean [L/min]	SD [L/min]	Total	Mean [L/min]	SD [L/min]	Total	Weight	IV, Random, 95% CI [L/min]	IV, Random, 95% CI [L/min]
.15.1 Similar Dose									
Boonsawat 2008	35.8	35.64	151	21.8	34.86	155	7.3%	14.00 [6.10, 21.90]	
Chuchalin 2002	65	55.9	111	36.3	49.57	114	6.0%	28.70 [14.88, 42.52]	
Kerwin 2008	57.1	43.47	210	33.6	43.68	212	7.2%	23.50 [15.19, 31.81]	
/lurray 2004	68.1	60.98	88	36.5	50.94	89	5.4%	31.60 [15.04, 48.16]	
lelson 2003	66.5	54.29	95	43	51.9	97	5.8%	23.50 [8.47, 38.53]	
D'Byrne 2001	31.81	46	231	15.12	46	228	7.2%	16.69 [8.27, 25.11]	
Rojas 2007	72	15	180	51	15	182	8.0%	21.00 [17.91, 24.09]	
SAS30039 2005	71.9	52.18	179	50.9	53.67	180	6.7%	21.00 [10.05, 31.95]	
SAS40068 2005	47.8	44.06	253	32.6	43.54	262	7.3%	15.20 [7.63, 22.77]	
Strand 2004	56	62	78	23	62	72	4.8%	33.00 [13.14, 52.86]	
Voodcock 2007	71.1	65.7	548	49.2	65.7	550	7.3%	21.90 [14.13, 29.67]	
Subtotal (95% CI)			2124			2141	73.0%	20.47 [18.00, 22.93]	♦
lataraganaitu Tau? -	1 22. Chi2 - 10 -	70 df = 10 /D	- 0.20	12 - 70/					
est for overall effect:			= 0.38)	; l <sup>2</sup> = 7%					
est for overall effect: .15.2 Higher Dose	: Z = 16.26 (P < 0	.00001)	,		43.6	955	7 0%	5 40 [ 0 30 - 1 50]	-
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: I.15.2 Higher Dose Chuchalin 2008	Z = 16.26 (P < 0 32.1	43.29	956	37.5	43.6	955	7.9%	-5.40 [-9.30, -1.50] 28 20 [45 45 40 95]	÷
est for overall effect: 1.15.2 Higher Dose Chuchalin 2008 SAM40034 2004	Z = 16.26 (P < 0 32.1 58.6	.00001) 43.29 39.84	956 75	37.5 30.4	40.89	79	6.3%	28.20 [15.45, 40.95]	
est for overall effect: 1 <b>5.2 Higher Dose</b> Chuchalin 2008 SAM40034 2004 SAM40036 2004	Z = 16.26 (P < 0 32.1 58.6 51.4	.00001) 43.29 39.84 44.12	956 75 288	37.5 30.4 33.9	40.89 45.9	79 289	6.3% 7.4%	28.20 [15.45, 40.95] 17.50 [10.15, 24.85]	
Fest for overall effect: 1.15.2 Higher Dose Chuchalin 2008 SAM40034 2004 SAM40036 2004 SAS30015 2004	Z = 16.26 (P < 0 32.1 58.6	.00001) 43.29 39.84	956 75 288 74	37.5 30.4	40.89	79 289 75	6.3% 7.4% 5.4%	28.20 [15.45, 40.95] 17.50 [10.15, 24.85] 37.70 [21.17, 54.23]	
est for overall effect: 1 <b>5.2 Higher Dose</b> Chuchalin 2008 SAM40034 2004 SAM40036 2004	: Z = 16.26 (P < 0 32.1 58.6 51.4 70.4 = 365.60; Chi <sup>2</sup> = 6	.00001) 43.29 39.84 44.12 60.4 4.75, df = 3 (I	956 75 288 74 <b>1393</b>	37.5 30.4 33.9 32.7	40.89 45.9	79 289	6.3% 7.4%	28.20 [15.45, 40.95] 17.50 [10.15, 24.85]	- 
Eest for overall effect: 1.15.2 Higher Dose Chuchalin 2008 SAM40034 2004 SAM40036 2004 SAM40036 2004 SAM40036 2004 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> =	: Z = 16.26 (P < 0 32.1 58.6 51.4 70.4 = 365.60; Chi <sup>2</sup> = 6	.00001) 43.29 39.84 44.12 60.4 4.75, df = 3 (I	956 75 288 74 <b>1393</b>	37.5 30.4 33.9 32.7	40.89 45.9	79 289 75 1398	6.3% 7.4% 5.4%	28.20 [15.45, 40.95] 17.50 [10.15, 24.85] 37.70 [21.17, 54.23]	
est for overall effect: .15.2 Higher Dose Chuchalin 2008 SAM40034 2004 SAM40036 2004 SAS30015 2004 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = est for overall effect:	: Z = 16.26 (P < 0 32.1 58.6 51.4 70.4 = 365.60; Chi <sup>2</sup> = 6 : Z = 1.86 (P = 0.0	.00001) 43.29 39.84 44.12 60.4 4.75, df = 3 (1 06)	956 75 288 74 1393 P < 0.00 3517	37.5 30.4 33.9 32.7 0001); l <sup>2</sup> = 95%	40.89 45.9 40.5	79 289 75 1398	6.3% 7.4% 5.4% <b>27.0%</b>	28.20 [15.45, 40.95] 17.50 [10.15, 24.85] 37.70 [21.17, 54.23] 18.54 [-0.98, 38.06]	

Figure 1: The effect of LABA/ICS versus ICS monotherapy on PEF AM (L	/min)
----------------------------------------------------------------------	-------

A subgroup analysis based on the relative size of the dose of the ICS comparator showed relative homogeneity ( $I^2 = 7\%$ ) for those trials in which LABA/ICS was compared with a similar dose ICS. However, there was little change in the magnitude and precision of the estimate (WMD=20.47 L/min; 95% CI: 18.00 to 22.93). There was considerable heterogeneity ( $I^2=95\%$ ) among the result from trials that compared LABA/ICS to a higher dose of ICS. The combined result was not statistically significant (WMD=18.54 L/min; 95% CI: -0.98 to 38.06), but it was potentially clinically significant. The trial that contributed most to the heterogeneity<sup>62</sup> included 68.4% (1911/2791) of all participants in the subgroup comparison. The participants came from 195 centres in 28 countries making it by far the largest trial in this comparison. In addition, the trial comprised only participants with mild asthma, while the participants in the other three trials varied in asthma severity (mild to moderate<sup>65</sup> and mild to severe<sup>66,68</sup>).

**PEF PM:** Eleven trials<sup>46,56,57,61,63-69</sup> involving 3,224 participants (LABA/ICS = 1,600, ICS = 1,624) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on PEF PM (L/min) (Figure 2). The combined result indicated a statistically significant difference favouring LABA/ICS (WMD=17.93 L/min; 95% CI: 14.95 to 20.92;  $I^2 = 0\%$ ). The difference was potentially clinically significant (MCID=18.79 L/min).

	LAI	BA/ICS		I	CS			Mean Difference	Mean Difference
Study or Subgroup	Mean [L/min]	SD [L/min]	Total	Mean [L/min]	SD [L/min]	Total	Weight	IV, Random, 95% CI [L/min]	IV, Random, 95% CI [L/min]
Boonsawat 2008	37.5	38.09	151	17.7	37.35	155	12.5%	19.80 [11.35, 28.25]	
Chuchalin 2002	55.2	52.14	111	33.6	46.3	114	5.4%	21.60 [8.70, 34.50]	
Kerwin 2008	48.7	40.58	210	27.9	40.77	212	14.8%	20.80 [13.04, 28.56]	
Murray 2004	51	50.66	88	30.4	45.28	89	4.4%	20.60 [6.44, 34.76]	— <b>-</b>
Nelson 2003	51.5	46.2	95	29.9	49.64	97	4.8%	21.60 [8.04, 35.16]	
SAM40034 2004	51	43.4	75	27.7	43.3	79	4.7%	23.30 [9.60, 37.00]	
SAM40036 2004	51	40.4	288	40.1	40.5	289	20.4%	10.90 [4.30, 17.50]	
SAS30015 2004	45.6	45.8	74	26.7	37.5	75	4.9%	18.90 [5.45, 32.35]	
SAS30039 2005	64.4	48.83	179	42.9	49.64	180	8.6%	21.50 [11.31, 31.69]	
SAS40068 2005	42.3	41.83	251	27.3	41.44	262	17.1%	15.00 [7.79, 22.21]	
Strand 2004	40	62	78	14	62	72	2.3%	26.00 [6.14, 45.86]	
Total (95% CI)			1600			1624	100.0%	17.93 [14.95, 20.92]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> = 8.15	5, df = 10 (P =	= 0.61);	l <sup>2</sup> = 0%					-50 -25 0 25
Test for overall effect:	Z = 11.78 (P < 0	.00001)							-50 -25 0 25 Favours ICS Favours LABA

#### Figure 2: The effect of LABA/ICS versus ICS monotherapy on PEF PM (L/min)

*FEV*<sub>1</sub> (absolute): Eleven trials<sup>29,46,55-57,61,62,64-66,69</sup> involving 5581 participants (LABA/ICS = 2,780, ICS = 2,801) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on absolute FEV<sub>1</sub> (L; Figure 3). The combined result indicated a statistically significant difference favouring LABA/ICS (WMD = 0.11; 95% CI: 0.06 to 0.15; I<sup>2</sup>=66%); however, the pooled result demonstrated heterogeneity and the 965% CI did not include a priori defined clinical significance (MCID=0.23 L).

#### **Figure 3:** The effect of LABA/ICS versus ICS monotherapy on FEV<sub>1</sub> (absolute) (L)

	L/	ABA/ICS			ICS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.17.1 Similar Dose									
Bateman 2004	0.52	0.462	533	0.34	0.461	531	12.7%	0.18 [0.12, 0.24]	
Boonsawat 2008	0.19	0.37	155	0.01	0.37	154	10.1%	0.18 [0.10, 0.26]	
Chuchalin 2002	0.55	0.591	111	0.39	0.599	114	5.2%	0.16 [0.00, 0.32]	
Creticos 1999	0.28	0.535	23	0.18	0.372	23	2.2%	0.10 [-0.17, 0.37]	
Kerwin 2008	0.48	0.435	210	0.36	0.437	212	10.0%	0.12 [0.04, 0.20]	
Murray 2004	0.51	0.47	88	0.5	0.47	89	6.0%	0.01 [-0.13, 0.15]	
Nelson 2003	0.69	0.487	95	0.51	0.492	97	6.0%	0.18 [0.04, 0.32]	
SAS40068 2005	0.1444	0.3096	229	0.0763	0.3057	243	12.7%	0.07 [0.01, 0.12]	
Subtotal (95% CI)			1444			1463	65.0%	0.13 [0.08, 0.18]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi	² = 12.93	, df = 7	(P = 0.0)	7); l <sup>2</sup> = 46	6%			
Test for overall effect:	Z = 5.48	(P < 0.00	001)						
1.17.2 Higher Dose									
Chuchalin 2008	0.107	0.468	973	0.08	0.436	970	14.2%	0.03 [-0.01, 0.07]	+=-
SAM40034 2004	0.5	0.3	75	0.38	0.3	79	9.0%	0.12 [0.03, 0.21]	
SAM40036 2004	0.5	0.4	288	0.427	0.4	289	11.8%	0.07 [0.01, 0.14]	
Subtotal (95% CI)			1336			1338	35.0%	0.06 [0.01, 0.11]	◆
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi	² = 3.82,	df = 2 (	P = 0.15	); l <sup>2</sup> = 48 <sup>0</sup>	%			
Test for overall effect:	Z = 2.35	(P = 0.02	)						
Total (95% CI)			2780			2801	100.0%	0.11 [0.06, 0.15]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi	² = 29.52	, df = 1	0 (P = 0.	001); l² =	66%		_	
Test for overall effect:					,,				-0.2 -0.1 0 0.1 0.2 Favours ICS Favours LABA/I

A subgroup analysis based on the relative size of the dose of the ICS comparator showed moderate heterogeneity ( $I^2=46\%$ ) for those trials in which LABA/ICS was compared with a similar dose ICS. However, there was little change in the point estimate (WMD=0.13; 95% CI: 0.08 to 0.18). The combined result for studies that compared LABA/ICS to a higher dose of ICS showed moderate heterogeneity ( $I^2=48\%$ ) and little change in magnitude and precision of the effect (WMD=0.06; 95% CI: 0.01 to 0.11).

*FEV*<sub>1</sub>% *predicted:* Four trials<sup>54,58,59,70</sup> involving 548 participants (LABA/ICS = 274, ICS = 274) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on percent (%) predicted  $FEV_1$  (Figure 4). The combined result failed to identify a statistically significant difference between the treatments (WMD = 1.68%; 95% CI: 0.13 to 3.24;  $I^2 = 0\%$ ). In addition, the precision of the confidence intervals suggest that any differences would not meet our a priori criteria for clinical importance (MCID=12%).

Figure 4: The e	effect of	LABA	VICS	S versus	S ICS	mon	othera	apy on FEV₁ % pre	edicted
-	Ly or Subgroup       Mean [%]       SD [%]       Total       Mean [%]       SD [%]       Total       Weight       IV, Random, 95% CI [%]       IV,			Mean Difference					
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]	IV, Random, 95% CI [%]
1.3.1 FORM/BUD vs E	BUD								
O'Byrne 2001	5.87	8.8	231	4.04	8.8	228	92.8%	1.83 [0.22, 3.44]	
Overbeek 2005 Subtotal (95% CI)	9.3	10.4		10.5	12.2				•
0,	,	,	1 (P =	0.41); l <sup>2</sup> = 0	%				
1.3.2 SAL/BDP vs BD	P								
DiFranco 1999	7	21.12	11	8	16.43	11	1.0%	-1.00 [-16.81, 14.81]	
Grutters 1999	14	17.3	12	10	17.7	15	1.4%	4.00 [-9.27, 17.27]	
Subtotal (95% CI)			23			26	2.3%	1.93 [-8.23, 12.10]	
• •			1 (P =	0.63); l² = 0	%				
Total (95% CI)			274			274	100.0%	1.68 [0.13, 3.24]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> =	0.91, df =	3 (P =	0.82); I <sup>2</sup> = 0	%			-	-10 -5 0 5 10
Test for overall effect:	Z = 2.13 (P =	0.03)							Favours ICS Favours LABA
Test for subgroup diffe	erences: Chi <sup>2</sup>	= 0.00, d	f = 1 (F	P = 0.96), l <sup>2</sup> =	= 0%				

c) Asthma symptom control measures *Total number of exacerbations:* Five trials<sup>29,56,60,62,69</sup> involving 4,159 participants (LABA/ICS = 2,073, ICS = 2,086) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on number of exacerbations (Figure 5). The combined estimate failed to identify a statistically significant difference between the treatments (WMD = -0.03; 95% CI: -0.06 to 0.01;  $I^2$ =84%). All trials compared SAL/FP with FP; however, the trial that most favoured LABA/ICS<sup>60</sup> (WMD = -0.10; 95% CI: -0.15 to -0.05) compared mediumdose FP (500 mcg/d) in a population with moderate asthma. Three trials  $\frac{56,62,69}{100}$  compared lowdose FP (100–200 mcg/d) and one trial<sup>29</sup> used a dose-escalation design from low-dose FP (200 mcg/d) to high-dose FP (1000 mcg/d). The participants in the four studies varied in asthma severity: intermittent to mild,  $^{56}$  mild,  $^{62,69}$  and mild to severe.<sup>29</sup>

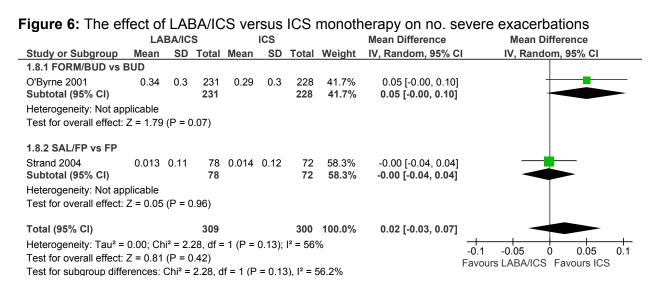
#### Figure 5: The effect of LABA/ICS versus ICS monotherapy on no. exacerbations

	LA	BA/ICS			ICS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.5.2 SAL/FP vs FP									
Bateman 2004	0.07	0.25	533	0.11	0.25	531	21.5%	-0.04 [-0.07, -0.01]	_ <b>_</b>
Boonsawat 2008	0.01987	0.14	151	0.0581	0.2608	155	17.2%	-0.04 [-0.08, 0.01]	
Chuchalin 2008	0.13	0.416	956	0.1	0.416	955	19.6%	0.03 [-0.01, 0.07]	+
Rojas 2007	0.1	0.25	180	0.2	0.25	182	16.1%	-0.10 [-0.15, -0.05]	
SAS40068 2005	0.012	0.0443	253	0.012	0.0434	263	25.6%	0.00 [-0.01, 0.01]	. +
Subtotal (95% CI)			2073			2086	100.0%	-0.03 [-0.06, 0.01]	$\bullet$
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 25.18,	df = 4 (	P < 0.00	01); l² = 8	34%			
Test for overall effect:	Z = 1.48 (F	P = 0.14)							
Total (95% CI)			2073			2086	100.0%	-0.03 [-0.06, 0.01]	
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 25.18,	df = 4 (	P < 0.00	01); l² = 8	34%		_	
Test for overall effect:	Z = 1.48 (F	P = 0.14)						Fa	-0.1 -0.05 0 0.05 0. vours LABA/ICS Favours IC
Test for subgroup diffe	erences: No	ot applica	ble					i a	Vouis LABANCS Tavouis IC

*Time to first exacerbation:* One trial<sup>68</sup> involving 156 participants (SAL/FP = 78, BDP = 78) provided data on the effects of SAL/FP compared with BDP on time to first exacerbation. The combined result indicated a statistically significant difference favouring SAL/FP (Hazard ratio = 0.44 (95% CI: 0.24 to 0.82).

**Percent participants experiencing**  $\geq 1$  **exacerbation:** One trial<sup>68</sup> involving 128 participants (SAL/FP = 67, BDP = 61) provided data on the effects of SAL/FP compared with BDP on percent of participants experiencing one or more exacerbations. The combined result indicated a statistically significant difference favouring SAL/FP (RR = 0.57; 95% CI: 0.35 to 0.91).

*Number of severe exacerbations:* Two trials<sup>58,63</sup> involving 609 participants (SAL/FP = 309, FP = 300) provided data for a meta-analysis of the effects of SAL/FP combination therapy compared with FP monotherapy number of severe exacerbations (Figure 6). The combined result failed to identify a statistically significant difference between the treatments (WMD = 0.02; 95% CI: - 0.03 to 0.07;  $I^2$ =56%).



*Short-acting beta*<sub>2</sub>*-agonist (SABA) use:* Nine trials<sup>46,57,58,61-65,67</sup> involving 4,468 participants (LABA/ICS = 2,234, ICS = 2,234) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on use of SABA reliever medication (puffs/d) (Figure 7). The combined result indicated a statistically significant reduction in SABA use favouring LABA/ICS (WMD = -0.23; 95% CI: -0.40 to -0.06; I<sup>2</sup>=79%).

J							- 1- 5	· · · · · · · · · · · · · · · · · · ·	
		BA/ICS			ICS			Mean Difference	Mean Difference
Study or Subgroup		SD [puff/sday]	Total	Mean [puff/sday]	SD [puff/sday]	Total	Weight	IV, Random, 95% CI [puff/sday]	IV, Random, 95% CI [puff/sday]
1.9.1 FORM/BUD vs E	BUD								
Chuchalin 2002	-2.6	1.95	111	-1.6	1.95	114	7.5%	-1.00 [-1.51, -0.49]	
O'Byrne 2001	0.51	0.77	231	0.51	0.77	228	19.5%	0.00 [-0.14, 0.14]	+
Subtotal (95% CI)			342			342	27.0%	-0.47 [-1.45, 0.51]	
Heterogeneity: Tau <sup>2</sup> =	0.46; Chi <sup>2</sup> = 13.74, d	f = 1 (P = 0.0002	); I <sup>2</sup> = 93	3%					
Test for overall effect:	Z = 0.94 (P = 0.35)								
1.9.2 SAL/FP vs FP									
Chuchalin 2008	0.13	0.227	956	0.11	0.227	955	22.5%	0.02 [-0.00, 0.04]	•
Kerwin 2008	-1.8	2.46	210	-1.5	2.77	212	7.7%	-0.30 [-0.80, 0.20]	
Murray 2004	-2.8	2.91	88	-1.8	2.17	89	4.1%	-1.00 [-1.76, -0.24]	
Nelson 2003	-2.4	3.02	95	-1.8	2.07	97	4.3%	-0.60 [-1.33, 0.13]	
SAS30039 2005	-1.3	0.67	177	-1.1	0.67	178	19.6%	-0.20 [-0.34, -0.06]	
Strand 2004	-1.2	1.67	78	-0.8	1.67	72	7.0%	-0.40 [-0.93, 0.13]	
Subtotal (95% CI)			1604			1603	65.2%	-0.24 [-0.46, -0.02]	•
Heterogeneity: Tau <sup>2</sup> =	0.04; Chi <sup>2</sup> = 22.78, d	f = 5 (P = 0.0004	); l <sup>2</sup> = 78	8%					
Test for overall effect:	Z = 2.17 (P = 0.03)								
1.9.3 SAL/FP vs BUD									
SAM40036 2004	-1.2	3.02	288	-1.2	3.02	289	7.8%	0.00 [-0.49, 0.49]	<u> </u>
Subtotal (95% CI)			288			289	7.8%	0.00 [-0.49, 0.49]	$\bullet$
Heterogeneity: Not app									
Test for overall effect:	Z = 0.00 (P = 1.00)								
Total (95% CI)			2234			2234	100.0%	-0.23 [-0.40, -0.06]	•
Heterogeneity: Tau <sup>2</sup> =	0.03; Chi <sup>2</sup> = 37.97, d	f = 8 (P < 0.0000	1); I <sup>2</sup> = 1	79%					
Test for overall effect:	Z = 2.62 (P = 0.009)							F	avours LABA/ICS Favours ICS
Test for subgroup diffe	rences: Chi <sup>2</sup> = 1.44,	df = 2 (P = 0.49),	$I^2 = 0\%$					1.	

#### Figure 7: The effect of LABA/ICS versus ICS monotherapy on SABA use (puffs/d)

*Symptom-free days (SFD):* Nine trials<sup>29,56-58,60,63,64,68,69</sup> involving 3,369 participants (LABA/ICS = 1,683, ICS = 1,686) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on the number of SFD (Figure 8). The estimate of change in number of SFD indicated a statistically significant difference favouring LABA/ICS (WMD=6.66; 95% CI: 3.70 to 9.61; I<sup>2</sup>=36%).

#### Figure 8: The effect of LABA/ICS versus ICS monotherapy on no. SFD

LAI	BA/ICS		1	CS			Mean Difference	Mean Difference	
Mean [median %]	SD [median %] 1	Γotal	Mean [median %]	SD [median %]	Total	Weight	IV, Random, 95% CI [median %]	IV, Random, 95% CI [median %	
ths									
93	21	151	87	21	155	18.4%	6.00 [1.29, 10.71]		
40.6	44.09	88	24.6	38.68	89	5.0%	16.00 [3.78, 28.22]		
30.3	41.62	95	24.9	36.54	97	5.9%	5.40 [-5.69, 16.49]	<b>+-</b>	
78	43	180	71	43	182	8.4%	7.00 [-1.86, 15.86]	+	
42	45	74	22	45	74	3.7%	20.00 [5.50, 34.50]	—	
		588			597	41.3%	8.59 [3.98, 13.20]	•	
71; Chi <sup>2</sup> = 5.22, df = 4	(P = 0.27); I <sup>2</sup> = 23%								
= 3.65 (P = 0.0003)									
ar									
81.5	35	533	76.6	35	531	20.3%	4.90 [0.69, 9.11]		
78.5	24	231	76.9	24	228	19.5%	1.60 [-2.79, 5.99]	+-	
42.2	34.52	253	34.4	34.53	258	14.3%	7.80 [1.81, 13.79]		
41	40	78	26	40	72	4.6%	15.00 [2.19, 27.81]		
	1	1095			1089	58.7%	5.30 [1.44, 9.16]	◆	
65; Chi <sup>2</sup> = 5.44, df = 3	(P = 0.14); I <sup>2</sup> = 45%								
= 2.69 (P = 0.007)									
	1	683			1686	100.0%	6.66 [3.70, 9.61]	•	
61: Chi <sup>2</sup> = 12.54, df = 8	$B(P = 0.13)$ ; $I^2 = 369$	%					· · · · · · · · · · · · · · · · · · ·	<u> </u>	
= 4.41 (P < 0.0001)								-20-10 0 10 20 Favours ICS Favours LABA/I	
	Mean [median %]           93           40.6           30.78           40.6           378           42           71; Chi² = 5.22, df = 4           3.65 (P = 0.0003)           ar           81.5           78.5           42.2           41           35; Chi² = 5.44, df = 3           > 2.69 (P = 0.007)           31; Chi² = 12.54, df = 4	ths $\begin{array}{c} 93 & 21 \\ 40.6 & 44.09 \\ 30.3 & 41.62 \\ 78 & 43 \\ 42 & 45 \end{array}$ r1; Chi <sup>2</sup> = 5.22, df = 4 (P = 0.27); l <sup>2</sup> = 23% = 3.65 (P = 0.0003) \\ ar \\ 81.5 & 35 \\ 78.5 & 24 \\ 42.2 & 34.52 \\ 41 & 40 \\ 55; Chi <sup>2</sup> = 5.44, df = 3 (P = 0.14); l <sup>2</sup> = 45\% = 2.69 (P = 0.007) \\ compared by the second secon	$\begin{tabular}{ c c c c c c c } \hline Mean [median %] & SD [median %] & Total \\ \hline & 93 & 21 & 151 \\ & 40.6 & 44.09 & 88 \\ & 30.3 & 41.62 & 95 \\ \hline & 78 & 43 & 180 \\ & 42 & 45 & 74 \\ & 588 \\ \hline & 1; Chi^2 = 5.22, df = 4 (P = 0.27); l^2 = 23\% \\ \hline & 3.65 (P = 0.0003) \\ \hline & ar \\ \hline & 81.5 & 35 & 533 \\ & 78.5 & 24 & 231 \\ & 42.2 & 34.52 & 253 \\ & 41 & 40 & 78 \\ \hline & 1095 \\ \hline & 52.69 (P = 0.007) \\ \hline & $2.69 (P = 0.03); l^2 = 36\% \\ \hline & $31; Chi^2 = 12.54, df = 8 (P = 0.13); l^2 = 36\% \\ \hline \end{tabular}$	$\begin{tabular}{ c c c c c } \hline Mean [median %] & SD [median %] & Total & Mean [median %] \\ \hline Ms & 93 & 21 & 151 & 87 \\ \hline 40.6 & 44.09 & 88 & 24.6 \\ \hline 30.3 & 41.62 & 95 & 24.9 \\ \hline 78 & 43 & 180 & 711 \\ \hline 42 & 45 & 74 & 22 \\ \hline 58 & 74 & 22 \\ \hline 58 & 74 & 22. \\ \hline 1; Chi^2 = 5.22, df = 4 (P = 0.27); l^2 = 23\% \\ \hline 3.66 (P = 0.0003) \\ \hline ar & & \\ \hline 81.5 & 55 & 533 & 76.6 \\ \hline 78.5 & 24 & 231 & 76.9 \\ \hline 42.2 & 34.52 & 253 & 34.4 \\ \hline 41 & 0 & 78 & 26 \\ \hline 1095 & & \\ \hline 52.69 (P = 0.007) \\ \hline \\ \hline 52.69 (P = 0.007) \\ \hline \hline \\ \hline 81; Chi^2 = 5.44, df = 8 (P = 0.13); l^2 = 36\% \\ \hline \end{tabular}$	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	$\begin{tabular}{ c c c c c c c } \hline Mean [median %] & SD [median %] & Total & Mean [median %] & SD [median %] & Total \\ \hline Mean [median %] & SD [median %] & Total \\ \hline Mean [median %] & SD [median %] & Total \\ \hline Mean [median %] & SD [median %] & Total \\ \hline Mean [median %] & SD [median %] & Total \\ \hline Mean [median %] & SD [median %] & Total \\ \hline 40.6 & 44.09 & 88 & 24.6 & 38.68 & 89 \\ \hline 30.3 & 41.62 & 95 & 24.9 & 36.54 & 97 \\ \hline 78 & 43 & 180 & 71 & 43 & 182 \\ \hline 42 & 45 & 74 & 22 & 45 & 74 \\ \hline 58 & 577 \\ \hline 1, Chi^2 = 5.22, df = 4 (P = 0.27); P = 23\% \\ \hline 3.66 (P = 0.0003) \\ \hline ar & & & & & & & & & & & & & & & & & & $	$\begin{tabular}{ c c c c } $LABA/ICS & ICS & I$	LABA/ICS         ICS         Mean Difference           Mean [median %]         SD [median %]         Total         Mean [median %]         SD [median %]         Total         Weight         IV, Random, 95% CI [median %]           ths         93         21         151         87         21         155         18.4% $6.00$ [1.29, 10.71]           40.6         44.09         88         24.6         38.68         89         5.0%         16.00 [3.76, 28.22]           30.3         41.62         95         24.9         36.54         97         5.9%         5.40 [-5.69, 16.49]           78         43         180         71         43         182         8.4%         7.00 [-1.86, 15.86]           42         45         74         2.7%         20.00 [5.50, 34.50]         587         41.3%         8.59 [3.88, 13.20]           71; Chi <sup>2</sup> = 5.22, df = 4 (P = 0.27); P = 23%         =         597         41.3%         4.90 [0.69, 9.11]           78.5         24         231         76.6         35         531         20.3%         4.90 [0.69, 9.11]           78.5         24         231         76.9         24         28         1.60 [-2.79, 5.99]           42.2         34.52	

A subgroup analysis based on the duration of the treatment period (<6 mo. vs 6–12 mo.) indicated little change in the magnitude and precision of the point estimate for shorter follow-ups (WMD=8.59; 95% CI: 3.98 to 13.20;  $I^2=23\%$ ). Four of the studies<sup>56,57,60,64</sup> compared SAL/FP with FP and one study<sup>58</sup> compared FORM/BUD with BUD. All studies compared the combination therapy to a similar dose of ICS. The studies varied in the range of asthma severity of the participants: intermittent to mild,<sup>56</sup> intermittent to severe,<sup>57</sup> mild to severe<sup>64,68</sup> and moderate.<sup>60</sup>

The combined result for studies with a treatment period from 6 to 12 mo. indicated little change in the magnitude and precision of the difference for longer follow-ups (WMD=5.30; 95% CI: 1.44 to 9.16;  $I^2$ =45%). Three of the studies<sup>29,63,69</sup> compared SAL/FP with FP and one study<sup>58</sup> compared FORM/BUD with BUD and all compared the combination therapy to a similar dose of ICS. The studies varied in the range of asthma severity of the participants: mild,<sup>69</sup> mild to moderate,<sup>58</sup> and mild to severe.<sup>29,63</sup>

**Proportion of participants achieving symptom-free day (SFD):** Nine trials<sup>29,56-58,60,63,64,68,69</sup> involving 3,369 participants (LABA/ICS = 1,683, ICS = 1,686) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on the ability for participants to achieve a symptom-free day (Figure 9). The combined estimate indicated a statistically significant difference favouring LABA/ICS (RR=1.06; 95% CI: 1.01 to 1.12).

**Figure 9:** The effect of LABA/ICS versus ICS monotherapy on proportion of participants achieving a symptom-free day

•	LAE	BA/ICS		I	cs			Mean Difference	Mean Difference
Study or Subgroup	Mean [median %]	SD [median %]	Total	Mean [median %]	SD [median %]	Total	Weight	IV, Random, 95% CI [median %]	IV, Random, 95% CI [median %]
1.10.1 FORM/BUD vs	BUD								
O'Byrne 2001 Subtotal (95% CI)	78.5	24	231 231	76.9	24	228 228	19.5% <b>19.5%</b>	1.60 [-2.79, 5.99] <b>1.60 [-2.79, 5.99]</b>	 ◆
Heterogeneity: Not app	olicable								
Test for overall effect: 2	Z = 0.71 (P = 0.48)								
1.10.2 SAL/FP vs FP									
Bateman 2004	81.5	35	533	76.6	35	531	20.3%	4.90 [0.69, 9.11]	
Boonsawat 2008	93	21	151	87	21	155	18.4%	6.00 [1.29, 10.71]	
Murray 2004	40.6	44.09	88	24.6	38.68	89	5.0%	16.00 [3.78, 28.22]	
Nelson 2003	30.3	41.62	95	24.9	36.54	97	5.9%	5.40 [-5.69, 16.49]	
Rojas 2007	78	43	180	71	43	182	8.4%	7.00 [-1.86, 15.86]	
SAS30015 2004	42	45	74	22	45	74	3.7%	20.00 [5.50, 34.50]	
SAS40068 2005	42.2	34.52	253	34.4	34.53	258	14.3%	7.80 [1.81, 13.79]	- <b>-</b> -
Strand 2004	41	40	78	26	40	72	4.6%	15.00 [2.19, 27.81]	
Subtotal (95% CI)			1452			1458	80.5%	7.39 [4.65, 10.12]	•
Heterogeneity: Tau <sup>2</sup> =	1.88; Chi <sup>2</sup> = 7.94, df =	= 7 (P = 0.34); l <sup>2</sup> =	12%						
Test for overall effect: 2	Z = 5.29 (P < 0.00001	)							
Total (95% CI)			1683			1686	100.0%	6.66 [3.70, 9.61]	•
Heterogeneity: Tau <sup>2</sup> =	6.61; Chi <sup>2</sup> = 12.54, df	= 8 (P = 0.13); l <sup>2</sup> =	= 36%					-	-20-10 0 10 20
Test for overall effect: 2	Z = 4.41 (P < 0.0001)								Favours ICS Favours LABA/IC
Test for subgroup diffe	rences: Chi <sup>2</sup> = 4.60, d	if = 1 (P = 0.03), l <sup>2</sup>	= 78.3	%					

*Participants achieving optimal control:* Three trials<sup>56,60,62</sup> involving 2,525 participants (LABA/ICS = 1256, ICS = 1269) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on the number of participants achieving optimal control as defined by the study authors (Figure 10). The combined results failed to identify a statistically significant difference between the treatments (RR = 1.14; 95% CI: 0.78 to 1.67; I<sup>2</sup> = 90%).

All three trials compared SAL/FP with FP. Two trials<sup>56,60</sup> compared LABA/ICS to a similar dose of ICS, and one trial<sup>62</sup> compared LABA/ICS to a higher (double) dose of ICS. The three studies varied in the range of asthma severity of the participants: intermittent to mild,<sup>56</sup> mild,<sup>62</sup> and moderate.<sup>60</sup> Two trials<sup>56,60</sup> had a treatment duration of 12 wk. In contrast, the trial<sup>62</sup> with a result favouring ICS had a treatment duration of 52 wk.

opunia oona oi							
	LABA/	ICS	ICS	;		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Boonsawat 2008	79	151	65	155	32.7%	1.25 [0.98, 1.59]	<b>⊢</b> ∎−−
Chuchalin 2008	259	925	317	932	35.7%	0.82 [0.72, 0.94]	
Rojas 2007	83	180	56	182	31.6%	1.50 [1.15, 1.96]	
Total (95% CI)		1256		1269	100.0%	1.14 [0.78, 1.67]	
Total events	421		438				
Heterogeneity: Tau <sup>2</sup> =	0.10; Chi <sup>2</sup>	= 19.7	8, df = 2 (	P < 0.0	001); l² =	90% —	
Test for overall effect:	Z = 0.67 (I	P = 0.5	1)				0.5 0.7 1 1.5 2 Favours ICS Favours LABA/ICS

**Figure 10:** The effect of LABA/ICS versus ICS monotherapy on no. participants achieving optimal control

e) Health-related quality of life measures

Asthma quality of life questionnaire (AQLQ): Two trials<sup>29,46</sup> involving 1,289 participants (LABA/ICS = 644, ICS = 645) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on the AQLQ (Figure 11). The combined result indicated a statistically significant difference favouring LABA/ICS (WMD = 0.17; 95% CI: 0.11 to 0.22;  $I^2 = 7\%$ ); however, the difference was not considered clinically significant (MCID = 0.5).

Figure 11: The effect of LABA/ICS versus ICS monotherapy on AQI	Q score
inguie in the check of E. (De the check of t	- 30 00010

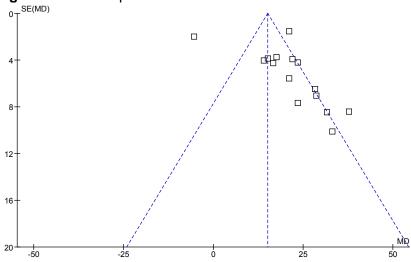
	LA	BA/IC	S		ICS			Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	Year	IV, Random, 95% CI	
1.12.1 FORM/BUD vs	BUD										
Chuchalin 2002	1.1	0.54	111	1	0.54	114	15.7%	0.10 [-0.04, 0.24]	2002		
Subtotal (95% CI)			111			114	15.7%	0.10 [-0.04, 0.24]			
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 1.39	(P = 0	).16)								
1.12.2 SAL/FP vs FP											
Bateman 2004	0.52	0.46	533	0.34	0.46	531	84.3%	0.18 [0.12, 0.24]	2004	-	-
Subtotal (95% CI)			533			531	84.3%	0.18 [0.12, 0.24]			
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 6.38	(P < 0	0.00001	)							
Total (95% CI)			644			645	100.0%	0.17 [0.11, 0.22]			
Heterogeneity: Tau <sup>2</sup> =	0.00; Cł	ni² = 1.	07, df =	= 1 (P =	0.30);	l² = 7%	,				-+
Test for overall effect:	Z = 5.75	(P < 0	.00001	)						-0.2 -0.1 0 0.1 Favours ICS Favours LA	0.2
Test for subgroup diffe	erences:	Chi <sup>2</sup> =	1.07. d	lf = 1 (P	= 0.30	$(),  ^2 = 0$	5.6%			Favouis ICS Favouis LA	٦DA/

It was not considered appropriate to conduct subgroup analyses based on asthma severity as only a small proportion of studies (< 20% of available studies for any single outcome) reported results for populations restricted to a single asthma severity class.

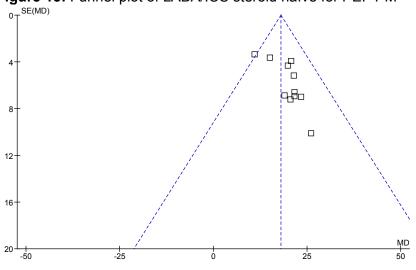
### f) Publication bias

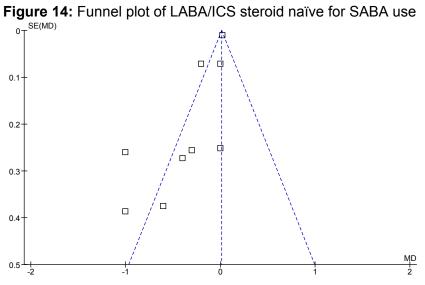
Meta-analyses for three measures (PEF AM, PEF PM, and SABA use) contained enough studies of varying size to warrant an assessment of publication bias through funnel plot analysis. There is evidence of asymmetry (small study effects) in the funnel plots for all three measures (Figures 12-14) indicating possible publication bias.











# 2.1.2 Effectiveness of LABA/ICS as maintenance therapy (versus similar dose ICS)

Thirty-seven unique RCTs<sup>29,45,47,58,72-104</sup> were identified that assessed the comparative effectiveness of LABA/ICS combination therapy versus a similar dose ICS monotherapy in adults already receiving ICS monotherapy for  $\geq 1$  mo. prior to the treatment period. Seventeen trials<sup>29,74-76,78,81,84,87,94,95,97-100,102-104</sup> compared SAL/FP versus FP, ten<sup>45,47,58,72,89,91-93,96,101</sup> compared FORM/BUD vs BUD, three<sup>73,82,83</sup> compared SAL/ICS (not described or mixed) versus ICS, three<sup>85,88,90</sup> compared FORM/ICS versus ICS (not described or mixed), one<sup>77</sup> compared SAL/FP versus BDP, one<sup>80</sup> compared SAL/FP versus BUD, one<sup>79</sup> compared SAL/TAA versus TAA, and one<sup>86</sup> compared SAL/BDP or BUD versus BDP or BUD.

Thirty-six trials<sup>29,45,47,58,72-94,96-104</sup> compared fixed dose LABA/ICS with a fixed dose ICS monotherapy and one<sup>95</sup> compared variable dose LABA/ICS to variable dose ICS monotherapy. The age of included participants was  $\geq$ 18 years in 9 (24.3%) studies.<sup>45,73,78,84-86,88-90</sup>

LABA/ICS was compared with low-dose ICS in 14 trials,<sup>45,47,58,72,74,77,79,81,86,91,98,100,102,103</sup> with medium-dose ICS in 15 trials,<sup>29,78,82-85,87-90,92,94-96,99</sup> and with high-dose ICS in eight trials.<sup>73,75,76,80,93,97,101,104</sup> In terms of asthma severity, three trials<sup>72,79,91</sup> included only participants with mild asthma, five<sup>83,85,87,93,95</sup> included only participants with moderate asthma, and one included only participants with severe asthma.<sup>73</sup> The remaining trials included participants covering a range of asthma severity: intermittent to mild (2 trials),<sup>58,74</sup> intermittent to moderate (2 trials),<sup>81,103</sup> intermittent to severe (6 trials),<sup>29,75,76,82,94,97</sup> mild to moderate (9 trials),<sup>45,47,77,78,84,86,88,90,98</sup> mild to severe (5 trials),<sup>89,99,100,102,104</sup> and moderate to severe (4 trials).<sup>80,92,96,101</sup> Treatment duration also varied across studies: 8 wk (1 trials),<sup>83</sup> 12 wk (19 trials),<sup>45,47,72-74,77,81,82,85-87,89,92-94,96-98,103} 16 wk (1 trial),<sup>102</sup> 24 wk (6 trials),<sup>76,79,80,88,90,104</sup> 28 wk (1 trial),<sup>75</sup> 30 wk (1 trial),<sup>91</sup> 40 wk (2 trials),<sup>95,99</sup> and 52 wk (6 trials).<sup>29,58,78,84,100,101</sup> The median treatment duration was 12 wk (IQR: 12, 28).</sup>

# Methodological quality

Overall, the methodological quality of included studies with similar dose maintenance ICS comparison groups (N = 37) was moderate (Table 4). Jadad scores ranged from 3 to 5 with a median score of 4 (IQR, 4 to 4.5). All included studies were randomized controlled trials; however, only 14 (37.8%) adequately described their method for randomization and used an appropriate method of randomization. Double-blinding was reported in 35 (94.6%) trials with 30 (81.1%) trials explicitly describing the methods by which investigator and participants were blinded to the intervention. Withdrawals or dropouts, if any occurred, and the accounting of all participants was reported in 37 (100%) trials. No studies were recorded as having used an inappropriate method of randomization. Allocation concealment was considered adequate in seven (18.9%) studies and unclear in 30 (81.1%). Due to the relatively high scores (Jadad score  $\geq$ 3) of almost all studies, no sensitivity analyses were conducted based on methodological quality.

Table 4: Methodological quality of LABA/ICS vs similar	ICS dose studies
Quality Components	No. Yes (%)
Randomization	37 (100)
Double-blinding	35 (94.6)
Description of withdrawals/dropouts	37 (100)
Appropriate method of randomization	14 (37.8)
Appropriate method of double-blinding	30 (81.1)
Inappropriate method of randomization	0 (0)
Inappropriate method of double-blinding	0 (0)
Adequate concealment of treatment allocation	7 (18.9)
Inadequate concealment of treatment allocation	0 (0)
Unclear concealment of treatment allocation	30 (81.1)

Participants in 32 trials were run-in on ICS monotherapy and all of these studies provided at least one clinical outcome for meta-analyses. Participants in five trials<sup>74,79,84,99,101</sup> were run-in on low-, medium- and high-dose ICS regiments or LABA/ICS combination therapy and the results were reported in aggregate form. For each outcome, the results from these mixed-treatment studies follow the results for studies that used only ICS monotherapy.

**Pulmonary function measures PEF AM:** Thirty trials<sup>29,45,47,58,72,73,75-78,80-83,85,87-98,100,102,104</sup> involving 12,565 participants (LABA/ICS = 6,992, ICS = 5,573) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on PEF AM (L/min) (Figure 15.1). The pooled result indicated a PEF difference favouring LABA/ICS (WMD = 24.45 L/min; 95% CI: 21.98 to 26.92;  $I^2 = 45\%$ ) which was considered clinically important (MCID = 18.79 L/min).

A subgroup analysis based on comparison ICS dose failed to demonstrate important differences in the treatment effect among the low (WMD = 20.98; 95% CI: 17.51 to 24.46;  $I^{2} = 41\%$ ), medium (WMD = 27.70; 95% CI: 24.15 to 31.26;  $I^2 = 14\%$ ), and high (WMD = 24.78; 95% CI: 21.05 to 28.52;  $I^{2} = 11\%$ ) dose studies.

		BA/ICS			ICS			Mean Difference	Mean Difference
udy or Subgroup	Mean [L/min]	SD [L/min]	Total	Mean [L/min]	SD [L/min]	Total	Weight	IV, Random, 95% CI [L/min]	IV, Random, 95% CI [L/min
19.1 Low dose ICS									
ateman 2001	44.52	39.1	330	24	39.1	162	4.9%	20.52 [13.17, 27.87]	-
uhl 2003	25.11	70	352	-0.951	70	171	2.6%	26.06 [13.27, 38.85]	
Corren 2007	54	51	123	24	39	119	3.0%	30.00 [18.58, 41.42]	
owler 2002	434	24.5	19	402	25.1	20	2.0%	32.00 [16.43, 47.57]	
avuru 2000	52.5	49.44	87	17.3	40.57	85	2.4%	35.20 [21.70, 48.70]	
una 2006	23.75	37.89	409	5.5	38.17	207	5.5%	18.25 [11.88, 24.62]	-
Byrne 2001b	18.5	25.72	315	1.73	25.72	312	7.0%	16.77 [12.74, 20.80]	+
rice 2002	36.8	42.45	313	17.8	42.45	313	5.3%	19.00 [12.35, 25.65]	-
AS40036 2005	4.4	44.59	169	-16.8	42.87	158	3.8%	21.20 [11.72, 30.68]	
FA103153 2007	15.6	53.8	239	1.4	52.54	236	3.8%	14.20 [4.64, 23.76]	
ubtotal (95% CI)			2356			1783	40.3%	20.98 [17.51, 24.46]	•
leterogeneity: Tau <sup>2</sup> = 11.56 est for overall effect: Z = 1			B); I <sup>2</sup> =	41%					
.19.2 Medium dose ICS									
ateman 2004	51.44		1161	25.8	95.01		4.6%	25.64 [17.75, 33.53]	
itzgerald 1999	31	107	89	16.6	107	170	0.7%	14.40 [-13.04, 41.84]	
emp 1998	47	60	252	14	60	254	3.4%	33.00 [22.54, 43.46]	
oenig 2008	31.3	113.66	156	21.17	110.97	310	1.1%	10.13 [-11.57, 31.83]	+
oopmans 2006	50	33.07	27	21	33.07	27	1.6%	29.00 [11.36, 46.64]	
angton Hewer 1995	26	49	11	-35	63	10	0.3%	61.00 [12.39, 109.61]	
lolimard 2001	25.7	36.5	130	4.5	32.7	129	4.3%	21.20 [12.76, 29.64]	
lorice 2007	29.98	41.95	463	0	41.95	217	5.2%	29.98 [23.22, 36.74]	-
lathan 2006	49.6	54.3	94	13.9	39.1	91	2.4%	35.70 [22.10, 49.30]	
loonan 2006	31.6	42.5	234	9	42.5	109	3.7%	22.60 [12.94, 32.26]	
hapiro 2000	53.5	50.4	81	15.2	41.4	81	2.2%	38.30 [24.10, 52.50]	
an der Molen 1997	25.9	39.4	125	-2.1	39.4	114	3.6%	28.00 [18.00, 38.00]	
Letterstrom 2001	33.91	106.6	238	0.2	107	124	1.0%	33.71 [10.51, 56.91]	
ubtotal (95% CI)			3061			2793	34.2%	27.70 [24.15, 31.26]	•
eterogeneity: Tau <sup>2</sup> = 5.92; est for overall effect: Z = 1			0); I² =	14%					
.19.3 High dose ICS									
ubier 1999	33.99	40.26	338	15	39.82	165	4.8%	18.99 [11.55, 26.43]	-
oyd 1995	45.2	98	53	22.8	121	62	0.4%	22.40 [-17.64, 62.44]	
nd 2003	42	52.3	171	16.9	52.3	165	3.1%	25.10 [13.91, 36.29]	
enkins 2000	406	48.27	173	380	48.94	165	3.4%	26.00 [15.63, 36.37]	
enkins 2006	37	36.35	341	4.5	36.35	115	4.7%	32.50 [24.82, 40.18]	-
LGQ97/SLGB4010 2005	42.1	42.6	167	16.9	34.7	154	4.3%	25.20 [16.73, 33.67]	
an Noord 2001 Subtotal (95% CI)	49.04	41.8	332 1575	27	41.8	171 997	4.7% 25.5%	22.04 [14.33, 29.75] 24.78 [21.05, 28.52]	•
leterogeneity: Tau <sup>2</sup> = 2.91; est for overall effect: Z = 1			l² = 11	%					
otal (95% CI)			6992			5573	100.0%	24.45 [21.98, 26.92]	
	0.052 - 50.74	f = 00 (D = 0)		- 450/		5575	.00.0/0	24.40 [21.00, 20.02]	
leterogeneity: Tau <sup>2</sup> = 18.43 est for overall effect: Z = 1			JUD), I <sup>-</sup>	- 4070					-100 -50 0 50 Favours ICS Favours LAE

# Figure 15.1: The effect of LABA/ICS versus ICS monotherapy on PEF AM (L/min)

Four trials<sup>74,84,99,123</sup> involving 1,363 participants (LABA/ICS = 768, ICS = 595) run-in on either LABA/ICS combination or ICS monotherapy provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on PEF AM (L/min) (Figure 15.2). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 24.88 L/min; 95% CI: 13.09 to 36.66;  $I^2 = 67\%$ ) which considered clinically important (MCID = 18.79 L/min).

A subgroup analysis based on comparison ICS dose indicated a statistically significant and clinically important difference for the low (WMD = 30.60; 95% CI: 15.91 to 45.29) and high (WMD = 34.70; 95% CI: 27.54 to 41.86) dose comparisons. The pooled result for the medium dose comparison identified a statistically significant difference between the treatments (WMD = 14.66; 95% CI: 3.24 to 26.08;  $I^{2}$  = 0%).

LABA/ICS US	se al bas	eime)									
	LAI	BA/ICS		I	ICS			Mean Difference		Mean Diff	erence
Study or Subgroup	Mean [L/min]	SD [L/min]	Total	Mean [L/min]	SD [L/min]	Total	Weight	IV, Random, 95% CI [L/min]	Year	IV, Random, 9	5% CI [L/min]
1.1.1 Low dose ICS											
Pearlman 2004 Subtotal (95% CI)	57.8	49.88	92 92	27.2	50.94	89 <b>89</b>	24.7% 24.7%	30.60 [15.91, 45.29] 30.60 [15.91, 45.29]	2004		
Heterogeneity: Not app Test for overall effect:		0001)									
1.1.2 Medium dose IC	s										
Lundback 2006	38	44	95	21.1	44	92	27.4%	16.90 [4.29, 29.51]	2006		<b>—</b>
SAM40065 2007 Subtotal (95% CI)	41.9	133.7	140 235	37.38	129.88	282 374	13.0% <b>40.5%</b>	4.52 [-22.32, 31.36] 14.66 [3.24, 26.08]	2007		•
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:			0.41); l <sup>:</sup>	<sup>2</sup> = 0%							
1.1.3 High dose ICS											
Peters 2008 Subtotal (95% CI)	40.31	41.09	441 441	5.61	35.47	132 1 <b>32</b>	34.9% <b>34.9%</b>	34.70 [27.54, 41.86] 34.70 [27.54, 41.86]	2008		•
Heterogeneity: Not app Test for overall effect:		00001)									
Total (95% CI)			768			595	100.0%	24.88 [13.09, 36.66]			•
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:			• 0.03);	l² = 67%					-	-50 -25 0 Favours ICS	25 50 Favours LABA/IO

# **Figure 15.2:** The effect of LABA/ICS versus ICS monotherapy on PEF AM (L/min) (mixed LABA/ICS use at baseline)

**PEF PM:** Twenty-five trials<sup>45,47,72,73,75-78,80-83,85,87-89,91-98,104</sup> involving 8,279 participants (LABA/ICS = 4,757, ICS = 3,522) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on PEF PM (L/min) (Figure 16). The pooled result indicated a statistically significant and clinically important difference favouring LABA/ICS (WMD = 21.31 L/min; 95% CI: 18.77 to 23.86; I<sup>2</sup> = 39%) (MCID = 18.79 L/min).

A subgroup analysis based on comparison ICS dose failed to identify important differences in the treatment effect for the low (WMD = 18.31; 95% CI: 15.39 to 21.24;  $I^2 = 0\%$ ), medium (WMD = 25.82; 95% CI: 21.11 to 30.52;  $I^2 = 38\%$ ), and high (WMD = 19.36; 95% CI: 15.06 to 23.66;  $I^2 = 29\%$ ) dose studies.

One trial<sup>74</sup> involving 181 participants (LABA/ICS = 92, ICS = 89) run-in on either LABA/ICS combination or ICS monotherapy provided data on the effects of LABA/ICS combination therapy compared with ICS monotherapy on PEF PM (L/min). The result indicated a statistically significant difference favouring LABA/ICS (WMD = 27.60 L/min; 95% CI: 14.40 to 40.80) which was considered clinically important (MCID = 18.79 L/min).

		BA/ICS			ICS			Mean Difference	Mean Difference
tudy or Subgroup	Mean [L/min]	SD [L/min]	Total	Mean [L/min]	SD [L/min]	Total	Weight	IV, Random, 95% CI [L/min]	IV, Random, 95% CI [L/min]
.20.1 Low dose ICS									
ateman 2001	36.48	36.8	330	18	36.8	162	6.2%	18.48 [11.56, 25.40]	-
Buhl 2003	15.3	33.25	352	-4.8	33.25	171	7.0%	20.10 [14.03, 26.17]	-
Corren 2007	40	46	123	17	38	119	3.8%	23.00 [12.38, 33.62]	-
owler 2002	436	24.5	19	408	22.8	20	2.3%	28.00 [13.13, 42.87]	
avuru 2000	35	43.84	87	18	42.41	85	2.9%	17.00 [4.11, 29.89]	
(una 2006	14	37.78	409	-1.7	38.17	207	6.7%	15.70 [9.34, 22.06]	-
Price 2002	25.95	40.5	313	10.25	40.5	313	6.7%	15.70 [9.35, 22.05]	-
Subtotal (95% CI)			1633			1077	35.8%	18.31 [15.39, 21.24]	•
leterogeneity: Tau <sup>2</sup> = 0.00;	Chi <sup>2</sup> = 4.05, df =	6 (P = 0.67);	$I^2 = 0\%$	, 0					
est for overall effect: Z = 1									
.20.2 Medium dose ICS									
Cemp 1998	29	60	252	11	60	254	3.9%	18.00 [7.54, 28.46]	
Coenig 2008	26.8	108.66	156	19.38	107.57	310	1.3%	7.42 [-13.42, 28.26]	+
Coopmans 2006	55	33.07	27	19	33.07	27	1.8%	36.00 [18.36, 53.64]	
angton Hewer 1995	48	52	11	-42	64	10	0.3%	90.00 [39.82, 140.18]	
Iolimard 2001	24.1	35.3	130	0.5	31.5	129	5.3%	23.60 [15.45, 31.75]	-
Norice 2007	24.7	41.95	462	-0.6	41.95	217	6.4%	25.30 [18.53, 32.07]	
lathan 2006	36.1	48.5	94	9	33.4	91	3.3%	27.10 [15.13, 39.07]	
loonan 2006	30.2	42.5	233	7	42.5	109	4.3%	23.20 [13.53, 32.87]	-
shapiro 2000	45.4	46.8	81	7.9	40.5	81	2.7%	37.50 [24.02, 50.98]	
an der Molen 1997	21.2	39.4	125	-5.9	39.4	114	4.2%	27.10 [17.10, 37.10]	
Letterstrom 2001	23.59	108.6	238	-3.7	108	124	1.1%	27.29 [3.80, 50.78]	
Subtotal (95% CI)			1809			1466	34.5%	25.82 [21.11, 30.52]	•
leterogeneity: Tau <sup>2</sup> = 21.84 est for overall effect: Z = 1		•	09); I² =	= 38%					
.20.3 High dose ICS									
ubier 1999	25.96	39.7	338	9		165	5.9%	16.96 [9.56, 24.36]	-
loyd 1995	23.1	98	53	14.7	115	62	0.4%	8.40 [-30.53, 47.33]	_ <del></del>
nd 2003	31.1	52.3	171	15.4	52.3	165	3.6%	15.70 [4.51, 26.89]	-
enkins 2000	416	41.3	173	398	41.75	165	4.8%	18.00 [9.14, 26.86]	-
enkins 2006	30.9	34.05	115	-0.1	34.05	115	4.9%	31.00 [22.20, 39.80]	
LGQ97/SLGB4010 2005	31.1	50.7	133	15.4	36.1	136	3.9%	15.70 [5.16, 26.24]	-
an Noord 2001	39.56	37.15	332	21	37.15	171	6.3%	18.56 [11.71, 25.41]	17
ubtotal (95% CI)			1315			979	29.7%	19.36 [15.06, 23.66]	•
leterogeneity: Tau <sup>2</sup> = 9.41; rest for overall effect: Z = 8			l² = 29	%					
otal (95% CI)			4757			3522	100.0%	21.31 [18.77, 23.86]	•
leterogeneity: Tau <sup>2</sup> = 14.57	$Chi^2 = 30.00 dt$	f = 24 (P = 0)	03)· I2 =	- 30%				-	
1eterogeneity. Tau <sup>2</sup> – 14.57	, on - 55.65, u	i = 24 (i = 0.)	uu, i -	- 3370					-100 -50 0 50 100

### Figure 16: The effect of LABA/ICS versus ICS monotherapy on PEF PM (L/min)

*FEV*<sub>1</sub> *absolute (L):* Twenty-four trials<sup>29,45,47,65,73,75,77,80-83,85,87,88,90,92-98,100,104</sup> involving 9,718 participants (LABA/ICS = 5,293, ICS = 4,425) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on absolute FEV<sub>1</sub> (L) (Figure 17.1). The pooled result indicated a statistically significant difference between the two treatments (WMD = 0.14 L; 95% CI: 0.12 to 0.17; I<sup>2</sup> = 39%); however, the precision of the confidence intervals did not suggest that the difference would meet the a priori criteria for clinical importance (MCID = 0.23 L).

A subgroup analysis based on comparison ICS dose failed to identify important differences in the treatment effect among the low (WMD = 0.14; 95% CI: 0.09 to 0.18;  $I^2=36\%$ ), medium (WMD = 0.18; 95% CI: 0.13 to 0.22;  $I^2=46\%$ ), and high (WMD = 0.10; 95% CI: 0.05 to 0.14;  $I^2=0\%$ ) dose comparisons. The majority of the heterogeneity in the overall result may be explained by the greater treatment difference indicated by the medium dose studies (test for subgroup differences  $I^2 = 66.3\%$ ).

		ABA/ICS			ICS			Mean Difference	Mean Difference
tudy or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
.22.1 Low dose ICS									
Bateman 2001	0.355	0.53	330	0.32	0.53	162	4.8%	0.03 [-0.06, 0.13]	- <b>-</b>
Corren 2007	0.37	0.37	123	0.23	0.4	119	5.0%	0.14 [0.04, 0.24]	
Fowler 2002	2.46	0.16	19	2.26	0.16	20	4.8%	0.20 [0.10, 0.30]	<del></del>
Kavuru 2000	0.51	0.47	87	0.28	0.46	85	3.0%	0.23 [0.09, 0.37]	— <del>.</del>
Kuna 2006	0.1	0.78	409	-0.01	0.78	207	3.3%	0.11 [-0.02, 0.24]	<u>⊢</u>
SAS40036 2005	0.03	0.393	170	-0.15	0.378	158	5.9%	0.18 [0.10, 0.26]	
SFA103153 2007 Subtotal (95% CI)	0.045	0.356	239 1377	-0.061	0.323	236 <b>987</b>	7.8% <b>34.6%</b>	0.11 [0.04, 0.17] <b>0.14 [0.09, 0.18]</b>	<b>→</b>
Heterogeneity: Tau <sup>2</sup> = 0.00;	$Chi^2 = 9$	40 df =	6 (P =	0 15) <sup>.</sup> l <sup>2</sup>	= 36%				
Test for overall effect: $Z = 5$			•	0.10), 1	0070				
1.22.2 Medium dose ICS									
Bateman 2004	0.345	0.476	1133	0.21	0.474	1119	9.9%	0.13 [0.10, 0.17]	
Fitzgerald 1999	0.13	0.8	89	0.02	0.81	182	1.6%	0.11 [-0.09, 0.31]	- <b></b>
Kemp 1998	0.42	0.78	252	0.15	0.78	254	3.2%	0.27 [0.13, 0.41]	
Koenig 2008	0.14	0.62	156	0.085	0.62	310	3.8%	0.06 [-0.06, 0.17]	-+
Langton Hewer 1995	0.22	0.32	11	-0.2	0.16	10	1.5%	0.42 [0.21, 0.63]	
Volimard 2001	0.17	0.46	130	0.06	0.45	129	4.2%	0.11 [-0.00, 0.22]	
Morice 2007	0.32	0.8	462	0.1	0.8	217	3.4%	0.22 [0.09, 0.35]	
Nathan 2006	0.41	0.38	94	0.19	0.38	91	4.3%	0.22 [0.11, 0.33]	
Noonan 2006	0.36	0.35	228	0.15	0.35	108	6.1%	0.21 [0.13, 0.29]	
Shapiro 2000	0.48	0.45	81	0.25	0.45	81	3.1%	0.23 [0.09, 0.37]	
van der Molen 1997 Subtotal (95% CI)	0.13	0.81	125 <b>2761</b>	0.04	0.82	114 <b>2615</b>	1.6% <b>42.7%</b>	0.09 [-0.12, 0.30] 0.18 [0.13, 0.22]	•
Heterogeneity: Tau <sup>2</sup> = 0.00;	Chi <sup>2</sup> = 1	8.66. df	= 10 (F	P = 0.04)	: l² = 46	%			
Test for overall effect: Z = 7			,	,	, -				
1.22.3 High dose ICS									
Aubier 1999	0.2	0.5	338	0.16	0.39	165	6.1%	0.04 [-0.04, 0.12]	+ <b>-</b> -
Boyd 1995	0.19	0.78	53	0.15	0.68	62	1.0%	0.04 [-0.23, 0.31]	<del></del>
lenkins 2000	2.53	0.74	173	2.44	0.74	165	2.5%	0.09 [-0.07, 0.25]	+
Jenkins 2006	0.3	0.38	115	0.14	0.38	115	4.9%	0.16 [0.06, 0.26]	<del></del>
SLGQ97/SLGB4010 2005	2.4	0.9	144	2.3	0.9	145	1.6%	0.10 [-0.11, 0.31]	- <del> </del>
van Noord 2001 Subtotal (95% CI)	0.246	0.4	332 1155	0.13	0.4	171 823	6.6% <b>22.8%</b>	0.12 [0.04, 0.19] <b>0.10 [0.05, 0.14]</b>	<b>→</b>
Heterogeneity: Tau <sup>2</sup> = 0.00;	Chi <sup>2</sup> = 3	.97, df =	5 (P =	0.55); l²	= 0%				
Test for overall effect: Z = 4	.35 (P <	0.0001)							
			5293			4425	100.0%	0.14 [0.12, 0.17]	•
Total (95% CI)									
Heterogeneity: Tau <sup>2</sup> = 0.00; Test for overall effect: Z = 1			· ·	<b>P</b> = 0.03)	; I² = 39	%		-	-0.5 -0.25 0 0.25 0.5

# Figure 17.1: The effect of LABA/ICS versus ICS monotherapy on FEV1 (absolute) (L)

Four trials<sup>74,84,99,123</sup> involving 1,349 participants (LABA/ICS = 764, ICS = 585) run-in on either LABA/ICS combination or ICS monotherapy provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on FEV<sub>1</sub> absolute (L) (Figure 17.2). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 0.10 L; 95% CI: 0.06 to 0.14; I<sup>2</sup> = 10%); however, the precision of the confidence intervals did not indicate that the difference would meet the a priori criteria for clinical importance (MCID = 0.23 L).

A subgroup analysis based on comparison ICS dose indicated little change in the magnitude and precision of the difference among the medium (WMD = 0.08; 95% CI: 0.00 to 0.15) and high (WMD = 0.10; 95% CI: 0.06 to 0.14) dose comparisons. The result for the low dose comparison (0.22 L; 95% CI: 0.08 to 0.36) indicated that the difference between treatments may also meet the a priori criteria for clinical importance (MCID = 0.23 L).

**Figure 17.2:** The effect of LABA/ICS versus ICS monotherapy on FEV<sub>1</sub> (absolute) (L) (mixed LABA/ICS use at baseline)

		BA/IC			ICS			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.4.1 Low dose ICS										
Pearlman 2004	0.58	0.48	92	0.36	0.47	89	8.3%	0.22 [0.08, 0.36]	2004	
Subtotal (95% CI)			92			89	8.3%	0.22 [0.08, 0.36]		
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 3.12	2 (P = 0	.002)							
1.4.2 Medium dose l	cs									
Lundback 2006	0.09	0.3	95	0.02	0.3	92	19.9%	0.07 [-0.02, 0.16]	2006	+
SAM40065 2007	0.14	0.71	141	0.046	0.7	272	7.7%	0.09 [-0.05, 0.24]	2007	
Subtotal (95% CI)			236			364	27.6%	0.08 [0.00, 0.15]		$\bullet$
Heterogeneity: Tau <sup>2</sup> =	0.00; Cł	ni² = 0.(	08, df =	: 1 (P =	0.78);	l² = 0%				
Test for overall effect:	Z = 2.03	6 (P = 0	.04)							
1.4.3 High dose ICS										
Peters 2008	0.18	0.24	436	0.08	0.2	132	64.1%	0.10 [0.06, 0.14]	2008	- <mark>-</mark>
Subtotal (95% CI)			436			132	64.1%	0.10 [0.06, 0.14]		•
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 4.79	) (P < 0	.00001	)						
Total (95% CI)			764			585	100.0%	0.10 [0.06, 0.14]		•
Heterogeneity: Tau <sup>2</sup> =	0.00: Cł	ni² = 3.3	34. df =	: 3 (P =	0.34):	$l^2 = 109$	%		_	
0 ,	,		'	`	//					-0.2 -0.1 0 0.1 0.2
Test for overall effect:										Favours ICS Favours LABA/IC

*FEV*<sub>1</sub> % *predicted:* Seven trials<sup>58,75,77,78,80,97,98</sup> involving 2,556 participants (LABA/ICS = 1,534, ICS = 1,022) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on FEV<sub>1</sub> % predicted (Figure 18). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 3.36; 95% CI: 2.02to 4.07; I<sup>2</sup> = 43%); however, the precision of the confidence interval suggests that no differences would meet the a priori criteria for clinical importance (MCID = 12%).

A subgroup analysis based on comparison ICS dose failed to identify important difference in the treatment effect for low (WMD = 3.86; 95% CI: 1.81 to 6.54; I<sup>2</sup> = 74%), medium (WMD = 2.70; 95% CI: -0.23 to 5.63), and high (WMD = 3.05; 95% CI: 1.01 to 5.10; I<sup>2</sup> = 15%) dose comparisons.

# Figure 18: The effect of LABA/ICS versus ICS monotherapy on $FEV_1 \%$ predicted

productod									
	LAE	BA/ICS			CS			Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]	IV, Random, 95% CI [%]
1.21.1 Low dose ICS									
Bateman 2001	10.83	16.34	330	9.4	16.34	162	12.5%	1.43 [-1.64, 4.50]	- <b>+</b> =
Fowler 2002	77	4.45	19	70	4.56	20	13.9%	7.00 [4.17, 9.83]	
O'Byrne 2001b	4.13	8.18	315	0.9	8.18	312	27.2%	3.23 [1.95, 4.51]	-
Subtotal (95% CI)			664			494	53.5%	3.86 [1.18, 6.54]	
Heterogeneity: Tau <sup>2</sup> =	4.11; Chi² =	7.79, df =	2 (P =	0.02); l <sup>2</sup> = 7	'4%				
Test for overall effect: 2	Z = 2.82 (P =	= 0.005)							
1.21.2 Medium dose I	cs								
Koopmans 2006	5	5.5	27	2.3	5.5	27	13.2%	2.70 [-0.23, 5.63]	
Subtotal (95% CI)			27			27	13.2%	2.70 [-0.23, 5.63]	◆
Heterogeneity: Not app	olicable								
Test for overall effect: 2	Z = 1.80 (P =	= 0.07)							
1.21.3 High dose ICS									
Aubier 1999	9.47	39.7	338	10	39.82	165	3.0%	-0.53 [-7.93, 6.87]	
Jenkins 2000	79	14.07	173	77	14.07	165	12.9%	2.00 [-1.00, 5.00]	+
van Noord 2001	7.94	12.55	332	3.7	12.55	171	17.4%	4.24 [1.92, 6.56]	
Subtotal (95% CI)			843			501	33.2%	3.05 [1.01, 5.10]	•
Heterogeneity: Tau <sup>2</sup> =	0.57; Chi² =	2.36, df =	2 (P =	0.31); l <sup>2</sup> = 1	5%				
Test for overall effect: 2	Z = 2.93 (P =	= 0.003)							
Total (95% CI)			1534			1022	100.0%	3.36 [2.02, 4.70]	•
Heterogeneity: Tau <sup>2</sup> =	1.29; Chi <sup>2</sup> =	10.51, df	= 6 (P	= 0.10); l <sup>2</sup> =	43%			-	
Test for overall effect: 2	Z = 4.92 (P <	< 0.00001	)						-10 -5 0 5 10 Favours ICS Favours LABA/IC
Test for subgroup diffe	rences: Chi <sup>2</sup>	= 0.37, d	f = 2 (F	P = 0.83), I <sup>2</sup>	= 0%				Favouis ICS Favouis LABA/IC

### Asthma control measures

*Total number of exacerbations:* Four trials<sup>29,88,90,100</sup> involving 3,303 participants (LABA/ICS = 1,614, ICS = 1,689) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on total number of exacerbations (Figure 19). Both trials used medium dose ICS as the comparator. The pooled result indicated a statistically significant difference favouring LABA/ICS (Rate ratio = 0.89; 95% CI: 0.80 to 0.99; I<sup>2</sup> = 35%).

### Figure 19: The effect of LABA/ICS versus ICS monotherapy on total no. exacerbations

			LABA/ICS	ICS		Rate Ratio	Rate Ratio
Study or Subgroup	log[Rate Ratio]	SE	Total	Total	Weight	IV, Random, 95% (	CI IV, Random, 95% CI
1.22.1 Low dose							
SFA103153 2007	-0.164	0.0917	239	236	23.1%	0.85 [0.71, 1.02	
Subtotal (95% CI)			239	236	23.1%	0.85 [0.71, 1.02]	i 🔶
Heterogeneity: Not app	olicable						
Test for overall effect: 2	Z = 1.79 (P = 0.07)						
1.22.2 Medium dose							
Bateman 2004	-0.184	0.0415	1161	1157	49.0%	0.83 [0.77, 0.90	ŋ <b>-∎</b> -
Fitzgerald 1999	0.0222	0.129	89	182	14.0%	1.02 [0.79, 1.32	j — <b>–</b> –
van der Molen 1997	0.039	0.129	125	114	14.0%	1.04 [0.81, 1.34	]
Subtotal (95% CI)			1375	1453	76.9%	0.92 [0.78, 1.09]	
Heterogeneity: Tau <sup>2</sup> = 0	0.01; Chi² = 4.59, d	df = 2 (P =	= 0.10); l <sup>2</sup> =	56%			
Test for overall effect: 2	Z = 0.92 (P = 0.36)	1					
Total (95% CI)			1614	1689	100.0%	0.89 [0.80, 0.99]	
Heterogeneity: Tau <sup>2</sup> = (	0.00; Chi² = 4.62, d	df = 3 (P =	= 0.20); l <sup>2</sup> =	35%			
Test for overall effect: 2	Z = 2.21 (P = 0.03)						0.5 0.7 1 1.5 Favours LABA/ICS Favours ICS
Test for subgroup differ	rences: Chi <sup>2</sup> = 0.03	3, df = 1 (	$P = 0.87$ ), $I^2$	= 0%			FAVOUIS LADAVICS FAVOUIS ICS

One trial<sup>101</sup> involving 576 participants (LABA/ICS = 443, ICS = 133) run-in on either LABA/ICS combination or ICS monotherapy provided data for a meta-analysis of the effects of

LABA/ICS combination therapy compared with ICS monotherapy for 52 weeks on total number of exacerbations. The result indicated a statistically significant difference favouring LABA/ICS (WMD = -0.14; 95% CI: -0.23 to -0.05).

*Number of patients with*  $\geq 1$  *exacerbation:* Thirteen trials<sup>72,76,80,81,83,88,90-95,104</sup> involving 4,402 participants (LABA/ICS = 2,180, ICS = 1,862) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on number of patients with  $\geq 1$  exacerbation (Figure 20.1). The pooled result indicated a statistically significant difference favouring LABA/ICS (RR = 0.80; 95% CI: 0.0.70 to 0.90; I<sup>2</sup> = 23%).

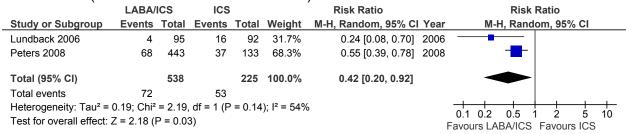
	LABA/		ICS			Risk Ratio	Risk Ratio
Study or Subgroup	Events	rotal	Events	rotal	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.21.1 Low dose							
Buhl 2003	180	352	97	171	23.2%	0.90 [0.76, 1.06]	-
Kavuru 2000	3	87	9	85	0.9%	0.33 [0.09, 1.16]	
Price 2002	69	164	101	177	17.6%	0.74 [0.59, 0.92]	
Subtotal (95% CI)		603		433	41.8%	0.80 [0.63, 1.01]	•
Total events	252		207				
Heterogeneity: Tau <sup>2</sup> = 0.02;			2 (P = 0.1	2); l² =	53%		
Test for overall effect: Z = 1	.85 (P = 0.	06)					
1.21.2 Medium dose							
Fitzgerald 1999	15	89	30	182	4.3%	1.02 [0.58, 1.80]	<b>_</b>
Koenig 2008	23	156	70	310	6.9%	0.65 [0.42, 1.00]	
Langton Hewer 1995	6	11	4	10	1.7%	1.36 [0.54, 3.46]	
Nathan 2006	7	94	11	91	1.8%	0.62 [0.25, 1.52]	
Noonan 2006	3	239	3	109	0.6%	0.46 [0.09, 2.22]	
van der Molen 1997	33	125	32	114	7.3%	0.94 [0.62, 1.42]	
Subtotal (95% CI)		714		816	22.5%	0.83 [0.65, 1.06]	•
Total events	87		150				
Heterogeneity: Tau <sup>2</sup> = 0.00;	Chi <sup>2</sup> = 4.1	8, df =	5 (P = 0.5	52); l² =	0%		
Test for overall effect: Z = 1	.49 (P = 0.	14)					
1.21.3 High dose							
Ind 2003	5	171	12	165	1.4%	0.40 [0.14, 1.12]	<del>_</del>
Jenkins 2000	54	180	52	173	11.0%	1.00 [0.73, 1.37]	_ <b>+</b> _
Jenkins 2006	158	341	74	115	21.9%	0.72 [0.60, 0.86]	
SLGQ97/SLGB4010 2005	5	171	12	160	1.4%	0.39 [0.14, 1.08]	+
Subtotal (95% CI)		863		613	35.7%	0.73 [0.53, 1.01]	$\bullet$
Total events	222		150				
Heterogeneity: Tau <sup>2</sup> = 0.05;	Chi <sup>2</sup> = 6.3	0, df = 3	3 (P = 0.1	0);   <sup>2</sup> =	52%		
Test for overall effect: Z = 1		'	,				
Total (95% CI)		2180		1862	100.0%	0.80 [0.70, 0.90]	•
Total events	561		507				
Heterogeneity: Tau <sup>2</sup> = 0.01;		58. df =		0.21): l <sup>a</sup>	² = 23%	_	
		,		· _ · /, ·			0.1 0.2 0.5 1 2 5

Figure 20.1: The effect of LABA/ICS versus ICS monotherapy on no. participants  $\geq$ 1 exacerbation

A subgroup analysis based on comparison ICS dose failed to indicate a statistically significant difference between treatments for low (RR = 0.80; 95% CI: 0.63, 1.01;  $I^2 = 53\%$ ), medium (RR= 0.83; 95% CI: 0.65 to 1.06;  $I^2 = 0\%$ ), and high (RR = 0.73; 95% CI: 0.53 to 1.01;  $I^2 = 52\%$ ) dose comparisons.

Two trials<sup>84,101</sup> involving 763 participants (LABA/ICS = 538, ICS = 225) run-in on either LABA/ICS combination or ICS monotherapy provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on number of patients with  $\geq$ 1 exacerbation (Figure 20.2). The result indicated a statistically significant difference favouring LABA/ICS (RR = 0.42; 95% CI: 0.20 to 0.92; I<sup>2</sup> = 54%).

**Figure 20.2:** The effect of LABA/ICS versus ICS monotherapy on no. patients with  $\geq$  1 exacerbation (mixed LABA/ICS use at baseline)



*Number of participants with*  $\geq 1$  *mild exacerbation:* Five trials<sup>72,76,80,91,93</sup> involving 2,009 participants (LABA/ICS = 1,208, ICS = 801) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on the number of mild exacerbations (Figure 21). The pooled result indicated a statistically significant difference favouring LABA/ICS (RR = 0.81; 95% CI: 0.74 to 0.90; I<sup>2</sup> = 0%).

A subgroup analysis based on comparison ICS dose indicated no change in the significance of the treatment effect for the high (RR = 0.75; 95% CI: 0.64 to 0.87;  $I^2 = 0$ ) dose studies. The pooled results failed to indicate a statistically significant difference between the two treatments (RR = 0.88; 95% CI: 0.76 to 1.01;  $I^2 = 0$ %).

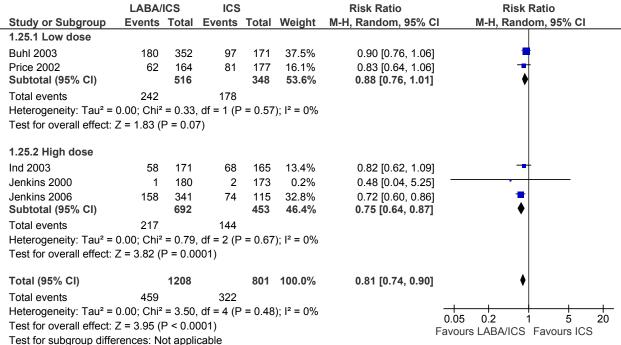
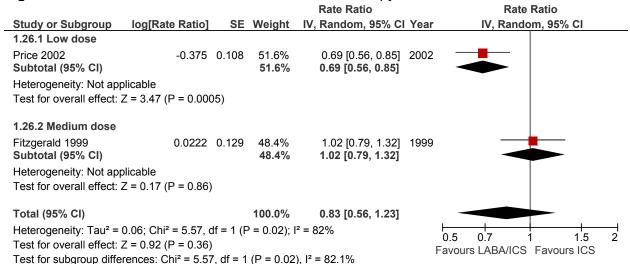


Figure 21: The effect of LABA/ICS versus ICS monotherapy on no. participants with  $\geq 1$  mild exacerbations

*Number of mild exacerbations:* Two trials<sup>90,91</sup> involving 612 participants (LABA/ICS = 253, ICS = 359) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on the number of mild exacerbations (Figure 22). The pooled result failed to indicate a statistically significant difference between treatments (Rate ratio = 0.83; 95% CI: 0.56 to 1.23;  $I^2 = 82\%$ ).

Figure 22: The effect of LABA/ICS versus ICS monothera	w on no mild ovacorbations
Figure 22. The effect of LADA/ICS versus ICS monothera	



*Number of participants with*  $\geq 1$  *severe exacerbation:* Six trials<sup>72,76,80,86,88,91</sup> involving 1,820 participants (LABA/ICS = 1,005, ICS = 815) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on the number of participants

with  $\geq 1$  severe exacerbation (Figure 23). The pooled result failed to indicate a statistically significant difference between the two treatments (RR = 0.96; 95% CI: 0.76 to 1.21; I<sup>2</sup> = 0%).

exacerbation							
	LABA/	ICS	ICS			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
1.23.1 Low dose							
Buhl 2003	30	352	19	171	17.5%	0.77 [0.44, 1.32]	
Li 1999	2	13	1	15	1.0%	2.31 [0.24, 22.62]	
Price 2002	11	164	19	177	10.3%	0.62 [0.31, 1.27]	
Subtotal (95% CI)		529		363	28.8%	0.74 [0.48, 1.13]	◆
Total events	43		39				
Heterogeneity: Tau <sup>2</sup> =				= 0.55	); I² = 0%		
Test for overall effect:	Z = 1.38 (F	P = 0.1	7)				
1.23.2 Medium dose							
van der Molen 1997	33	125	32	114	30.2%	0.94 [0.62, 1.42]	
Subtotal (95% CI)		125		114	30.2%	0.94 [0.62, 1.42]	<b>•</b>
Total events	33		32				
Heterogeneity: Not app	olicable						
Test for overall effect: 2	Z = 0.29 (F	P = 0.7	7)				
1.23.3 High dose							
Ind 2003	21	171	20	165	15.8%	1.01 [0.57, 1.80]	_ <b>+</b> _
Jenkins 2000	36	180	27	173	25.3%	1.28 [0.81, 2.02]	
Subtotal (95% CI)		351		338	41.1%	1.17 [0.82, 1.67]	•
Total events	57		47				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 0.40,	df = 1 (P	= 0.53	); l² = 0%		
Test for overall effect: 2	Z = 0.87 (F	⊃ = 0.38	3)				
Total (95% CI)		1005		815	100.0%	0.96 [0.76, 1.21]	•
Total events	133		118				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 4.22,	df = 5 (P	= 0.52	); l <sup>2</sup> = 0%		Image: 1         Image: 1
Test for overall effect:	Z = 0.34 (F	<sup>-</sup> = 0.73	3)				0.05 0.2 1 5 20 Favours LABA/ICS Favours ICS
Test for subgroup diffe	rences: N	ot appli	cable			I	

**Figure 23:** The effect of LABA/ICS versus ICS monotherapy on no. participants with  $\geq 1$  severe exacerbation

A subgroup analysis based on dose of comparison ICS failed to indicated statistically significant differences between the two treatments for low (RR = 0.74; 95% CI: 0.48 to 1.13;  $I^2 = 0\%$ ), medium (RR = 0.94; 95% CI: 0.62 to 1.42), and high (RR = 1.17; 95% CI: 0.82 to 1.67;  $I^2 = 0\%$ ) dose studies.

### Number severe exacerbations:

Two trials<sup>90,91</sup> } involving 612 participants (LABA/ICS = 253, ICS = 359) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on the number of severe exacerbations (Figure 24). The pooled result failed to indicate a statistically significant difference between treatments (Rate ratio = 0.82; 95% CI: 0.54 to 1.25; I<sup>2</sup> = 84%).

				Rate Ratio		Rate Ratio
Study or Subgroup	log[Rate Ratio]	SE	Weight	IV, Random, 95% CI	Year	IV, Random, 95% Cl
1.24.1 Low dose						
Price 2002	-0.405	0.108	51.4%	0.67 [0.54, 0.82]	2002	2
Subtotal (95% CI)			51.4%	0.67 [0.54, 0.82]		
Heterogeneity: Not app	plicable					
Test for overall effect:	Z = 3.75 (P = 0.000	)2)				
1.24.2 Medium dose						
Fitzgerald 1999	0.0222	0.129	48.6%	1.02 [0.79, 1.32]	1999	) — 📮 — —
Subtotal (95% CI)			48.6%	1.02 [0.79, 1.32]		
Heterogeneity: Not app	olicable					
Test for overall effect:	Z = 0.17 (P = 0.86)					
Total (95% CI)			100.0%	0.82 [0.54, 1.25]		
Heterogeneity: Tau <sup>2</sup> =	0.08; Chi <sup>2</sup> = 6.45, c	df = 1 (F	P = 0.01); I	² = 84%		
Test for overall effect:	Z = 0.92 (P = 0.36)		,.			0.5 0.7 1 1.5 Favours LABA/ICS Favours ICS
Test for subgroup diffe	,		(P = 0.01)	),   <sup>2</sup> = 84.5%		FAVOUIS LADA/ICS FAVOUIS ICS

Figure 24: The effect of LABA/ICS versus ICS monotherapy on no. severe exacerbations

*SABA Use (puffs/d):* Nineteen trials<sup>47,58,72,73,77,78,81,82,85,87,88,90-96,104</sup> involving 6,006 participants (LABA/ICS = 3,160, ICS = 2,846) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on SABA use (puffs/d) (Figure 25.1). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = -0.75; 95% CI: -0.96 to -0.54; I<sup>2</sup> = 78%). The majority of the heterogeneity in the overall result may be explained by the greater treatment difference indicated by the high dose studies (test for subgroup differences I<sup>2</sup> = 93.3%).

A subgroup analysis based on comparison ICS dose indicated statistically significant differences favouring LABA/ICS for treatment effect that varied in magnitude among the low (WMD = - 0.39; 95% CI: -0.64 to -0.14;  $I^2 = 67\%$ ), medium (WMD = -0.78; 95% CI: -1.02 to -0.55;  $I^2 = 54\%$ ), and high (WMD = -1.60; 95% CI: -2.80 to -0.41;  $I^2 = 87\%$ ) dose studies. The majority of the heterogeneity in the overall result is explained by the greater treatment difference indicated by the medium dose studies (test for subgroup differences  $I^2 = 66.3\%$ ).

-									,
	LA	BA/ICS	ICS				Mean Difference	Mean Difference	
tudy or Subgroup	Mean [puff/sday]	SD [puff/sday]	Total	Mean [puff/sday]	SD [puff/sday]	Total	Weight	IV, Random, 95% CI [puff/sday]	IV, Random, 95% CI [puff/sda
27.1 Low dose ICS									
uhl 2003	-0.41	0.85	352	-0.1	0.85	171	8.2%	-0.31 [-0.47, -0.15]	+
orren 2007	-2.01	2.36	123	-1.86	2.59	119	4.9%	-0.15 [-0.77, 0.47]	
owler 2002	2.6	2.7	19	3.5	2.7	20	1.3%	-0.90 [-2.60, 0.80]	
avuru 2000	-1.9	2.43	87	-0.4	1.94	85	4.7%	-1.50 [-2.16, -0.84]	
Byrne 2001b	0.63	1.77	315	0.75	1.77	312	7.5%	-0.12 [-0.40, 0.16]	+
rice 2002	-1.185	1.45	313	-0.845	1.26	313	7.9%	-0.34 [-0.55, -0.13]	-
ubtotal (95% CI)			1209			1020	34.5%	-0.39 [-0.64, -0.14]	•
leterogeneity: Tau <sup>2</sup> = 0.05;	Chi <sup>2</sup> = 15.20, df = 5 (	P = 0.010); I <sup>2</sup> = 6	7%						
est for overall effect: Z = 3.	05 (P = 0.002)								
.27.2 Medium dose ICS									
itzgerald 1999	-0.52	4.7	89	-0.19	4.7	182	2.3%	-0.33 [-1.52, 0.86]	-+-
(emp 1998	-2.74	4.7	252	-1.04	4.7	254	3.8%	-1.70 [-2.52, -0.88]	
loenig 2008	-1.2	2.25	156	-0.75	2.18	310	6.4%	-0.45 [-0.88, -0.02]	
loopmans 2006	-1.5	1.1	27	-0.6	1.1	27	5.2%	-0.90 [-1.49, -0.31]	
Iolimard 2001	-0.4	1.27	130	0.1	1.27	129	7.2%	-0.50 [-0.81, -0.19]	-
lorice 2007	-0.93	2.1	462	-0.35	2.1	217	7.0%	-0.58 [-0.92, -0.24]	-
athan 2006	-1.6	2.9	94	-0.5	1.9	91	4.4%	-1.10 [-1.80, -0.40]	
loonan 2006	-1.24	2.1	234	-0.78	2.1	109	6.0%	-0.46 [-0.94, 0.02]	
hapiro 2000	-2.3	3.6	81	-0.9	1.8	81	3.5%	-1.40 [-2.28, -0.52]	
an der Molen 1997	-1.5	1.39	125	-0.4	1.39	114	6.9%	-1.10 [-1.45, -0.75]	-
ubtotal (95% CI)		1650				1514	52.8%	-0.78 [-1.02, -0.55]	◆
leterogeneity: Tau <sup>2</sup> = 0.07; est for overall effect: Z = 6.		P = 0.02); l <sup>2</sup> = 54	%						
.27.3 High dose ICS									
oyd 1995	-5.1	4.7	53	-2.5	4	62	1.5%	-2.60 [-4.21, -0.99]	
enkins 2006	0.97	1.5	115	1.61	1.5	115	6.7%	-0.64 [-1.03, -0.25]	-
LGQ97/SLGB4010 2005	0	2.8	133	2	2.8	135	4.6%	-2.00 [-2.67, -1.33]	
ubtotal (95% CI)			301			312	12.8%	-1.60 [-2.80, -0.41]	
leterogeneity: Tau <sup>2</sup> = 0.90; est for overall effect: Z = 2.		P = 0.0004); l <sup>2</sup> = 8	37%						
otal (95% CI)			3160			2846	100.0%	-0.75 [-0.96, -0.54]	•
Heterogeneity: Tau <sup>2</sup> = 0.14;	Chi <sup>2</sup> = 80.09. df = 18	(P < 0.00001); l <sup>2</sup>	= 78%					- / -	<u>- t t t t t t</u>
est for overall effect: Z = 6.		,						-	-4 -2 0 2 4
est for subgroup difference		2 (P < 0.00001)	<sup>2</sup> = 93 <sup>4</sup>	3%				F	avours LABA/ICS Favours ICS

### Figure 25.1: The effect of LABA/ICS versus ICS monotherapy on SABA use (puffs/d)

Two trials<sup>99,101</sup> involving 985 participants (LABA/ICS = 575, ICS = 410) run-in on either LABA/ICS combination or ICS monotherapy provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on SABA use (puffs/d) (Figure 25.2). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = -0.60; 95% CI: -0.85 to -0.36;  $I^2 = 0\%$ ).

A subgroup analysis based on comparison ICS dose indicated a statistically significant difference favouring LABA/ICS for the high<sup>101</sup> (WMD = -0.65; 95% CI: -0.91 to -0.39) dose comparison. The result for the low dose<sup>99</sup> comparison failed to indicate a statistically significant difference between the two treatments<sup>101</sup> (WMD = -0.30; 95% CI: -0.95 to 0.35).

# **Figure 25.2:** The effect of LABA/ICS versus ICS monotherapy on SABA use (puffs/d) (mixed LABA/ICS use at baseline)

LABA/ICS			ICS				Mean Difference	Mean Difference		
Study or Subgroup	Mean [puff/sday]	SD [puff/sday]	Total	Mean [puff/sday]	SD [puff/sday]	Total	Weight	IV, Random, 95% CI [puff/sday]	IV, Random, 95	% CI [puff/sday]
Peters 2008	-0.8	1.42	438	-0.15	1.33	130	85.8%	-0.65 [-0.91, -0.39]	— <b>—</b> —	
SAM40065 2007	-1.3	3.51	137	-1	2.36	280	14.2%	-0.30 [-0.95, 0.35]		
Total (95% CI)			575			410	100.0%	-0.60 [-0.85, -0.36]	•	
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:			= 0%					Fa	-1 -0.5 0 avours LABA/ICS	0.5 1 Favours ICS

*Symptom-free days (SFD):* Twenty-six trials<sup>29,45,47,58,72,73,75,76,80-83,85,87,89,91-98,100,102,104</sup> involving 11,796 participants (LABA/ICS = 6,579, ICS = 5,217) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on SFD (Figure

26.1). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 12.15; 95% CI: 8.43 to 15.87;  $I^2 = 87\%$ ).

A subgroup analysis based on comparison ICS dose indicated greater treatment effect for the medium (WMD = 15.20; 95% CI: 9.52 to 20.87;  $I^2 = 80\%$ ) and high (WMD = 14.20; 95% CI: 9.83 to 18.57;  $I^2 = 49\%$ ) dose comparisons than for the low (WMD = 6.87; 95% CI: 3.41 to 10.38;  $I^2 = 61\%$ ) dose comparison. The majority of the heterogeneity in the overall result may be explained by the smaller treatment difference indicated by the low dose studies (test for subgroup differences  $I^2 = 98.2\%$ ).

		BA/ICS			ICS			Mean Difference	Mean Difference
tudy or Subgroup	Mean [median %]	SD [median %]	Total	Mean [median %]	SD [median %]	Total	Weight	IV, Random, 95% CI [median %]	IV, Random, 95% CI [median
.28.1 Low dose ICS									
ateman 2001	53.48	68	330	25	68	162	3.1%	28.48 [15.69, 41.27]	— <b>—</b>
uhl 2003	58.4	27.55	352	51.3	27.55	171	4.6%	7.10 [2.07, 12.13]	-
orren 2007	26.47	39.46	123	29.77	38.19	119	3.7%	-3.30 [-13.08, 6.48]	-+
avuru 2000	22.6	42.81	87	7.2	37.71	85	3.3%	15.40 [3.35, 27.45]	
una 2006	50.15	29.15	409	43.4	29.36	207	4.6%	6.75 [1.85, 11.65]	
)'Byrne 2001b	74.9	25.2	315	70.3	25.2	312	4.7%	4.60 [0.65, 8.55]	<del>-</del> -
Price 2002	34.6	32.3	313	26.8	32.3	313	4.6%	7.80 [2.74, 12.86]	
AS40036 2005	5.7	35.2	167	-0.5	33.94	154	4.1%	6.20 [-1.37, 13.77]	+
SFA103153 2007	10.8	38.03	239	8.9	33.95	236	4.3%	1.90 [-4.58, 8.38]	
ubtotal (95% CI)	10.0	00.00	2335	0.0	00.00	1759	36.9%	6.87 [3.41, 10.34]	♦
leterogeneity: Tau <sup>2</sup> = 15.44 est for overall effect: Z = 3		(P = 0.009); l <sup>2</sup> = 6	1%						
.28.2 Medium dose ICS									
Bateman 2004	65.12	28	1161	40.44	28	1157	4.9%	24.68 [22.40, 26.96]	
Cemp 1998	42	46	252	21	46	254	4.0%	21.00 [12.98, 29.02]	
Coenig 2008	19.9	68.45	156	15.5	67.13	310	3.1%	4.40 [-8.69, 17.49]	- <del> -</del>
angton Hewer 1995	27.7	33.3	11	-10.1	33.3	10	1.3%	37.80 [9.28, 66.32]	
Iolimard 2001	17.8	36.7	130	6.6	37.1	129	3.9%	11.20 [2.21, 20.19]	
lorice 2007	31.07	44	462	19.1	44	217	4.2%	11.97 [4.87, 19.07]	
lathan 2006	18.5	37.8	94	15	31.5	91	3.7%	3.50 [-6.51, 13.51]	+
loonan 2006	23.14	31.95	121	9.5	31.95	109	4.0%	13.64 [5.37, 21.91]	
hapiro 2000	33.8	41.4	81	15.4	37.8	81	3.2%	18.40 [6.19, 30.61]	
etterstrom 2001	23.7	37.04	238	8	40	124	4.0%	15.70 [7.23, 24.17]	<del></del> -
ubtotal (95% CI)			2706			2482	36.2%	15.20 [9.52, 20.87]	•
leterogeneity: Tau <sup>2</sup> = 57.70 rest for overall effect: Z = 5		(P < 0.00001); l <sup>2</sup> =	80%						
.28.3 High dose ICS									
ubier 1999	37	30	338	27	30	165	4.5%	10.00 [4.42, 15.58]	<del>_</del>
oyd 1995	22	30	53	13	22	62	3.7%	9.00 [-0.76, 18.76]	<u>+</u>
nd 2003	21	60	171	0	60	165	3.1%	21.00 [8.17, 33.83]	<del></del>
enkins 2000	60	45.95	173	54	45.95	165	3.7%	6.00 [-3.80, 15.80]	+
enkins 2006	31.5	27.85	341	15.6	27.85	115	4.4%	15.90 [10.01, 21.79]	
LGQ97/SLGB4010 2005	21	27.8	130	0.0	27.2	133	4.3%	21.00 [14.35, 27.65]	
an Noord 2001	32.25	68	332	14	68	171	3.2%	18.25 [5.70, 30.80]	— <del>•</del>
ubtotal (95% CI)	52.20		1538			976	26.9%	14.20 [9.83, 18.57]	•
leterogeneity: Tau <sup>2</sup> = 15.97 est for overall effect: Z = 6		(P = 0.07); I <sup>2</sup> = 49 <sup>6</sup>	%						
otal (95% CI)			6579			5217	100.0%	12.15 [8.43, 15.87]	•
leterogeneity: Tau <sup>2</sup> = 72.56	6; Chi <sup>2</sup> = 186.96, df = 2	25 (P < 0.00001); I		6					
est for overall effect: Z = 6									-50 -25 0 25 50 Favours ICS Favours LAB
	· /	2 (P < 0.00001), I							Favours ICS Favours LAB

Figure 26.1:	The effect of LABA/ICS	versus ICS monotherap	v on no SFD
1 19010 2011		verous ros monourerup	y on no. or D

Three trials<sup>84,99,101</sup> involving 1,179 participants (LABA/ICS = 673, ICS = 506) run-in on either LABA/ICS combination or ICS monotherapy provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on SFD (Figure 26.2). The pooled result failed to indicate a statistically significant difference between the two treatments (WMD = 7.30; 95% CI: -2.14 to 16.73;  $I^2 = 54\%$ ).

A subgroup analysis based on comparison ICS dose indicated a statistically significant difference favouring LABA/ICS for the high<sup>101</sup> (WMD = 13.07; 95% CI: 8.10 to 18.04) dose comparison. The result for the medium<sup>84,99</sup> dose comparison failed to indicate a statistically significant difference between the two treatments (WMD = 1.06; 95% CI: -9.43 to 11.55).

use at basel	,										
	LAE	BA/ICS		1	CS			Mean Difference	Mean Difference		
Study or Subgroup	Mean [median %]	SD [median %]	Total	Mean [median %]	SD [median %]	Total	Weight	IV, Random, 95% CI [median %] Year	IV, Random, 95% CI [median %]		
1.12.1 Medium dose IC	S										
Lundback 2006	66.7	50	95	67.9	50	92	25.2%	-1.20 [-15.53, 13.13] 2006			
SAM40065 2007	27.8	76.08	137	24.13	74.09	282	23.1%	3.67 [-11.73, 19.07] 2007			
Subtotal (95% CI)			232			374	48.4%	1.06 [-9.43, 11.55]	<b>•</b>		
Heterogeneity: Tau <sup>2</sup> = 0.	.00; Chi <sup>2</sup> = 0.21, df =	= 1 (P = 0.65); I <sup>2</sup> =	0%								
Test for overall effect: Z	= 0.20 (P = 0.84)										
1.12.2 High dose ICS											
Peters 2008	19	30.08	441	5.93	24.07	132	51.6%	13.07 [8.10, 18.04] 2008			
Subtotal (95% CI)			441			132	51.6%	13.07 [8.10, 18.04]	•		
Heterogeneity: Not appli	icable										
Test for overall effect: Z	= 5.15 (P < 0.00001	)									
Total (95% CI)			673			506	100.0%	7.30 [-2.14, 16.73]	•		
Heterogeneity: Tau <sup>2</sup> = 3	8.47; Chi <sup>2</sup> = 4.32, df	= 2 (P = 0.12); I <sup>2</sup>	= 54%								
Test for overall effect: Z	= 1.51 (P = 0.13)								-50 -25 0 25 50 Favours ICS Favours LABA/IC		
Test for subgroup differe	. ,	lf = 1 (P = 0.04), l <sup>2</sup>	² = 75.7	%					Favours ICS Favours LABAVIC		

Figure 26.2: The effect of LABA/ICS versus ICS monotherapy on no. SFD (mixed LABA/ICS use at baseline)

**Days with optimal control:** Six trials<sup>45,72,89,91,93,96</sup> involving 3,262 participants (LABA/ICS = 2,115, ICS = 1,147) provided data for a meta-analysis on the effect of LABA/ICS combination therapy compared with ICS monotherapy on days with optimal control (defined as the reported measure for best asthma control in a study, e.g., optimal control, total control, well-controlled) (Figure 27.1). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 10.10; 95% CI: 6.77 to 13.42;  $I^2 = 53\%$ ).

A subgroup analysis based on comparison ICS dose indicated greater treatment differences for the medium<sup>89,96</sup> (WMD = 12.97; 95% CI: 8.32 to 17.61;  $I^2 = 0\%$ ), and high<sup>93</sup> (WMD = 16.05; 95% CI: 10.08 to 22.02) dose comparisons than for the low (WMD = 6.92; 95% CI: 4.11 to 9.73;  $I^2 = 0\%$ ) comparisons. The majority of the heterogeneity in the overall result may be explained by the greater treatment difference indicated by the medium and high dose studies (test for subgroup differences  $I^2 = 80.0\%$ ).

-	LA	ABA/ICS	S		ICS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.29.1 Low dose ICS									
Buhl 2003	54.35	28.05	352	47.6	28.05	171	18.1%	6.75 [1.63, 11.87]	<b>_</b>
Kuna 2006	47.3	28.78	409	40	28.63	207	19.1%	7.30 [2.51, 12.09]	│ — <b>∎</b> —
Price 2002	27.1	30	313	20.4	30	313	19.4%	6.70 [2.00, 11.40]	
Subtotal (95% CI)			1074			691	56.6%	6.92 [4.11, 9.73]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Cł	ni² = 0.04	4, df = 3	2 (P = 0	.98); l²	= 0%			
Test for overall effect:	Z = 4.83	(P < 0.	00001)						
1.29.2 Medium dose I	cs								
Morice 2007	29.77	36	462	18.3	36	217	16.1%	11.47 [5.66, 17.28]	<b>_</b>
Zetterstrom 2001	27.73	33.94	238	12.1	36.6	124	11.6%	15.63 [7.88, 23.38]	
Subtotal (95% CI)			700			341	27.7%	12.97 [8.32, 17.61]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Cł	ni² = 0.7	1, df =	1 (P = 0	.40); l²	= 0%			
Test for overall effect:	Z = 5.47	(P < 0.	00001)						
1.29.3 High dose ICS									
Jenkins 2006	32.35	28.25	341	16.3	28.25	115	15.7%	16.05 [10.08, 22.02]	
Subtotal (95% CI)			341			115	15.7%	16.05 [10.08, 22.02]	
Heterogeneity: Not app	olicable								
Test for overall effect:		(P < 0.	00001)						
Total (95% CI)			2115			1147	100.0%	10.10 [6.77, 13.42]	•
Heterogeneity: Tau <sup>2</sup> =	9 07 <sup>.</sup> Cł	$ni^2 = 10^{-1}$	74 df =	5 (P =	0 06) <sup>,</sup> i				-++
Test for overall effect:				•	0.00), 1	5070			-20 -10 0 10 20
Test for subgroup diffe		•	,		= 0 007	$l^2 = 80$	1.0%		Favours ICS Favours LABA/I
i cor ioi cubgicup une	101003.	0111 - 0	, ui	<u> </u>	5.007	,. 00			

Figure 27.1: The effect of LABA/ICS versus ICS monotherapy on no. days with optimal control

Two trials<sup>74,101</sup> involving 749 participants (LABA/ICS = 530, ICS = 219) run-in on either LABA/ICS combination or ICS monotherapy provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on the number of days with optimal control (Figure 27.2). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 21.58; 95% CI: 6.58 to 36.57;  $I^2 = 82\%$ ). The heterogeneity may be explained by the differences in the magnitude of treatment effect between the low<sup>74</sup> (WMD = 30.20; 95% CI: 18.55 to 41.85) and high<sup>101</sup> (WMD = 14.79; 95% CI: 9.55 to 20.03) dose comparisons.

**Figure 27.2:** The effect of LABA/ICS versus ICS monotherapy on no. days with optimal control (mixed LABA/ICS use at baseline)

	LABA/ICS				ICS Mean Difference					Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI		
Pearlman 2004	39.7	42.2	92	9.5	37.74	89	44.1%	30.20 [18.55, 41.85]	2004	<b></b>		
Peters 2008	22.41	30.56	438	7.62	25.51	130	55.9%	14.79 [9.55, 20.03]	2008			
Total (95% CI)			530			219	100.0%	21.58 [6.58, 36.57]				
Heterogeneity: Tau <sup>2</sup> =	97.48; C	hi² = 5.	59, df =	= 1 (P =	0.02); l²	² = 82%	,		-	-20 -10 0 10 20		
Test for overall effect:	Z = 2.82	(P = 0.	005)							Favours ICS Favours LABA/IC		

#### Health-related quality of life measures

Asthma quality of life questionnaire (AQLQ): Five trials<sup>29,77,82,91,96</sup> involving 2,999 participants (LABA/ICS = 1,638, ICS = 1,361) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on AQLQ score (Figure 28). The pooled result indicated a statistically significant difference between the two treatments (WMD = 0.29; 95% CI: 0.18 to 0.39;  $I^2 = 43\%$ ); however, the precision of the confidence interval suggested that the difference would not meet the a priori criteria for clinical importance (MCID = 0.5).

A subgroup analysis based on comparison ICS dose indicated little change in the magnitude and precision of the treatment effect among the low (WMD = 0.21; 95% CI: 0.07 to 0.35;  $I^2 = 0\%$ ) and medium (WMD = 0.32; 95% CI: 0.17 to 0.46;  $I^2 = 61\%$ ) dose comparisons.

	LA	BA/IC	S		ICS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.30.1 Low dose ICS									
Fowler 2002	0.09	0.76	19	-0.34	0.73	20	4.6%	0.43 [-0.04, 0.90]	
Price 2002	0.67	0.95	313	0.48	0.95	313	24.7%	0.19 [0.04, 0.34]	
Subtotal (95% CI)			332			333	29.3%	0.21 [0.07, 0.35]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Cł	ni² = 0.	92, df =	= 1 (P =	0.34);	$I^2 = 0\%$	)		
Test for overall effect: 2	Z = 2.93	(P = 0	0.003)						
1.30.2 Medium dose I	cs								
Bateman 2004	1.36	1.09	592	1.16	1.1	557	28.7%	0.20 [0.07, 0.33]	-
Kemp 1998	1.08	1.27	252	0.61	1.12	254	16.7%	0.47 [0.26, 0.68]	
Morice 2007	0.704	0.9	462	0.37	0.9	217	25.3%	0.33 [0.19, 0.48]	
Subtotal (95% CI)			1306			1028	70.7%	0.32 [0.17, 0.46]	•
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 2				•	0.08);	l² = 61º	%		
Total (95% CI)			1638			1361	100.0%	0.29 [0.18, 0.39]	◆
Heterogeneity: Tau <sup>2</sup> =				•	0.14);	l² = 43	%	-	-1 -0.5 0 0.5 1
Test for overall effect:	Z = 5.37	(P < 0	0.00001	)					Favours ICS Favours LABA/ICS
Test for subgroup diffe	rences:	Chi² =	0.95, d	lf = 1 (P	= 0.33	3), I <sup>2</sup> = (	0%		

#### Figure 28: The effect of LABA/ICS versus ICS monotherapy on AQLQ score

It was not considered appropriate to conduct subgroup analyses based on asthma severity as only a small proportion of studies (< 20% of available studies for any single outcome) reported results for populations restricted to a single asthma severity class.

#### **Publication bias**

Meta-analyses for four measures (PEF AM, PEF PM, no. participants with  $\geq 1$  exacerbations, SABA use, and SFD) contained sufficient studies of varying size to warrant an assessment of publication bias through funnel plot analysis. There was no evidence of asymmetry (small study effects) in the funnel plots for PEF AM and PM (Figures 29.1 and 29.2) indicating limited publication bias. There was evidence of asymmetry in the funnel plot for no. participants with  $\geq 1$  exacerbations and SABA use (Figure 29.3 and 29.4) indicating possible publication bias and an associated overestimation of the treatment effect. There was also evidence of asymmetry in the funnel plot for SFD (Figure 29.5) indicating possible publication bias; however, the direction of the asymmetry suggests that the bias may serve to underestimate the treatment effect associated with LABA/ICS.

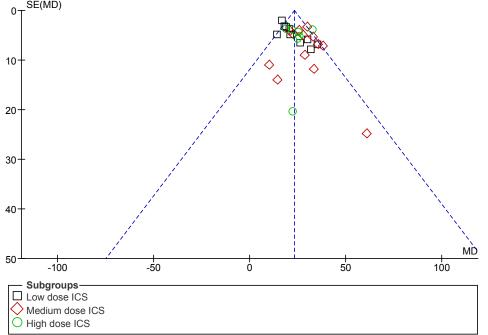


Figure 29.1: Funnel plot of LABA/ICS vs. similar dose ICS for PEF AM

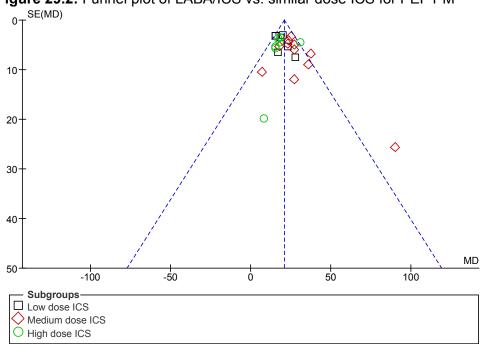
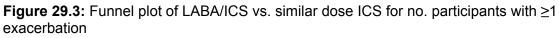
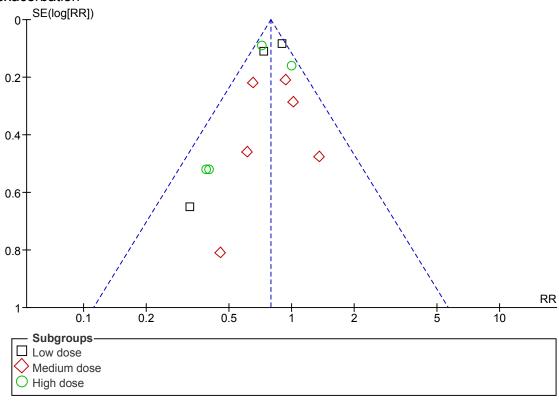


Figure 29.2: Funnel plot of LABA/ICS vs. similar dose ICS for PEF PM





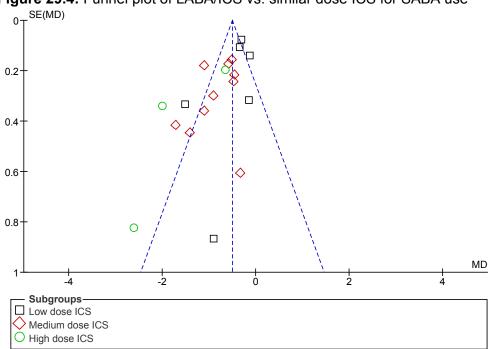
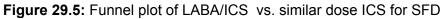
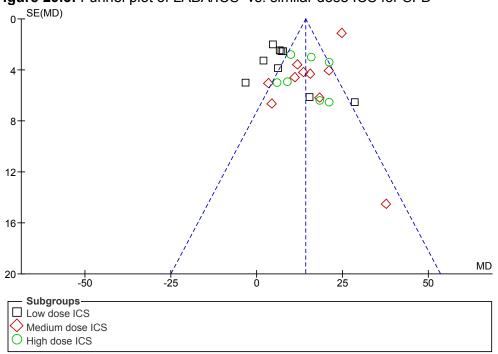


Figure 29.4: Funnel plot of LABA/ICS vs. similar dose ICS for SABA use





# 2.1.3 Effectiveness of LABA/ICS as maintenance therapy (versus higher dose ICS)

Thirty-one unique RCTs<sup>53,58,65,66,76,79,101,103-126</sup> were identified that assessed the comparative effectiveness of LABA/ICS combination therapy versus ICS monotherapy in patients on maintenance ICS (those receiving ICS therapy prior to the treatment period). Thirteen trials<sup>53,66,76,103,104,108-110,116,120,123,125,126</sup> compared SAL/FP versus FP, six compared FORM/BUD versus BUD,<sup>58,101,105,113,119,122</sup> five compared SAL/BDP versus BDP,<sup>111,114,117,118,121</sup> three compared SAL/FP versus BUD,<sup>65,112,124</sup> two compared FORM/BDP versus BDP,<sup>107,115</sup> one compared FORM/BUD versus FP,<sup>106</sup> and one compared SAL/TAA versus TAA.<sup>79</sup> One study that compared SAL/FP versus FP also compared SAL/FP versus TAA.<sup>109</sup> Two trials compared variable dose LABA/ICS with a fixed dose ICS monotherapy.<sup>105,119</sup> All remaining trials compared fixed dose LABA/ICS with fixed dose ICS monotherapy.

All trials compared LABA/ICS with a higher dose (double or greater) of ICS. The age of included participants was  $\geq 18$  years in 12 (38.7%) studies.<sup>53,66,106,108,111,113-115,117,118,120,121</sup> In terms of asthma severity, three trials<sup>79,121,123</sup> included only participants with mild asthma, and four<sup>106,108,114,124</sup> included only participants with moderate asthma. The remaining trials examined participants covering a range of asthma severity: intermittent to mild (1 trial),<sup>58</sup> intermittent to moderate (2 trials),<sup>103,113</sup> intermittent to severe (5 trials),<sup>76,105,111,115,125</sup> mild to moderate (5 trials),<sup>65,112,120,122,126</sup> mild to severe (4 trials),<sup>53,66,104,107</sup> and moderate to severe (7 trials).<sup>101,109,110,116-119</sup> Treatment duration also varied among studies: 12 wk (15 trials),<sup>53,65,66,106-109,112,113,115,116,120,121,124,126</sup> 16 wk (1 trial),<sup>123</sup> 24 wk (8 trials),<sup>76,79,104,110,114,117,118,125</sup> 26 wk (1 trial),<sup>111</sup> 36 wk (1 trial),<sup>103</sup> 48 wk (1 trial),<sup>105</sup> 52 wk (3 trials),<sup>58,101,119</sup> and 72 wk (1 trial).<sup>122</sup> The median duration of treatment was 16 weeks (IQR: 12, 24).

### Methodological quality

Overall, the methodological quality of included higher dose maintenance ICS studies (N = 31) was moderate (Table 5). Jadad scores ranged from 2-5 with a median score of 4 (IQR, 3 to 4.5). Allocation concealment was considered adequate in 4 (12.9%) studies and unclear in 27 (87.1%). All studies were randomized controlled trials; 23 (38.7%) of which described the method of randomization and were considered to have employed an appropriate randomization method. Double-blinding was reported in 30 (96.8%) trials with 17 (54.8%) explicitly describing the methods by which investigator and participants were blinded to the intervention. Withdrawals or dropouts, if any occurred, and the accounting of all participants was reported in all trials. Due to the relatively high scores (Jadad score  $\geq$ 3) of almost all studies, no sensitivity analyses were conducted based on quality.

Table 5: Methodological quality of maintenance ICS studies: highe	er dose (N = 31)
Quality Components	No. Yes (%)
Randomization	31 (100)
Double-blinding	30 (96.8)
Description of withdrawals/dropouts	31 (100)
Appropriate method of randomization	23 (38.7)
Appropriate method of double-blinding	17 (54.8)
Inappropriate method of randomization	0 (0)
Inappropriate method of double-blinding	0 (0)
Adequate concealment of treatment allocation	4 (12.9)
Inadequate concealment of treatment allocation	0 (0)
Unclear concealment of treatment allocation	27 (87.1)

**Pulmonary function measures** *PEF AM:* Twenty five trials<sup>53,58,65,66,76,104-120,122,125,126</sup> involving 13,389 participants (LABA/ICS = 7,135, ICS = 6,254) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with higher-dose ICS monotherapy on morning PEF (L/min) (Figure 30). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 18.24 L/min; 95% CI: 15.72 to 20.76;  $I^2 = 49\%$ ). The precision of the confidence interval suggests that the difference may meet the a priori criteria for clinical importance (MCID = 18.79 L/min).

#### Figure 30: The effect of LABA/ICS versus ICS monotherapy on PEF AM

1.1.1 Low does ICS         L1.1 Low does ICS         DByme 2001       12.89       45       333       1.73       45       312       5.6%       9.20 [3.45, 14.95]         Abbe 2006       3.45       37.7       35.5       9.6       37.7       34.5       6.7%       22.00 [19.40, 30.00]         SAM40038 2004       51.4       42.7       270       33.9       44.6       273       5.4%       17.50 [10.16, 24.84]         SAM40038 2004       51.4       42.7       270       33.9       44.6       273       5.4%       17.50 [10.16, 24.84]         Stobiotal (5%)CI)       1178       1164       24.2%       15.77 [8.13, 23.41]       •         Heterogeneity: Tau <sup>2</sup> = 49.96; Ch <sup>2</sup> = 17.29, df = 3 (P = 0.0006); P = 83%       Feat for overall effect. Z = 4.05 (P < 0.0001)       11.42       42.4%       11.00 [4.31, 26.31]       •         Staraniuk 1999       33       50.4       68       12.64       64       1.8%       22.30 [3.16, 37.66]       •         Genering 1999       46.5       52.03       22.1       2.8       47.03       216       4.2%       22.70 [13.41, 31.99]       •         Objerne 2005       35.05.4       60       18.5       7.5       24.5       5.8%       <	-	LA	BA/ICS		1	CS			Mean Difference	Mean Difference
Lalios 2003 16.5 31.7 230 7.3 31.7 237 6.5% 9.20 [3.45, 14.95] Polyme 2001 12.89 45 233 1.73 45 312 5.6% 11.61 41.61 16.16 16.16 Rabe 2006 34.5 37.7 355 9.5 37.7 342 5.6% 12.00 [19.40, 30.60] Tarte 2006 34.5 37.7 355 9.5 37.7 342 5.6% 17.50 [10.16, 24.84] Subtate (195% CI) 1178 17.29, df = 3 (P = 0.006); P = 83% Test for overall effect: Z = 4.05 (P < 0.0006); P = 83% Test for overall effect: Z = 4.05 (P < 0.0006); P = 83% Test for overall effect: Z = 4.05 (P < 0.0006); P = 83% Test for overall effect: Z = 4.05 (P < 0.0006); P = 83% Test for overall effect: Z = 4.05 (P < 0.0006); P = 83% Test for overall effect: Z = 4.05 (P < 0.0006); P = 83% Test for overall effect: Z = 4.05 (P < 0.0006); P = 83% Test for overall effect: Z = 4.05 (P < 0.0006); P = 83% Test for overall effect: Z = 4.05 (P < 0.0006); P = 83% Test for overall effect: Z = 4.05 (P < 0.0006); P = 83% Test for overall effect: Z = 4.05 (P < 0.0006); P = 83% Test for overall effect: Z = 4.05 (P < 0.0006); P = 83% Test for overall effect: Z = 4.05 (P < 0.0006); P = 83% Test for overall effect: Z = 4.05 (P < 0.0006); P = 83% Test for overall effect: Z = 1.73, 4.75 2.24 2.23, 8.476, 20.30 [3.16, 37.66] Test for overall effect: Z = 1.74, 4.75 2.24 2.9 173, 4.439, 20.30 [3.16, 37.66] Test for overall effect: Z = 1.74, 4.75 2.26 2.9 173, 4.439, 20.30 [18.77, 33.83] Test for overall effect: Z = 1.149 (P < 0.0006); P = 4.2% Test for overall effect: Z = 1.149 (P < 0.0005); P = 4.2% Test for overall effect: Z = 1.149 (P < 0.005); P = 4.2% Test for overall effect: Z = 1.149 (P < 0.005); P = 4.2% Test for overall effect: Z = 1.149 (P < 0.005); P = 4.2% Test for overall effect: Z = 1.149 (P < 0.005); P = 4.2% Test for overall effect: Z = 1.149 (P < 0.005); P = 4.2% Test for overall effect: Z = 1.149 (P < 0.005); P = 4.2% Test for overall effect: Z = 0.12 (P < 0.0001) To 3.75 5.2 100 12.2 51.8 101 2.4% Test for overall effect: Z = 0.12 (P < 0.0001) To 3.77 14 17 16.7 52.3 325 4.0% 2.000 (Z = 3.2,000] Test for overall effect: Z = 0.	Study or Subgroup	Mean [L/min]	SD [L/min]	Total	Mean [L/min]	SD [L/min]	Total	Weight	IV, Random, 95% CI [L/min]	IV, Random, 95% CI [L/min]
$\begin{array}{c} \text{OByme 2001} & 12.89 & 45 & 323 & 1.73 & 45 & 312 & 5.6\% & 11.16 [1.16, 14.6, 18.16] \\ \text{SAM4003 2004} & 51.4 & 42.7 & 270 & 33.9 & 44.6 & 273 & 5.4\% & 17.50 [10.16, 24.84] \\ \text{Subtotal (86% CI)} & 1178 & 1164 & 24.2\% & 15.77 [8.13, 23.41] \\ \text{Heterogeneity: Tau" = 49.96, Ch" = 17.29, df = 3 (P = 0.0006); l" = 83\% \\ \text{Test for overall effect Z = 4.05 (P < 0.0001) \\ \textbf{1.1.2 Medlum dose ICS} \\ \text{Baraniuk 1999} & 58 & 91.19 & 231 & 47 & 74.67 & 223 & 2.1\% & 11.00 [-4.31, 26.31] \\ \text{Test for overall effect Z = 4.05 (P < 0.0001) \\ \textbf{1.1.2 Medlum dose ICS} \\ \text{Baraniuk 1999} & 46.5 & 52.03 & 221 & 23.8 & 47.03 & 216 & 4.2\% & 22.70 [13.41, 31.99] \\ \text{Test for overall effect Z = 4.05 (P < 0.0001) \\ \textbf{4.5 & 42.9 & 176 & 32.5 & 42.9 & 173 & 4.4\% & 11.00 [2.00, 20.00] \\ \text{Test for overall effect C = 11.4\% & 23.5 & 31.37 & 75 & 126 & 26\% & 21.00 (7.67, 34.33] \\ \text{Test for overall effect C = 11.4\% & 13.5 & 260 & 19.6 & 38.2 & 254 & 56\% & 18.10 [11.03, 25.17] \\ \text{Test for overall effect C = 11.4\% (P < 0.00001) \\ \textbf{4.5 & 41.4\% & 13.99 & 57.7 & 13.5 & 260 & 19.6 & 38.2 & 254 & 56\% & 18.10 [11.03, 25.17] \\ \text{Test for overall effect C = 11.49 (P < 0.00001) \\ \textbf{4.1072 1999} & 37.7 & 43.5 & 260 & 19.6 & 38.2 & 254 & 56\% & 18.10 [11.03, 25.17] \\ \text{Test for overall effect C = 11.49 (P < 0.00001) \\ \textbf{4.1073 199 & 37.7 & 43.5 & 260 & 19.6 & 36.5 & 276 & 53\% & 26.30 [18.77, 38.3] \\ \text{Test for overall effect C = 11.49 (P < 0.00001) \\ \textbf{4.1073 199 & 37.7 & 43.7 & 19.7 & 12.7 & 42.1 & 94.3 & 8.1\% & 17.50 [1.35, 25.49] \\ \text{Test for overall effect C = 211.49 (P < 0.00001) \\ \textbf{4.113 High dose ICS \\ \text{Bergmann 2004 } 52 & 76 & 170 & 36 & 65 & 177 & 2.2\% & 16.00 [1.09, 30.91] \\ Test for overall effect C = 11.49 (P < 0.00001) \\ \textbf{4.1149 (13.03 & 37.7 & 11 & 16.7 & 52.3 & 32.5 & 4.0\% & 25.30 [15.62, 34.98] \\ \text{Test for overall effect C = 11.49 (P < 0.00001) \\ \textbf{4.1149 (13.03 & 37.7 & 11 & 17 & 16 & 30\% & 20.0007.81 , 32.49] \\ \text{Test for overall effect C = 11.49 (P < 0.00001) \\ \textbf{4.1149 (13.20 & 4.13 & 4.1\% & 17 & 116 & 30\% & 20.0007.81$	.1.1 Low dose ICS									
Rabe 2006 34.5 37.7 365 9.5 37.7 342 6.7% 25.00 [19.40, 30.60] Subtotal (95% CI) 1178 1178 1164 24.2% 15.77 [8.13, 23.41] Heterogeneity: Tau <sup>2</sup> = 49.96; Ch <sup>2</sup> = 17.29, df = 3 (P = 0.0006); P = 83% Test for overall effect Z = 4.05 (P < 0.0001) 1.1.2 Medium dose ICS Baraniuk 1999 58 91.19 231 47 74.67 223 2.1% 11.00 [-4.31, 26.31] Test for overall effect Z = 4.05 (P < 0.0001) 1.1.2 Medium dose ICS Baraniuk 1999 58 91.19 231 47 74.67 223 2.1% 11.00 [-4.31, 26.31] Test for overall effect Z = 4.05 (P < 0.0001) 1.1.2 Medium dose ICS Baraniuk 1999 58 91.19 231 47 74.67 223 2.1% 11.00 [-4.31, 26.31] Test for overall effect Z = 4.05 (P < 0.0001) 1.1.2 Medium dose ICS Baraniuk 1999 46.5 52.03 221 23.8 47.03 216 42.9% 22.70 [13.41, 31.99] Test for overall effect Z = 4.05 (P < 0.0001) 4.3.5 42.9 176 32.5 42.9 173 4.4% 11.00 [2.00, 20.00] Test Source 1999 40.8 46.4 239 14.5 37.5 244 5.3% 26.30 [18.77, 33.83] Test Source 1999 40.8 46.4 239 14.5 37.5 244 5.3% 26.30 [18.77, 33.83] Test Source 1999 40.8 46.4 239 14.5 37.5 244 5.3% 26.30 [18.77, 33.83] Test Source 1999 40.8 46.4 239 14.5 37.5 244 5.3% 26.30 [18.77, 33.83] Test Source 1999 40.8 46.4 239 14.5 37.5 24.5 5.6 4.9 % 11.00 [2.00, 20.00] Test Source 10.5 44.4 67.1 121 30.7 65.7 116 1.8% 13.70 [-3.21, 30.61] SAM40013 2005 36.85 30.65 6 8.95 30.65 9 0.6% 12.6 20.01 [4.47, 68.56] Test Source 10.5 43.7 61.97 240 30 24.2 238 4.1% 12.70 [4.13, 23.27] Test Source 10.5 43.7 61.97 240 30 24.2 238 4.1% 12.70 [4.13, 23.27] Test Source 10.5 (Ch <sup>2</sup> = 3.74, 61 = 3 (P = 0.05); P = 42% Test Source 10.95 (Ch <sup>2</sup> = 3.74, 61 = 13 (P = 0.05); P = 42% Test Source 10.95 (Ch <sup>2</sup> = 3.74, 61 = 13 (P = 0.05); P = 42% Test Source 10.96 (Ch <sup>2</sup> = 3.71, 16.7 52.3 325 4.0% 25.30 [16.52, 34.98] Test Source 10.96 (Ch <sup>2</sup> = 3.74, 61 = 13 (P = 0.05); P = 42% Test Source 10.96 (Ch <sup>2</sup> = 3.74, 61 = 13 (P = 0.05); P = 42% Test Source 10.96 (Ch <sup>2</sup> = 3.74, 61 = 13 (P = 0.05); P = 42% Test For overall effect Z = 11.49 (C = 0.00001) Test For overall effect Z = 11.49 (C = 0.00001)	alloo 2003	16.5	31.7	230	7.3	31.7	237	6.5%	9.20 [3.45, 14.95]	-
Rabe 2006 34.5 37.7 365 9.5 37.7 342 6.7% 25.00 [19.40, 30.60] Subtotal (95% CI) 1178 1178 1164 24.2% 15.77 [8.13, 23.41] Heterogeneity: Tau <sup>2</sup> = 49.96; Ch <sup>2</sup> = 17.29, df = 3 (P = 0.0006); P = 83% Test for overall effect Z = 4.05 (P < 0.0001) 1.1.2 Medium dose ICS Baraniuk 1999 58 91.19 231 47 74.67 223 2.1% 11.00 [-4.31, 26.31] Test for overall effect Z = 4.05 (P < 0.0001) 1.1.2 Medium dose ICS Baraniuk 1999 58 91.19 231 47 74.67 223 2.1% 11.00 [-4.31, 26.31] Test for overall effect Z = 4.05 (P < 0.0001) 1.1.2 Medium dose ICS Baraniuk 1999 58 91.19 231 47 74.67 223 2.1% 11.00 [-4.31, 26.31] Test for overall effect Z = 4.05 (P < 0.0001) 1.1.2 Medium dose ICS Baraniuk 1999 46.5 52.03 221 23.8 47.03 216 42.9% 22.70 [13.41, 31.99] Test for overall effect Z = 4.05 (P < 0.0001) 4.3.5 42.9 176 32.5 42.9 173 4.4% 11.00 [2.00, 20.00] Test Source 1999 40.8 46.4 239 14.5 37.5 244 5.3% 26.30 [18.77, 33.83] Test Source 1999 40.8 46.4 239 14.5 37.5 244 5.3% 26.30 [18.77, 33.83] Test Source 1999 40.8 46.4 239 14.5 37.5 244 5.3% 26.30 [18.77, 33.83] Test Source 1999 40.8 46.4 239 14.5 37.5 244 5.3% 26.30 [18.77, 33.83] Test Source 1999 40.8 46.4 239 14.5 37.5 24.5 5.6 4.9 % 11.00 [2.00, 20.00] Test Source 10.5 44.4 67.1 121 30.7 65.7 116 1.8% 13.70 [-3.21, 30.61] SAM40013 2005 36.85 30.65 6 8.95 30.65 9 0.6% 12.6 20.01 [4.47, 68.56] Test Source 10.5 43.7 61.97 240 30 24.2 238 4.1% 12.70 [4.13, 23.27] Test Source 10.5 43.7 61.97 240 30 24.2 238 4.1% 12.70 [4.13, 23.27] Test Source 10.5 (Ch <sup>2</sup> = 3.74, 61 = 3 (P = 0.05); P = 42% Test Source 10.95 (Ch <sup>2</sup> = 3.74, 61 = 13 (P = 0.05); P = 42% Test Source 10.95 (Ch <sup>2</sup> = 3.74, 61 = 13 (P = 0.05); P = 42% Test Source 10.96 (Ch <sup>2</sup> = 3.71, 16.7 52.3 325 4.0% 25.30 [16.52, 34.98] Test Source 10.96 (Ch <sup>2</sup> = 3.74, 61 = 13 (P = 0.05); P = 42% Test Source 10.96 (Ch <sup>2</sup> = 3.74, 61 = 13 (P = 0.05); P = 42% Test Source 10.96 (Ch <sup>2</sup> = 3.74, 61 = 13 (P = 0.05); P = 42% Test For overall effect Z = 11.49 (C = 0.00001) Test For overall effect Z = 11.49 (C = 0.00001)	D'Byrne 2001	12.89	45	323	1.73	45	312	5.6%	11.16 [4.16, 18.16]	
Subtat (95% CI) 1178 1164 24.2% 15.77 [8.13, 23.41] Heterogeneity: Tau <sup>2</sup> = 49.8(-Df) = 17.29, df = 3 (P = 0.0006); l <sup>2</sup> = 83% Test for overall effect: Z = 4.05 (P < 0.0001) 1.1.2 Medium dose ICS Baraniuk 1999 58 91.19 231 47 74.67 223 2.1% 11.00 [-4.31, 26.31] T. 2 Medium dose ICS Baraniuk 1999 58 91.19 231 47 74.67 223 2.1% 11.00 [-4.31, 26.31] T. 2 Medium dose ICS Baraniuk 1999 58 91.19 231 47 74.6 ft = 24.2% 22.70 [13.41, 31.99] T. 2 Medium dose ICS Baraniuk 1999 46.5 52.03 221 22.8 47.03 216 4.2% 22.70 [13.41, 31.99] T. 2 Medium 1994 28 53 137 7 57 126 2.6% 21.00 [7.67, 34.33] T. 2 Median 2001 43.5 42.9 176 32.5 42.9 173 4.4% 11.00 [2.00, 02.00] T. 2 Median 2001 43.5 42.9 176 32.5 42.9 173 4.4% 11.00 [2.00, 02.00] T. 2 Median 1999 40.8 46.4 239 14.5 37.5 244 5.3% 26.30 [18.77, 38.83] T. 2 Murray 1999 37.7 43.5 260 19.6 38.2 254 5.6% 18.10 [11.03, 25.71] T. 2 Murray 1999 37.7 43.5 260 19.6 38.2 254 5.6% 18.10 [11.03, 25.17] T. 2 Murray 1999 37.7 61.6 75 15.9 51.6 7 1.9 1.9% 24.10 [7.80, 40.40] SAM40013 2005 34.4 67.1 121 30.7 65.7 116 1.8% 13.70 [-3.21, 30.61] SAM40012 2005 35.85 30.65 6 8.95 30.65 9 0.6% 26.90 [-4.76, 58.66] T. 2 Murray 1999 30.5 42.1 947 12.7 42.1 94.8 1.1% 13.70 [-4.31, 23.27] SAM40012 2005 35.85 30.65 6 8.95 30.65 9 0.6% 26.90 [-4.76, 58.66] T. 3 Metray 1999 39.1 111 139 367 115 135 0.6% 26.30 [15.67, 34.88] Heterogeneity: Tau <sup>2</sup> = 11.49 (P < 0.0001) Heterogeneity: Tau <sup>2</sup> = 11.49 (P < 0.0001) Heterogeneity: Tau <sup>2</sup> = 11.49 (P < 0.0001) T. 44 17 17 16 3.0% 24.00 [-2.77, 60.77] Wollock 1996 46.5 86.5 45.7 16 104 251 2.2% 30.50 [15.51, 45.49] Murray 199 391 111 139 367 115 135 0.8% 24.00 [-2.77, 60.77] Wollock 1996 46.5 86.5 45.7 16 104 251 2.2% 30.50 [15.51, 45.49] Heterogeneity: Tau <sup>2</sup> = 1.16 (P = 0.03); l <sup>2</sup> = 49% Total (95% CI) 123 71.46 (P = 0.003); l <sup>2</sup> = 49% Total (95% CI) 71.57 16.69 (Ch <sup>2</sup> = 3.7.46, df = 24 (P = 0.003); l <sup>2</sup> = 49% Total (95% CI) 71.57 15.05 0.25 90 25 90 25 90 25 90 25 90 25 90 25 90 25 90 25 90 25 90 25 90 25 90 25 90 25 90 25 90		34.5	37.7	355	9.5	37.7	342	6.7%		-
Heterogeneity: Tau <sup>2</sup> = 49.96; Ch <sup>2</sup> = 17.29, df = 3 (P = 0.0006); P = 83% Test for overall effect: Z = 4.05 (P < 0.0001) 1.1.2 Medium dose ICS Baraniuk 1999 58 91.19 231 47 74.67 223 2.1% 11.00 [-4.31, 26.31] Eateman 2003 27.4 29.1 168 7.7 29.1 176 62.% 19.70 [13.65, 25.856] Condemi 1999 46.5 52.03 221 23.8 47.03 216 42% 22.70 [13.41, 31.99] Greening 1994 28 53 137 7 57 128 2.6% 21.00 (7.67, 34.33] Johansson 2001 43.5 42.9 176 32.5 42.9 173 4.4% 11.00 [2.00, 0.00] Toloransson 2001 43.5 42.9 176 32.5 42.9 173 4.4% 10.00 [2.00, 0.00] Ferening 1994 40.8 46.4 239 14.5 37.5 244 5.3% 26.30 [18.77, 33.83] Toloransson 2001 43.5 42.9 176 32.5 42.5 45.6% 11.50 [11.03, 25.17] Toloransson 2001 43.5 42.9 176 33.2 524 55.6% 11.50 [11.03, 25.17] Toloransson 2001 43.5 42.9 176 33.2 524 56.6% 11.50 [11.03, 25.17] Toloransson 2001 43.5 42.9 176 33.2 524 56.6% 11.50 [11.03, 25.17] Toloransson 2001 43.5 42.9 176 33.2 524 56.6% 11.50 [11.03, 25.17] Toloransson 2001 43.5 42.9 176 33.2 524 56.6% 11.50 [11.02, 20.00] Toloransson 2005 44.4 67.1 121 30.7 65.7 116 18.8% 13.70 [3.21, 30.61] SAM4003 2005 44.2 67.1 121 30.7 65.7 116 18.8% 13.70 [4.13, 23.27] SAM4003 2005 43.7 61.97 240 30 43.2 238 4.1% 13.70 [4.13, 23.27] SaMa0013 2005 43.7 61.97 240 30 43.2 238 4.1% 13.70 [4.13, 23.27] Heterogeneity: Tau <sup>2</sup> = 11.49 (P < 0.0001) 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] Tol 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [10.63, 34.88] Tol 30.3 12.1% 25.30 [10.53, 34.68] Tolorans 2000 [1.65, 34.68] Tolorans 2000 [1.65, 34.68] Tolorans 2000 [1.65, 13.6, 34.88] Tolorans 2000 [1.65, 13.6, 34.88] Tolorans 2000 [1.65, 13.6, 34.88] Tolorans 2000 [1.65, 13.6, 34.88] Tolorans 2000 [1.65, 13.6, 26.03] Tolorans 2000 [1.65, 13.6, 34.88] Tolorans 2000 [1.65, 13.6, 26.03] Tolorans 2000 [1.65, 13.6, 26.00001] Tol 2005 26 2.6 47.9 153 9.	SAM40036 2004	51.4	42.7	270	33.9	44.6	273	5.4%	17.50 [10.16, 24.84]	<del></del>
Test for overall effect: $Z = 4.05 (P < 0.0001)$ 1.1.2 Medium dose ICS Baraniuk 1999 58 91.19 231 47 74.67 223 2.1% 11.00 [-4.31, 26.31] Baraniuk 1999 46.5 52.03 221 23.8 47.03 216 4.2% 22.70 [13.41, 31.99] Greening 1994 46.5 52.03 221 23.8 47.03 216 4.2% 22.70 [13.41, 31.99] Greening 1994 46.5 52.03 221 23.8 47.03 216 4.2% 22.70 [13.41, 31.99] Greening 1994 46.4 239 14.5 37.5 244 5.3% 22.70 [13.41, 31.99] Greening 1994 0.8 46.4 239 14.5 37.5 244 5.3% 22.50 [15.67, 34.33] Johansson 2001 43.5 42.9 176 32.5 44.2 9 173 4.4% 11.00 [2.00, 20.00] Tollyme 2005 350.54 50 1834 339 50 926 8.0% 11.54 [7.7, 38.83] SAM30013 2005 44.4 67.1 121 30.7 65.7 116 1.8% 13.70 [-3.21, 30.61] SAM40120 2005 350.54 50 1834 339 50 926 8.0% 11.54 [7.59, 15.49] SAM40120 2005 350.55 6 8.895 30.65 9 0.6% 26.90 [-4.76, 58.56] Sicochiano 2004 32.9 42.1 947 12.7 42.1 943 8.1% 20.20 [16.40, 24.00] Subtotal (95% CI) 4723 3787 56.7% 17.93 [14.87, 20.99] Heterogeneity: Tau <sup>2</sup> = 11.69; Ch <sup>2</sup> = 22.48, df = 13 (P = 0.05); P = 42% Test for overall effect: Z = 11.49 (P < 0.0001) 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] Ind 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.62, 34.98] Mitchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.62, 34.98] Mitchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.62, 34.98] Mutchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.62, 34.98] Mutchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.62, 34.98] Mutchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.62, 34.98] Mutchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.62, 34.98] Mutchell 2003 37.7 17 14 17 17 16 30.0% 20.00 [7.81, 32.19] Wallm 2003 37 17 14 17 17 16 30% 20.00 [7.81, 32.19] Wallm 2003 37 17 14 17 17 16 100% 21.02.77, 50.77] Wallm 2005 46.5 86.5 487 16 104 251 2.2% Test for overall effect: Z = 9.12 (P < 0.0001) Total (95% CI) 124 = 0.00; Ch <sup>2</sup> = 3.74, d, df = 6 (P = 0.003);   <sup>2</sup> = 49% Test for overall effect: Z = 9.12 (P < 0.0001) -50 -25 0 25 0 25 0 0 25 0 0 25 0 0 25 0 0 25 0 0	Subtotal (95% CI)			1178			1164	24.2%	15.77 [8.13, 23.41]	•
1.1.2 Medium dose ICS         Baraniuk 1999       58       91.19       231       47       74.67       223       2.1%       11.00 [-4.31, 26.31]         Batema 2003       27.4       29.1       168       7.7       29.1       176       6.2%       19.70 [13.55, 25.85]         Greening 1999       46.5       52.03       221       23.8       47.03       216       4.2%       22.70 [13.41, 31.99]         Johanson 2001       43.5       42.9       176       32.5       44.9       11.00 [2.00, 20.00]         Greening 1999       40.8       46.4       239       14.5       37.5       244       5.3%       26.30 [18.77, 33.83]         Johanson 2001       43.5       42.9       176       32.5       18.10 [1.03, 25.17]          OByme 2005       350.54       50       18.34       339       50       92.6       6.0%       11.54 [7.59, 15.49]         SAM40032 2005       43.7       6.71       12.1       30.7       65.7       11.8       13.70 [2.31, 30.61]          SAM40032 2005       43.7       6.19.7       24.0       3.8       1%       20.20 [16.40, 24.00]          Stickolar 2005       3.7       5.2	eterogeneity: Tau <sup>2</sup> =	49.96; Chi <sup>2</sup> = 17	.29, df = 3 (P	= 0.00	06); I² = 83%					
Baraniuk 1999 58 91.19 231 47 74.67 223 2.1% 11.00 [4.31, 26.31] Batema 2003 27.4 29.1 168 7.7 29.1 176 6.2% 19.70 [13.55, 25.85] Condemi 1999 33 50.4 68 12.64 50.4 64 1.8% 20.36 [3.16, 37.56] Tenening 1999 46.5 52.03 221 23.8 47.03 216 4.2% 22.70 [13.41, 31.99] Tenening 1994 28 53 137 7 57 126 2.6% 21.00 76.7 34.33] Johansson 2001 43.5 42.9 176 32.5 42.9 173 4.4% 11.00 [2.00, 20.00] Kelsen 1999 40.8 46.4 239 14.5 37.5 244 5.3% 26.30 [18.77, 33.83] Johansson 2001 43.5 44.4 67.1 121 30.7 65.7 116 1.8% 13.70 [-3.21, 30.61] SAM30013 2005 44.4 67.1 121 30.7 65.7 116 1.8% 13.70 [-3.21, 30.61] SAM4003 2004 40 51.6 75 15.9 51.6 79 1.9% 24.10 [7.80, 40.40] SAM40120 2005 35.05.4 50 1834 339 50 926 8.0% 11.54 [7.59, 15.49] Testfor overall effect Z = 11.69; Chi <sup>2</sup> = 22.48, df = 13 (P = 0.05); I <sup>2</sup> = 42% Test for overall effect Z = 11.69; Chi <sup>2</sup> = 22.48, df = 13 (P = 0.05); I <sup>2</sup> = 42% Test for overall effect Z = 11.49 (P < 0.0001) 11.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] Test for overall effect Z = 11.49 (P < 0.0001) 11.1 319 367 115 135 0.8% 24.00 [-2.77, 50.77] Walin 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.54, 23.498] Witchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.54, 23.498] Test for overall effect Z = 11.49 (P < 0.0001) 11.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] Test for overall effect Z = 11.49 (P < 0.0001) 11.3 High dose ICS Bergmann 2004 52 76 170 36 62 38.43 298 4.5% 17.28 [8.53, 26.03] Test for overall effect Z = 11.49 (P < 0.0001) 11.1 319 367 115 135 0.8% 24.00 [-2.77, 50.77] Walin 2003 37 17 14 17 17 16 30.% 20.00 [7.81, 32.19] Witchell 2003 37 17 14 177 17 16 30.% 20.00 [7.81, 32.19] Welchell (95% Cl) 1234 1303 19.1% 21.78 [17.10, 26.46] Test for overall effect Z = 9.12 (P < 0.0001) Test for overall effect Z = 9.12 (P < 0.0001) Test for overall effect Z = 9.12 (P < 0.0001) Test for overall effect Z = 9.12 (P < 0.0001) Test for overall effect Z = 9.12 (P < 0.0001) Test for overall effect Z	est for overall effect:	Z = 4.05 (P < 0.0	0001)							
Baraniuk 1999 58 91.19 231 47 74.67 223 2.1% 11.00 [4.31, 26.31] Batema 2003 27.4 29.1 168 7.7 29.1 176 6.2% 19.70 [13.55, 25.85] Condemi 1999 33 50.4 68 12.64 50.4 64 1.8% 20.36 [3.16, 37.56] Greening 1999 46.5 52.03 221 23.8 47.03 216 4.2% 22.70 [13.41, 31.99] Greening 1994 28 53 137 7 57 126 2.6% 21.00 [7.67, 34.33] Johansson 2001 43.5 42.9 176 32.5 42.9 173 4.4% 11.00 [2.00, 20.00] Kelsen 1999 40.8 46.4 239 14.5 37.5 244 5.3% 26.30 [18.77, 33.83] Johansson 2001 43.5 42.9 176 32.5 42.9 173 4.4% 11.00 [2.00, 20.00] Kelsen 1999 40.8 46.4 239 14.5 37.5 244 5.3% 26.30 [18.77, 33.83] Johansson 2005 350.54 50 1834 339 50 926 8.0% 11.54 [7.59, 15.49] SAM30013 2005 44.4 67.1 121 30.7 65.7 116 1.8% 13.70 [3.21, 30.61] SAM4003 2004 40 51.6 75 15.9 51.6 79 1.9% 24.10 [7.80, 40.40] SAM40120 2005 35.85 30.665 6 8.95 30.65 9 0.6% 22.69 [4.76, 58.56] Sicchitano 2004 32.9 42.1 947 12.7 42.1 943 8.1% 20.20 [16.40, 24.00] Fletorogeneity: Tau <sup>2</sup> = 11.69; Chi <sup>2</sup> = 22.48, df = 13 (P = 0.05); l <sup>2</sup> = 42% Test for overall effect Z = 11.49 (P < 0.00001) 11.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] Johanson 2004 32.9 42.1 947 12.7 42.1 81 10: 24% 25.30 [15.62, 34.98] Mitchel 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.62, 34.98] Johanson 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] Johanson 2004 52 76 170 36 62 38.43 298 4.5% J72.8[ 53.26.03] Johanson 2004 52 76 170 36 23 342 298 4.5% J72.8[ 53.26.03] Johanson 2004 52 76 170 36 62 36.43 298 4.5% J72.8[ 53.26.03] Johanson 2004 52 76 170 36 62 37.5 52.00 [15.62, 34.98] Johanson 2004 52 76 170 36 62 37.5 52.00 [15.62, 34.98] Johanson 2004 52 76 170 36 62 37.5 52.00 [15.62, 34.98] Johanson 2004 52 76 170 36 62 38.43 298 4.5% J72.8[ 53.26.03] Johanson 2004 52 76 170 36 62 38.43 298 4.5% J72.8[ 53.26.03] Johanson 2004 32.9 4.5 9.75 52.0 0.5 12.2 50.8 30.65 J15.51, 45.44 J25.3 21.90 J15.51, 45.45 J2.5% J	.1.2 Medium dose l	cs								
Batema 2003 27.4 29.1 168 7.7 29.1 176 6.2% 19.70 13.65, 25.85 Bouros 1999 33 50.4 68 12.64 50.4 64 1.8% 20.36 [3.16, 37.56] Condemi 1999 46.5 52.03 221 23.8 47.03 216 4.2% 22.07 [13.41, 31.99] Greening 1994 28 53 137 7 57 126 2.6% 21.00 [7.67, 34.33] Johanson 2001 43.5 42.9 176 32.5 42.9 173 4.4% 11.00 [2.00, 20.00] Kelsen 1999 40.8 46.4 239 14.5 37.5 244 5.3% 26.30 [18.77, 33.83] Murray 1999 37.7 43.5 260 19.6 38.2 254 5.6% 18.10 [11.03, 25.17] TOByme 2005 350.54 50 1834 339 50 926 8.0% 11.54 [7.59] 54.9] SAM40031 2005 44.4 67.1 121 30.7 65.7 116 1.8% 13.70 [4.3, 22.1, 30.61] SAM4004 2004 40 51.6 75 15.9 51.6 79 1.9% 24.40 [7.8, 04.40] SAM4004 2004 32.9 42.1 947 12.7 42.1 943 8.1% 20.20 [16.40, 24.00] Sciechtiano 2004 32.9 42.1 947 12.7 42.1 943 8.1% 20.20 [16.40, 24.00] Sciechtiano 2004 32.9 42.1 947 12.7 42.1 943 8.1% 20.20 [16.40, 24.00] Fleterogeneity: Tau <sup>2</sup> = 11.69; Ch <sup>2</sup> = 22.48, df = 13 (P = 0.05); P = 42% Test for overall effect: Z = 11.49 (P < 0.00001) 11.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] Ind 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.63, 24.98] Mitchel 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.63, 24.98] Mitchel 2003 37.7 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Walin 2003 37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Walin 2003 37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Walin 2003 37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Walin 2003 37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Walin 2003 37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Walin 2003 37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Walin 2003 37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Heterogeneity: Tau <sup>2</sup> = 16.66; Ch <sup>2</sup> = 47.46, df = 24 (P = 0.003); P = 49% Total (95% Cl) 71 7135 6254 100.0% 18.24 [15.72, 20.76] +00000ck t1986 46.5 36.5 44.7 16 104 251 2.2% 30.50 [15.51, 15.45, 49] +00000ck t1986 46.5 44.7 44.6 df = 24 (P = 0.003); P = 49% Total (95% Cl) 71 7135 6254 100.0% 18.24 [15.72, 20.76] +00000ck 1960 46.00 10001			91 19	231	47	74 67	223	2 1%	11 00 [-4 31 26 31]	<u> </u>
Bouros 1999 33 504 68 12.64 50.4 64 1.8% 20.36 [3.16, 37.56] Condemi 1999 46.5 52.03 221 23.8 47.03 216 4.2% 22.70 [13.41, 31.99] Greening 1994 28 53 137 7 57 126 2.6% 21.00 [7.67, 34.33] Johansson 2001 43.5 42.9 176 32.5 42.9 173 4.4% 11.00 [2.00, 20.00] Kelsen 1999 40.8 46.4 239 14.5 37.5 244 5.3% 28.30 [18.77, 38.83] Winray 1999 37.7 43.5 260 19.6 38.2 254 5.6% 18.10 [11.03, 25.17] TOByme 2005 350.54 50 1834 339 50 926 8.0% 11.54 [7.59, 15.49] SAM30013 2005 44.4 67.1 121 30.7 65.7 116 1.8% 13.70 [-5.17, 30.61] SAM40120 2005 35.85 30.65 6 8.95 30.65 9 0.6% 26.90 [4.76, 58.56] Sacchtano 2004 32.9 42.1 947 12.7 42.1 943 8.1% 20.20 [16.00, 24.00] SLGA5021 2005 43.7 61.97 240 30 43.2 238 4.1% 13.70 [4.13, 23.27] Waltoral 09% (1) 4723 3787 56.7% 17.93 [14.87, 20.99] Heterogeneity: Tau <sup>2</sup> = 11.69; Chi <sup>2</sup> = 22.48, df = 13 (P = 0.05); P = 42% Test for overall effect Z = 11.49 (P < 0.00001) Hiterogeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); P = 49% Woolcock 1996 46.5 86.5 44.7 16 (P = 0.0001); P = 0.0001 Total (95% C1) 7135 624 100.0% 18.24 [15.72, 20.76] Heterogeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); P = 49% Total (95% C1) 7135 624 100.0% 18.24 [15.72, 20.76] Heterogeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); P = 49% Total (95% C1) 7135 624 100.0% 18.24 [15.72, 20.76] Heterogeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); P = 49% Total (95% C1) 7135 624 (P = 0.0001); P = 3.74, df = 6 (P = 0.003); P = 49% Total (95% C1) 7135 624 100.0% 18.24 [15.72, 20.76] Heterogeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); P = 49% Total (95% C1) 7135 624 100.0% 18.24 [15.72, 20.76] Heterogeneity: Tau <sup>2</sup> = 10.000 Chi <sup>2</sup> = 3.74, df = 6 (P = 0.003); P = 49% Total (95% C1) 7135 624 100.0% 18.24 [15.72, 20.76] Heterogeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); P = 49% Total (95% C1) 7135 725 726 725 727 Heterogeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); P = 49% Total (95% C1) 7135 726 725 70										
Condemi 1999 46.5 52.03 221 23.8 47.03 216 4.2% 22.70 [ $13.41, 31.99$ ] Greening 1994 28 53 137 7 57 126 2.6% 21.00 [ $7.67, 34.33$ ] Johansson 2001 43.5 42.9 176 32.5 42.9 173 4.4% 11.00 [ $2.00, 20.00$ ] Kelsen 1999 40.8 46.4 239 14.5 37.5 244 5.3% 26.30 [ $18.77, 33.83$ ] Murray 1999 37.7 43.5 260 19.6 38.2 254 5.6% 18.10 [ $11.03, 25.17$ ] O'Byme 2005 350.54 50 1834 339 50 926 8.0% 11.54 [ $7.59, 15.49$ ] SAM30013 2005 44.4 67.1 121 30.7 65.7 116 1.8% 13.70 [ $-3.21, 30.61$ ] SAM4002 2005 38.65 6 8.95 30.65 6 8.95 30.65 9 0.6% 26.90 [ $-4.76, 88.56$ ] Sickohiano 2004 32.9 42.1 947 12.7 42.1 943 8.1% 20.20 [ $16.40, 24.00$ ] Sickohiano 2004 32.9 42.1 947 12.7 42.1 943 8.1% 20.20 [ $16.40, 24.00$ ] Sickohiano 2004 32.9 42.1 947 12.7 42.1 943 8.1% 20.20 [ $16.40, 24.00$ ] Subtotal (95% CI) 47 61.97 240 30 43.2 238 4.1% 13.70 [ $14.37, 20.99$ ] Heterogeneity: Tau" = 11.69; Chi" = 22.48, df = 13 (P = 0.05); I" = 42% Test for overall effect: Z = 11.49 (P < 0.00001) Heterogeneity: Tau" = 0.0; Chi" = 3.74, df = 6 (P = 0.71); I" = 0.9% Subtotal (95% CI) 106 37 7 7 14 17 17 16 3.0% 20.00 [ $1.96, 39.65$ ] Wolcock 1996 46.5 86.5 487 16 104 251 2.2% 30.50 [ $15.61, 32.19$ ] Wolcock 1996 46.5 86.5 487 16 104 251 2.2% 30.50 [ $15.61, 32.19$ ] Wolcock 1996 46.5 86.5 487 16 104 251 2.2% 30.50 [ $15.145.49$ ] Subtotal (95% CI) 713 5 6254 100.0% 18.24 [ $15.72, 20.76$ ] Heterogeneity: Tau" = 0.0; Chi" = 3.74, df = 6 (P = 0.71); I" = 0% Test for overall effect: Z = 9.12 (P < 0.00001) Total (95% CI) 7135 6254 100.0% 18.24 [ $15.72, 20.76$ ] Heterogeneity: Tau" = 16.60; Chi" = 47.46, df = 24 (P = 0.003); I" = 49% Total (95% CI) 7135 6254 100.0% 18.24 [ $15.72, 20.76$ ] -50 - 25 0 25 50										
Greening 1994 28 53 137 7 57 126 2.6% 21.00 [7.67, 34.33] Johansson 2001 43.5 42.9 176 32.5 42.9 173 4.4% 11.00 [2.00, 20.00] Kelsen 1999 40.8 46.4 239 14.5 37.5 244 5.6% 18.10 [11.03, 25.17] S7.7 43.5 260 19.6 38.2 254 5.6% 18.10 [11.03, 25.17] SAM30013 2005 44.4 67.1 121 30.7 65.7 116 1.8% 13.70 [-3.21, 30.61] SAM40123 2005 44.4 67.1 121 30.7 65.7 116 1.8% 25.00 [1.640, 24.00] SAM40120 2005 35.85 30.65 6 8.95 30.65 9 0.6% 25.00 [1.640, 24.00] Scienchiano 2004 32.9 42.1 947 12.7 42.1 943 8.1% 20.20 [16.40, 24.00] Scienchiano 2004 32.9 42.1 947 12.7 42.1 943 8.1% 20.20 [16.40, 24.00] Subtotal (95% Cl) 4723 3787 56.7% 17.39 [14.87, 20.99] Heterogeneity: Tau <sup>2</sup> = 11.69; Chi <sup>2</sup> = 22.48, df = 13 ( $P = 0.05$ ); $P = 42\%$ Test for overall effect: Z = 11.49 ( $P < 0.00001$ ) Hill 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.62, 34.98] Mitchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [10.95, 39.65] Vaolocock 1996 46.5 86.5 487 16 104 251 2.2% 10.00 [7.81, 32.19] Wallin 2003 37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Wallin 2003 37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Woolcock 1996 46.5 86.5 487 16 104 251 2.2% 10.00 [1.02, 30.50 [15.51, 45.49] Subtotal (95% Cl) 1224 1234 1303 19.1% 21.78 [17.10, 26.46] Heterogeneity: Tau <sup>2</sup> = 10.69; Chi <sup>2</sup> = 3.74, df = 6 ( $P = 0.71$ ); $P = 0\%$ Test for overall effect: Z = 9.12 ( $P < 0.00001$ )										
Johansson 2001 43.5 42.9 176 32.5 42.9 173 4.4% 11.00 [2.00, 20.00] Kelsen 1999 40.8 46.4 239 14.5 37.5 244 5.3% 26.30 [18.77, 33.83] Wurray 1999 37.7 45.5 260 19.6 38.2 254 5.6% 18.10 [11.03, 25.17] O'Byme 2005 350.54 50 1834 339 50 926 8.0% 11.54 [7.59, 15.49] SAM30013 2005 44.4 67.1 121 30.7 65.7 116 1.8% 13.70 [-3.21, 30.61] SAM40021 2005 35.85 30.65 6 8.95 30.65 9 0.6% 26.90 [-4.76, 58.56] Scicchitano 2004 32.9 42.1 947 12.7 42.1 943 8.1% 20.20 [16.40, 24.00] SciGA5021 2005 43.7 61.97 240 30 43.2 238 4.1% 13.70 [4.13, 23.27] Subtotal (95% CI) 4723 3787 56.7% 17.93 [14.87, 20.99] Heterogeneity: Tau <sup>2</sup> = 11.69; Chi <sup>2</sup> = 22.48, df = 13 (P = 0.05); l <sup>2</sup> = 42% Test for overall effect: Z = 11.49 (P < 0.00001) 1.1.3 High dose ICS SLGQ97 2005 26.9 47.9 153 9.62 38.43 298 4.5% 17.28 [8.53, 26.03] Van Noord 1999 391 111 139 367 115 135 0.8% 24.00 [-2.77, 50.77] Woolcock 1996 46.5 86.5 487 16 104 251 2.2% 30.50 [15.51, 45.49] Subtotal (95% CI) 122 F1.34, df = 6 (P = 0.71); l <sup>2</sup> = 0% Test for overall effect: Z = 9.12 (P < 0.00001) 1.1.3 High dose ICS Lectorgeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); l <sup>2</sup> = 49% Total (95% CI) 7135 6254 100.0% 18.24 [15.72, 20.76] -50 - 25 0 25 50										<del></del>
Kelsen 1999 40.8 46.4 239 14.5 37.5 244 5.3% 26.30 [18.77, 33.83] Murray 1999 37.7 43.5 260 19.6 38.2 254 5.6% 13.10 [11.03, 25.17] O'Byme 2005 350.54 50 1834 339 50 926 8.0% 11.54 [7.59, 15.49] SAM30013 2005 44.4 67.1 121 30.7 65.7 116 1.8% 13.70 [-3.21, 30.61] SAM40120 2005 35.85 30.65 6 8.95 30.65 9 0.6% 26.90 [-4.76, 85.66] Scicchitano 2004 32.9 42.1 947 12.7 42.1 943 8.1% 20.20 [16.40, 24.00] SLGASO21 2005 43.7 61.97 240 30 43.2 238 4.1% 13.70 [-4.13, 23.27] Subtotal (95% Cl) 4723 3787 56.7% 17.93 [14.87, 20.99] Heterogeneity: Tau <sup>2</sup> = 11.69; Chi <sup>2</sup> = 22.48, df = 13 (P = 0.05); I <sup>2</sup> = 42% Test for overall effect: Z = 11.49 (P < 0.0001) 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] Ind 2003 42 52.3 171 16.7 52.3 325 4.0% 25.30 [15.62, 34.98] Mitchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.62, 34.98] Mitchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.62, 34.98] Tau Nord 1999 391 111 139 367 115 135 0.8% 24.00 [-2.77, 50.77] Wallin 2003 37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Woolcock 1996 46.5 86.5 487 16 104 251 2.2% 30.50 [15.51, 45.49] Subtotal (95% Cl) 1234 1303 19.1% 21.78 [17.10, 26.46] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.74, df = 6 (P = 0.77); I <sup>2</sup> = 0% Test for overall effect: Z = 9.12 (P < 0.00001) Total (95% Cl) 7135 6254 100.0% 18.24 [15.72, 20.76] + 000001	•									
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$										
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$										<del>-</del>
SAM30013 2005 44.4 67.1 121 30.7 65.7 116 1.8% 13.70 [ $3.21$ , 30.61] SAM401034 2004 40 51.6 75 15.9 51.6 79 1.9% 24.10 [ $7.80$ , 40.40] SAM40120 2005 35.85 30.65 6 8.95 30.65 9 0.6% 26.90 [ $4.76$ , 58.66] Scicchitano 2004 32.9 42.1 947 12.7 42.1 943 8.1% 20.20 [ $16.40$ , 24.00] SLGAS021 2005 43.7 61.97 240 30 43.2 238 4.1% 13.70 [ $4.13$ , 23.27] Subtotal ( $95\%$ CI) 47.23 3787 56.7% 17.93 [ $14.87$ , 20.99] Heterogeneity: Tau <sup>2</sup> = 11.69; Chi <sup>2</sup> = 22.48, df = 13 (P = 0.05); I <sup>2</sup> = 42% Test for overall effect: $Z = 11.49$ (P < 0.00001) 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [ $1.09$ , 30.91] Ind 2003 42 52.3 171 16.7 52.3 325 4.0% 25.30 [ $15.62$ , 34.98] Mitchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [ $10.95$ , 39.65] SLGQP 2005 26.9 47.9 153 9.62 38.43 298 4.5% 17.28 [ $8.53$ , 26.03] van Noord 1999 391 111 139 367 115 135 0.8% 24.00 [ $-2.77$ , 50.77] Wallin 2003 37 17 14 17 17 16 3.0% 20.00 [ $7.81$ , 32.19] Woolcock 1996 46.5 86.5 487 16 104 251 2.2% 30.50 [ $15.51$ , 45.49] Subtotal ( $95\%$ CI) 7135 624 100.0% 18.24 [ $15.72$ , 20.76] + Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.74, df = 6 (P = 0.71); I <sup>2</sup> = 0% Test for overall effect: $Z = 9.12$ (P < 0.00001) Total ( $95\%$ CI) 7135 624 100.0% 18.24 [ $15.72$ , 20.76] + Go 25 0 25 50										-
SAM40034 2004 40 51.6 75 15.9 51.6 79 1.9% 24.10 [7.80, 40.40] SAM40120 2005 35.85 30.65 6 8.95 30.65 9 0.6% 26.90 [-4.76, 58.56] Scicchitano 2004 32.9 42.1 947 12.7 42.1 943 8.1% 20.20 [16.40, 24.00] SLGA5021 2005 43.7 61.97 240 30 43.2 238 4.1% 13.70 [4.13, 23.27] Subtotal (95% Cl) 4723 3787 56.7% 17.93 [14.87, 20.99] 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] 1.1.3 High dose ICS Bergmann 2004 52 76 170 12.2 51.8 101 2.4% 25.30 [10.95, 30.65] 1.1.3 High dose ICS Bergmann 2004 52 2.2.4% 17.28 [8.53, 26.03] 1.1.4 High dose ICS Bergmann 2005 3.37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] 1.1.4 High dose ICS Bubtotal (95% Cl) 12 124 18 (B C O - 0.71); I <sup>2</sup> = 0% Test for overall effect: Z = 9.12 (P < 0.00001) 1.2.4 (95% Cl) 12 12 4 9 (B C O 0.0001) 12 4 4 (B C O 0.0001) 50 -25 0 25 50										<u> </u>
SAM40120 2005 35.85 30.65 6 8.95 30.65 9 0.6% 26.90 [4.76, 58.56] Scicchitano 2004 32.9 42.1 947 12.7 42.1 943 8.1% 20.20 [16.40, 24.00] SLGA5021 2005 43.7 61.97 240 30 43.2 32.8 4.1% 13.70 [4.13, 23.27] Subtotal (95% CI) 4723 3787 56.7% 17.93 [14.87, 20.99] Heterogeneity: Tau <sup>2</sup> = 11.69; Chi <sup>2</sup> = 22.48, df = 13 (P = 0.05); I <sup>2</sup> = 42% Test for overall effect: Z = 11.49 (P < 0.00001) 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] Ind 2003 42 52.3 171 16.7 52.3 325 4.0% 25.30 [15.62, 34.98] Mitchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [10.95, 39.65] SLGQ97 2005 26.9 47.9 153 9.62 38.43 298 4.5% 17.28 [8.53, 26.03] van Noord 1999 391 111 139 367 115 135 0.8% 24.00 [2.77, 50.77] Wallin 2003 37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Woolcock 1996 46.5 86.5 487 16 104 251 2.2% 30.50 [15.51, 45.49] Subtotal (95% CI) 1234 130/3 19.1% 21.78 [17.10, 26.46] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.74, df = 6 (P = 0.71); I <sup>2</sup> = 0% Test for overall effect: Z = 9.12 (P < 0.00001) Total (95% CI) 7135 6254 100.0% 18.24 [15.72, 20.76] + eterogeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); I <sup>2</sup> = 49%										<u> </u>
Scicchitano 2004 32.9 42.1 947 12.7 42.1 943 8.1% 20.20 [16.40, 24.00] SLGASO21 2005 43.7 61.97 240 30 43.2 238 4.1% 13.70 [4.13, 23.27] SLGASO21 2005 43.7 61.97 240 30 43.2 238 4.1% 13.70 [4.13, 23.27] Heterogeneity: Tau <sup>2</sup> = 11.69; Chi <sup>2</sup> = 22.48, df = 13 (P = 0.05); l <sup>2</sup> = 42% Test for overall effect: $Z = 11.49$ (P < 0.00001) 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] ind 2003 42 52.3 171 16.7 52.3 325 4.0% 25.30 [15.62, 34.98] Mitchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [10.95, 39.65] SLGQP 2005 26.9 47.9 153 9.62 38.43 298 4.5% 17.28 [8.53, 26.03] van Noord 1999 391 111 139 367 115 135 0.8% 24.00 [-2.77, 50.77] Wollicock 1996 46.5 86.5 487 16 104 251 2.2% 30.50 [15.51, 45.49] Subtotal (95% CI) 1234 1303 19.1% 21.78 [17.10, 26.46] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.74, df = 6 (P = 0.71); l <sup>2</sup> = 0% Test for overall effect: $Z = 9.12$ (P < 0.00001) Total (95% CI) 713 6254 100.0% 18.24 [15.72, 20.76] -50 -25 0 25 50										
SLGA5021 2005 43.7 61.97 240 30 43.2 238 4.1% 13.70 [4.13, 23.27] Subtotal (95% Cl) 4723 3787 56.7% 17.93 [14.87, 20.99] Heterogeneity: Tau <sup>2</sup> = 11.69; Chi <sup>2</sup> = 22.48, df = 13 (P = 0.05); l <sup>2</sup> = 42% Test for overall effect: Z = 11.49 (P < 0.00001) 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] Ind 2003 42 52.3 171 16.7 52.3 325 4.0% 25.30 [15.62, 34.98] Mitchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [10.95, 39.65] SLGQ97 2005 26.9 47.9 153 9.62 38.43 298 4.5% 17.28 [8.53, 26.03] Vallin 2003 37 17 14 17 17 16 3.0% 24.00 [-2.77, 50.77] Wallin 2003 37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Woolcock 1996 46.5 86.5 487 16 104 251 2.2% 30.50 [15.51, 45.49] Subtotal (95% Cl) 1234 1303 19.1% 21.78 [17.10, 26.46] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.74, df = 6 (P = 0.71); l <sup>2</sup> = 0% Test for overall effect: Z = 9.12 (P < 0.00001) Total (95% Cl) 7135 624 100.0% 18.24 [15.72, 20.76] 										-
Subtotal (95% CI) 4723 3787 56.7% 17.93 [14.87, 20.99] Heterogeneity: Tau <sup>2</sup> = 11.69; Chi <sup>2</sup> = 22.48, df = 13 (P = 0.05); I <sup>2</sup> = 42% Test for overall effect: Z = 11.49 (P < 0.00001) 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] Ind 2003 42 52.3 171 16.7 52.3 325 4.0% 25.30 [15.62, 34.98] Mitchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.62, 34.98] Mitchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.62, 34.98] Mitchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [15.62, 34.98] Wallin 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [10.95, 39.65] SLGQ97 2005 26.9 47.9 153 9.62 38.43 298 4.5% 17.28 [8.53, 26.03] wan Noord 1999 391 111 139 367 115 135 0.8% 24.00 [2.77, 50.77] Wallin 2003 37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Woolcock 1996 46.5 86.5 487 16 104 251 2.2% 30.50 [15.51, 45.49] Subtotal (95% CI) 1224 1303 19.1% 21.78 [17.10, 26.46] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.74, df = 6 (P = 0.71); I <sup>2</sup> = 0% Test for overall effect: Z = 9.12 (P < 0.00001) Total (95% CI) 7135 6254 100.0% 18.24 [15.72, 20.76] + $\frac{-50 - 25 0 25 50}{-50 25 50}$										
Heterogeneity: Tau <sup>2</sup> = 11.69; Chi <sup>2</sup> = 22.48, df = 13 (P = 0.05); l <sup>2</sup> = 42% Test for overall effect: Z = 11.49 (P < 0.00001) 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] Ind 2003 42 52.3 171 16.7 52.3 325 4.0% 25.30 [15.62, 34.98] Mitchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [10.95, 39.65] SLGQ97 2005 26.9 47.9 153 9.62 38.43 298 4.5% 17.28 [8.53, 26.03] van Noord 1999 391 111 139 367 115 135 0.8% 24.00 [-2.77, 50.77] Wallin 2003 37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Woolcock 1996 46.5 86.5 487 16 104 251 2.2% 30.50 [15.51, 45.49] Subtotal (95% Cl) 1224 1303 19.1% 21.78 [17.10, 26.46] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.74, df = 6 (P = 0.71); l <sup>2</sup> = 0% Test for overall effect: Z = 9.12 (P < 0.00001) Total (95% Cl) 7135 6254 100.0% 18.24 [15.72, 20.76] -50 -25 0 25 50		43.7	01.57		50	45.2				•
Test for overall effect: $Z = 11.49 (P < 0.00001)$ 1.1.3 High dose ICS Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] Ind 2003 42 52.3 171 16.7 52.3 325 4.0% 25.30 [15.62, 34.98] Mitchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [10.95, 39.65] Van Noord 1999 391 111 139 367 115 135 0.8% 24.00 [-2.77, 50.77] Wallin 2003 37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Woolcock 1996 46.5 86.5 487 16 104 251 2.2% 30.50 [15.51, 45.49] Subtotal (95% Cl) 1234 1303 19.1% 21.78 [17.10, 26.46] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.74, df = 6 (P = 0.71); l <sup>2</sup> = 0% Test for overall effect: $Z = 9.12 (P < 0.0001)$ Total (95% Cl) 7135 6254 100.0% 18.24 [15.72, 20.76] Heterogeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); l <sup>2</sup> = 49%		11.69: Chi <sup>2</sup> = 22	.48. df = 13 (	P = 0.0	5): l <sup>2</sup> = 42%				- / -	
Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] Ind 2003 42 52.3 171 16.7 52.3 325 4.0% 25.30 [15.62, 34.98] Mitchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [10.95, 39.65] SLGQ97 2005 26.9 47.9 153 9.62 38.43 298 4.5% 17.28 [8.53, 26.03] van Noord 1999 391 111 139 367 115 135 0.8% 24.00 [-2.77, 50.77] Wallin 2003 37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Woolcock 1996 46.5 86.5 487 16 104 251 2.2% 30.50 [15.51, 45.49] Subtotal (95% Cl) 1234 1303 19.1% 21.78 [17.10, 26.46] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.74, df = 6 (P = 0.71); l <sup>2</sup> = 0% Test for overall effect: Z = 9.12 (P < 0.0001) Total (95% Cl) 7135 6254 100.0% 18.24 [15.72, 20.76] Heterogeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); l <sup>2</sup> = 49%	• •				-,,:					
Bergmann 2004 52 76 170 36 65 177 2.2% 16.00 [1.09, 30.91] Ind 2003 42 52.3 171 16.7 52.3 325 4.0% 25.30 [15.62, 34.98] Mitchell 2003 37.5 52 100 12.2 51.8 101 2.4% 25.30 [10.95, 39.65] SLGQ97 2005 26.9 47.9 153 9.62 38.43 298 4.5% 17.28 [8.53, 26.03] van Noord 1999 391 111 139 367 115 135 0.8% 24.00 [-2.77, 50.77] Wallin 2003 37 17 14 17 17 16 3.0% 20.00 [7.81, 32.19] Woolcock 1996 46.5 86.5 487 16 104 251 2.2% 30.50 [15.51, 45.49] Subtotal (95% Cl) 1234 1303 19.1% 21.78 [17.10, 26.46] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.74, df = 6 (P = 0.71); l <sup>2</sup> = 0% Test for overall effect: Z = 9.12 (P < 0.0001) Total (95% Cl) 7135 6254 100.0% 18.24 [15.72, 20.76] Heterogeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); l <sup>2</sup> = 49%	.1.3 High dose ICS									
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	-	52	76	170	36	65	177	2.2%	16.00 [1.09, 30.91]	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	nd 2003	42	52.3	171	16.7	52.3	325	4.0%	25.30 [15.62, 34.98]	
van Noord 1999       391       111       139       367       115       135       0.8%       24.00 [2.77, 50.77]         Wallin 2003       37       17       14       17       17       16       3.0%       20.00 [7.81, 32.19]         Woolcock 1996       46.5       86.5       487       16       104       251       2.2%       30.50 [15.51, 45.49]         Subtotal (95% CI)       1234       1303       19.1%       21.78 [17.10, 26.46]         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.74, df = 6 (P = 0.71); l <sup>2</sup> = 0%       6254       100.0%       18.24 [15.72, 20.76]         Total (95% CI)       7135       6254       100.0%       18.24 [15.72, 20.76]	/litchell 2003	37.5	52	100	12.2	51.8	101	2.4%	25.30 [10.95, 39.65]	——
Wallin 2003 37 17 14 17 17 16 $3.0\%$ 20.00 [7.81, 32.19] Woolcock 1996 46.5 86.5 487 16 104 251 2.2% $30.50$ [15.51, 45.49] Subtotal (95% Cl) 1234 1303 19.1% 21.78 [17.10, 26.46] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.74, df = 6 (P = 0.71); l <sup>2</sup> = 0% Test for overall effect: Z = 9.12 (P < 0.00001) Total (95% Cl) 7135 6254 100.0% 18.24 [15.72, 20.76] Heterogeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); l <sup>2</sup> = 49% Test for overall effect: 2 = 14 149 (B < 0.0001)	SLGQ97 2005	26.9	47.9	153	9.62	38.43	298	4.5%	17.28 [8.53, 26.03]	
Woolcock 1996 46.5 86.5 487 16 104 251 2.2% $30.50$ [15.51, 45.49] Subtotal (95% CI) 1234 1303 19.1% 21.78 [17.10, 26.46] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.74, df = 6 (P = 0.71); l <sup>2</sup> = 0% Test for overall effect: Z = 9.12 (P < 0.00001) Total (95% CI) 7135 6254 100.0% 18.24 [15.72, 20.76] Heterogeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); l <sup>2</sup> = 49% Test for overall effect: Z = 14 19 (P < 0.0001)	an Noord 1999	391	111	139	367	115	135	0.8%	24.00 [-2.77, 50.77]	<u> </u>
Subtotal (95% CI)       1234       1303       19.1%       21.78 $[17.10, 26.46]$ Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.74, df = 6 (P = 0.71); l <sup>2</sup> = 0%       Test for overall effect: Z = 9.12 (P < 0.00001)	Vallin 2003	37	17	14	17	17	16	3.0%	20.00 [7.81, 32.19]	<del></del>
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.74, df = 6 (P = 0.71); l <sup>2</sup> = 0% Test for overall effect: Z = 9.12 (P < 0.00001) Total (95% Cl) 7135 6254 100.0% 18.24 [15.72, 20.76] Heterogeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); l <sup>2</sup> = 49% Test for overall effect: Z = 14 14 (P, 0.00001) -50 -25 0 25 50	Voolcock 1996	46.5	86.5	487	16	104	251	2.2%	30.50 [15.51, 45.49]	
Test for overall effect: Z = 9.12 (P < 0.00001) Total (95% Cl) 7135 6254 100.0% 18.24 [15.72, 20.76] Heterogeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); l <sup>2</sup> = 49% Tot for porcent of fort Z = 14 19 (P < 0.00001) -50 -25 0 25 50	Subtotal (95% CI)			1234			1303	19.1%	21.78 [17.10, 26.46]	•
Heterogeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); l <sup>2</sup> = 49% -50 -25 0 25 50				0.71); I	<sup>2</sup> = 0%					
Heterogeneity: Tau <sup>2</sup> = 16.69; Chi <sup>2</sup> = 47.46, df = 24 (P = 0.003); l <sup>2</sup> = 49% -50 -25 0 25 50	otal (95% CI)			7135			6254	100.0%	18.24 [15.72, 20.76]	•
Tot for overall effect: $7 = 14.18$ (B < 0.00001) $-50 - 25 = 0.25 = 50$	. ,	16 69 <sup>.</sup> Chi <sup>2</sup> = 47	46 df = 24 (		03): l <sup>2</sup> = 49%					
				- 0.0	00,1 - 40/0					-50 -25 0 25 50 Favours ICS Favours LABA

A subgroup analysis based on comparison ICS indicated a clinically important difference for the high dose comparison (WMD = 21.79; 95% CI: 17.10, 26.46). The low and medium dose comparisons did not indicate clinically important differences between treatments.

Three trials<sup>79,101,124</sup> involving 710 participants (LABA/ICS = 352, ICS = 358) receiving either LABA/ICS combination or higher-dose ICS monotherapy at run-in provided data for a metaanalysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on PEF AM (L/min) (Figure 31). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 17.85; 95% CI: 2.09 to 33.61;  $I^2 = 71\%$ ). The difference does not meet the a priori criteria for clinical importance (MCID = 18.79 L/min); however, due to lack of precision clinical equivalence (MCID = ±18.79 L/min) cannot be claimed.

A subgroup analysis based on comparison ICS dose failed to indicate a statistically significant difference between treatments for the low (WMD = 3.90; 95% CI: -12.18 to 19.98) and medium (WMD = 18.60; 95% CI: -2.33 to 39.53) dose comparisons. In addition the precision of the confidence intervals suggests that the difference is not clinically important. The pooled result for the medium dose comparison identified a statistically significant and clinically important difference between the treatments (WMD = 28.00; 95% CI: 19.45 to 36.55).

at baseline)									
	LAE	BA/ICS			CS			Mean Difference	Mean Difference
Study or Subgroup	Mean [L/min]	SD [L/min]	Total	Mean [L/min]	SD [L/min]	Total	Weight	IV, Random, 95% CI [L/min]	IV, Random, 95% CI [L/min]
1.1.1 Low dose ICS									
Lemanske 2001	44.7	49.9	74	40.8	49.9	74	32.0%	3.90 [-12.18, 19.98]	
Subtotal (95% CI)			74			74	32.0%	3.90 [-12.18, 19.98]	
Heterogeneity: Not appli	cable								
Test for overall effect: Z	= 0.48 (P = 0.6	3)							
1.1.2 Medium dose ICS	5								
SAS30002 2008	367.5	93	148	348.9	91.9	152	26.0%	18.60 [-2.33, 39.53]	+
Subtotal (95% CI)			148			152	26.0%	18.60 [-2.33, 39.53]	
Heterogeneity: Not appli	cable								
Test for overall effect: Z	= 1.74 (P = 0.0	8)							
1.1.3 High dose ICS									
Peters 2008	33.61	35.12	130	5.61	35.47	132	42.0%	28.00 [19.45, 36.55]	
Subtotal (95% CI)			130			132	42.0%	28.00 [19.45, 36.55]	•
Heterogeneity: Not appli	cable								
Test for overall effect: Z	= 6.42 (P < 0.0	0001)							
Total (95% CI)			352			358	100.0%	17.85 [2.09, 33.61]	
Heterogeneity: Tau <sup>2</sup> = 13	34.86; Chi <sup>2</sup> = 6.	86, df = 2 (P	= 0.03	); l² = 71%				-	<u> </u>
Test for overall effect: Z	= 2.22 (P = 0.0	3)							-20 -10 0 10 20 Favours ICS Favours LABA/I
		,							Favours ICS Favours LABA/I

**Figure 31:** The effect of LABA/ICS versus ICS monotherapy on PEF AM (mixed LABA/ICS use at baseline)

**PEF PM:** Twenty three trials<sup>53,65,66,76,104-119,122,125,126</sup> involving 12,510 participants (LABA/ICS = 6,685, ICS = 5,825) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with higher-dose ICS monotherapy on PEF PM (L/min) (Figure 32). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 15.24; 95% CI: 13.19 to 17.30; I<sup>2</sup> = 31%). The precision of the confidence interval, however, suggests that the two treatments are clinically equivalent (MCID =  $\pm 18.79$  L/min).

J	LA	BA/ICS			ICS			Mean Difference	Mean Difference
Study or Subgroup			Total			Total	Weight	IV, Random, 95% CI [L/min]	IV, Random, 95% CI [L/min]
.2.1 Low dose ICS	· · ·							· · •	
alloo 2003	13.7	30.3	230	4.2	30.3	237	7.5%	9.50 [4.00, 15.00]	-
Rabe 2006	25.4	37.05	355	6.6	37.05	342	7.5%	18.80 [13.30, 24.30]	-
SAM40036 2004	51.4	38.95	270	40.5	38.95	273	6.1%	10.90 [4.35, 17.45]	
Subtotal (95% CI)	01.4	00.00	855	40.0	00.00	852	21.1%	13.15 [7.23, 19.07]	•
Heterogeneity: Tau <sup>2</sup> =	= 18.52: Chi <sup>2</sup> = 6.1	19. df = 2 (P =	= 0.05):	$l^2 = 68\%$					
Test for overall effect			,,						
I.2.2 Medium dose I	cs								
Baraniuk 1999	44	75.99	231	38	59.73	223	2.3%	6.00 [-6.55, 18.55]	
Bateman 2003	24	28.4	168	6.8	28.4	176	6.8%	17.20 [11.20, 23.20]	<del></del>
Bouros 1999	30	48	68	13	48	64	1.4%	17.00 [0.62, 33.38]	
Condemi 1999	38.2	52.03	221	21.2	48.5	216	3.7%	17.00 [7.57, 26.43]	<del></del>
Greening 1994	15	49	135	-4	55	126	2.3%	19.00 [6.33, 31.67]	—
Johansson 2001	43.8	40.5	176	32.3	40.5	173	4.3%	11.50 [3.00, 20.00]	
Kelsen 1999	28.9	41.7	239	11.3	35.9	244	5.7%	17.60 [10.65, 24.55]	<del></del>
Aurray 1999	27.4	35.5	260	14.6	35.1	254	6.7%	12.80 [6.70, 18.90]	
D'Byrne 2005	354.55	50	1834	345	50	926	10.1%	9.55 [5.60, 13.50]	-
SAM30013 2005	41.8	63.8	121	24.3	62.47	116	1.5%	17.50 [1.42, 33.58]	
SAM40034 2004	39.2	43.5	75	15.9	43.5	79	2.0%	23.30 [9.55, 37.05]	— <del>,</del>
SAM40120 2005	15	28	6	-9	20	9	0.6%	24.00 [-1.94, 49.94]	
Scicchitano 2004	20.6	39.4	947	6.6	39.4	943	10.9%	14.00 [10.45, 17.55]	-
SLGA5021 2005	36.3	54.22	240	21.8	46.28	238	3.9%	14.50 [5.47, 23.53]	<del></del>
Subtotal (95% CI)			4721			3787	62.0%	13.72 [11.84, 15.60]	•
-leterogeneity: Tau <sup>2</sup> =	= 0.00; Chi <sup>2</sup> = 12.5	59, df = 13 (P	= 0.48	); I <sup>2</sup> = 0%					
Test for overall effect				,,,					
I.2.3 High dose ICS									
Bergmann 2004	46	73	170	29	65	177	1.8%	17.00 [2.44, 31.56]	
nd 2003	31.1	52.3	171	12.4	52.3	325	3.5%	18.70 [9.02, 28.38]	
Vitchell 2003	21	38	100	4	38	101	3.1%	17.00 [6.49, 27.51]	
SLGQ97 2005	42.1	42.6	167	16.69	36.8	316	5.0%	25.41 [17.78, 33.04]	
Wallin 2003	27	27	14	3	27	16	1.1%	24.00 [4.63, 43.37]	
Voolcock 1996	31	80	487	7	80	251	2.4%	24.00 [11.82, 36.18]	<u> </u>
Subtotal (95% CI)			1109			1186	16.9%	21.48 [17.05, 25.90]	◆
-leterogeneity: Tau <sup>2</sup> =	= 0.00; Chi <sup>2</sup> = 2.63	3, df = 5 (P =	0.76); I	<sup>2</sup> = 0%					
Test for overall effect:	Z = 9.51 (P < 0.0	00001)							
Fotal (95% CI)			6685			5825	100.0%	15.24 [13.19, 17.30]	•
Heterogeneity: Tau <sup>2</sup> =	= 6.83; Chi <sup>2</sup> = 32.7	10, df = 22 (P	= 0.08	); I² = 31%				-	-50 -25 0 25 50
Test for overall effect:	Z = 14.53 (P < 0	.00001)							-50 -25 0 25 50 Favours ICS Favours LABA
est for subgroup diff			= 0.0	05), l <sup>2</sup> = 81.3%					Tavouisios Favouis LAB/

#### Figure 32: The effect of LABA/ICS versus ICS monotherapy on PEF PM

A subgroup analysis based on comparison ICS dose failed to demonstrate a clinically important difference among the low (WMD = 13.15; 95% CI: 7.23 to 19.07;  $I^2 = 68\%$ ) and medium (WMD = 13.72; 95% CI: 11.84 to 15.60;  $I^2 = 0\%$ ) dose comparisons. There was a statistically significant difference favouring LABA/ICS for the high dose (WMD = 21.48; 95% CI: 17.05 to 25.90;  $I^2 = 0\%$ ) comparison that met the a priori criteria for clinical importance (MCID = 18.79 L/min).

One trial<sup>124</sup> involving 300 participants (LABA/ICS = 148, ICS = 152) receiving either LABA/ICS combination or ICS monotherapy at run-in produced a statistically significant difference favouring LABA/ICS (WMD = 24.60; 95% CI: 3.40 to 45.80) which meets the a priori criteria for clinical importance (MCID = 18.79 L/min).

*FEV*<sub>1</sub> (*absolute*): Seventeen trials<sup>65,66,104-107,109-112,114,115,115,116,120,122,126</sup> involving 8,297 participants (LABA/ICS = 4,543, ICS = 3,754) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with higher-dose ICS monotherapy on absolute FEV<sub>1</sub> (L) (Figure 33). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 0.09; 95% CI: 0.04 to 0.23; I<sup>2</sup> = 16%). The precision of the confidence interval suggests that the two treatments are clinically equivalent (MCID = ±0.23 L/min).

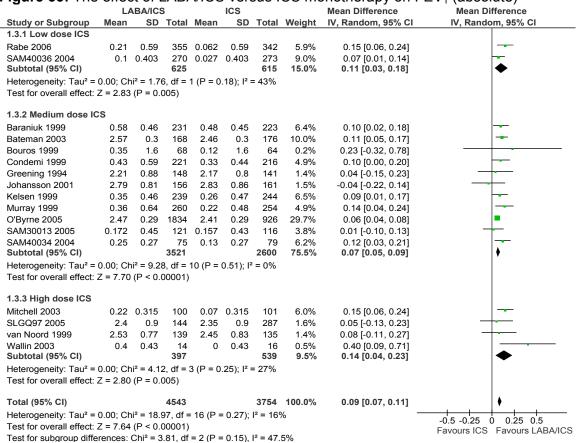


Figure 33: The effect of LABA/ICS versus ICS monotherapy on FEV<sub>1</sub> (absolute)

A subgroup analysis based on comparison ICS dose failed to demonstrate a difference among the low (WMD = 0.11; 95% CI: 0.03 to 0.18;  $I^2 = 43\%$ ), medium (WMD = 0.07; 95% CI: 0.05 to 0.09;  $I^2 = 0\%$ ) and high (WMD = 0.14; 95% CI: 0.04 to 0.23;  $I^2 = 27\%$ ) dose comparisons. The precision of the confidence intervals suggests that the two treatments are clinically equivalent (MCID = ±0.23 L/min) for all three subgroups.

Three trials<sup>79,101,124</sup> involving 710 participants (LABA/ICS = 352, ICS = 358) receiving either LABA/ICS combination or ICS monotherapy at run-in provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with higher-dose ICS monotherapy on absolute FEV<sub>1</sub> (Figure 34). The pooled result failed to indicate a statistically significant difference between treatments (WMD = 0.04; 95% CI: -0.04 to 0.12; I<sup>2</sup> = 71%); %); however, the lack of precision of the estimates prevents conclusions regarding the equivalence of the two treatments (MCID =  $\pm 0.23$  L/min).

A subgroup analysis based on comparison ICS dose failed to demonstrate a difference among the low (WMD = -0.02; 95% CI: -0.07 to 0.03) and medium (WMD = 0.07; 95% CI: -0.11 to 0.25) dose comparisons. There was an increase in the magnitude and precision of the treatment effect for the high (WMD = 0.08; 95% CI: 0.03 to 0.13) dose comparison. The precision of the confidence intervals suggests that the two treatments are clinically equivalent (MCID =  $\pm 0.23$  L/min) for all three subgroups.

## **Figure 34:** The effect of LABA/ICS versus ICS monotherapy on FEV<sub>1</sub> (absolute) (mixed LABA/ICS use at baseline)

LADA 100 USC		1301	110)							
	LA	BA/IC	s		ICS			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.3.1 Low dose ICS										
Lemanske 2001	-0.06	0.17	74	-0.04	0.17	74	42.4%	-0.02 [-0.07, 0.03]		
Subtotal (95% CI)			74			74	42.4%	-0.02 [-0.07, 0.03]		-
Heterogeneity: Not app	olicable									
Test for overall effect:	Z = 0.72	2 (P = 0	).47)							
1.3.2 Medium dose IC	s									
SAS30002 2008	2.29	0.8	148	2.22	0.8	152	14.4%	0.07 [-0.11, 0.25]	2008	
Subtotal (95% CI)			148			152	14.4%	0.07 [-0.11, 0.25]		
Heterogeneity: Not app	olicable									
Test for overall effect:	Z = 0.76	6 (P = 0	).45)							
1.3.3 High dose ICS										
Peters 2008	0.16	0.23	129	0.08	0.2	132	43.1%	0.08 [0.03, 0.13]		
Subtotal (95% CI)			129			132	43.1%	0.08 [0.03, 0.13]		
Heterogeneity: Not app	olicable									
Test for overall effect:	Z = 3.00	) (P = 0	0.003)							
Total (95% CI)			351			358	100.0%	0.04 [-0.04, 0.12]		
Heterogeneity: Tau <sup>2</sup> =	0.00; Ch	ni² = 6.	85, df =	= 2 (P =	0.03);	$l^2 = 719$	%		-	
Test for overall effect:	Z = 0.88	(P = 0	.38)							-0.2 -0.1 0 0.1 0.2 Favours ICS Favours LABA/ICS
Test for subgroup diffe	rences:	Chi <sup>2</sup> =	6.85, c	lf = 2 (P	= 0.03	3), l² = 7	70.8%			FAVOUISICS FAVOUIS LABA/ICS

*FEV*<sub>1</sub> (% *predicted*): Five trials<sup>58,108,109,118,123</sup> involving 2,503 participants (LABA/ICS = 1,372, ICS = 1,131) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with higher-dose ICS monotherapy on % predicted FEV<sub>1</sub> (Figure 35). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 2.14; 95% CI: 0.95 to 3.34; I<sup>2</sup> = 31%). The precision of the confidence interval suggests that the two treatments are clinically equivalent (MCID =  $\pm 12\%$ ).

#### Figure 35: The effect of LABA/ICS versus ICS monotherapy on FEV<sub>1</sub> (% predicted)

	LAB	BA/ICS		1	CS			Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]	IV, Random, 95% CI [%]
1.4.1 Low dose ICS									
O'Byrne 2001	2.55	9	323	0.9	9	312	34.8%	1.65 [0.25, 3.05]	-
Peters 2007	91.8	9.1	161	91.1	9.9	168	22.5%	0.70 [-1.35, 2.75]	
Subtotal (95% CI)			484			480	57.3%	1.35 [0.19, 2.51]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> =	0.56, df =	= 1 (P =	0.45); I <sup>2</sup> = 0	%				
Test for overall effect:	Z = 2.28 (P =	= 0.02)							
1.4.2 Medium dose IC	s								
Baraniuk 1999	16.7	15.2	231	14	13.44	223	15.7%	2.70 [0.06, 5.34]	
Subtotal (95% CI)			231			223	15.7%	2.70 [0.06, 5.34]	◆
Heterogeneity: Not app	plicable								
Test for overall effect:	Z = 2.01 (P =	= 0.04)							
1.4.3 High dose ICS									
Bergmann 2004	84	24	170	82	22	177	5.6%	2.00 [-2.85, 6.85]	_ <del></del>
Woolcock 1996	6.8	14	487	2.7	14	251	21.4%	4.10 [1.97, 6.23]	
Subtotal (95% CI)			657			428	27.0%	3.76 [1.81, 5.71]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> =	0.60, df =	= 1 (P =	0.44); l <sup>2</sup> = 0	%				
Test for overall effect:	Z = 3.78 (P =	= 0.0002)							
Total (95% CI)			1372			1131	100.0%	2.14 [0.95, 3.34]	◆
Heterogeneity: Tau <sup>2</sup> =	0.56; Chi <sup>2</sup> =	5.76, df =	= 4 (P =	0.22); I <sup>2</sup> = 3	1%				-20 -10 0 10
Test for overall effect:	Z = 3.51 (P =	= 0.0004)							Favours ICS Favours LAE
Test for subgroup diffe	rences: Chi <sup>2</sup>	= 4.59, d	f = 2 (F	P = 0.10), I <sup>2</sup> =	= 56.5%				1 avours 100 T avours LAL

A subgroup analysis based on comparison ICS dose failed to demonstrate a difference among the low (WMD = 1.35; 95% CI: 0.19 to 2.51;  $I^2 = 0\%$ ), medium (WMD = 2.70; 95% CI: 0.06 to 5.34) and high (WMD = 3.76; 95% CI: 1.81 to 5.71;  $I^2 = 0\%$ ) dose comparisons. Moreover, the precision of the 95% CIs for all differences suggest that the two treatments are clinically equivalent (MCID = ±12%) for all three subgroups.

One trial<sup>124</sup> involving 300 participants (LABA/ICS = 148, ICS = 152) receiving either LABA/ICS combination or ICS monotherapy at run-in provided data for a comparison of the effects of LABA/ICS combination therapy compared with higher-dose ICS monotherapy on FEV<sub>1</sub> (% predicted). The result failed to indicate a statistically significant difference between the two treatments (WMD = 2.40; 95% CI: -0.76 to 5.56). Moreover, the precision of the 95% CI suggests that the two treatments are clinically equivalent (MCID =  $\pm 12\%$ ).

#### Asthma control measures

*Total number of exacerbations:* Six trials<sup>58,111,114,117,119,122</sup> involving 4,645 participants (LABA/ICS = 2,344, ICS = 2,301) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with higher-dose ICS monotherapy on number of exacerbations (Figure 36). The pooled result indicated a statistically significant difference favouring LABA/ICS (Rate ratio = 0.72; 95% CI = 0.56 to 0.94; I<sup>2</sup> = 95%). The low dose ICS trials<sup>58,122</sup> compared FORM/BUD with BUD; however, the trial that most favoured LABA/ICS<sup>58</sup> (Rate ratio = 0.58; 95% CI: 0.50 to 0.68) compared low dose BUD (400 mcg/d) in a population with intermittent to mild asthma. Heterogeneity may be explained by variations in the asthma severity of participants as the trials included various spectrums of severity: intermittent to mild, <sup>58</sup> intermittent to severe, <sup>111</sup> mild to moderate, <sup>122</sup> moderate, <sup>114</sup> and moderate to severe<sup>117,119</sup>.

			LABA/ICS	ICS		Rate Ratio	Rate Ratio
Study or Subgroup	log[Rate Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.17.1 Low dose							
O'Byrne 2001	-0.539	0.0793	323	312	16.7%	0.58 [0.50, 0.68]	
Rabe 2006	-0.821	0.0757	355	342	16.8%	0.44 [0.38, 0.51]	
Subtotal (95% CI)			678	654	33.5%	0.51 [0.38, 0.67]	$\bullet$
Heterogeneity: Tau <sup>2</sup> =	0.03; Chi <sup>2</sup> = 6.62, d	df = 1 (P	= 0.01); l <sup>2</sup> =	85%			
Test for overall effect: 2	Z = 4.83 (P < 0.000	001)					
1.17.2 Medium dose							
Greening 1994	0.143	0.0968	220	206	16.2%	1.15 [0.95, 1.39]	+
Kelsen 1999	-0.0885	0.0909	239	244	16.4%	0.92 [0.77, 1.09]	
Murray 1999	-0.0953	0.0881	260	254	16.5%	0.91 [0.76, 1.08]	
Scicchitano 2004	-0.505	0.046	947	943	17.4%	0.60 [0.55, 0.66]	-
Subtotal (95% CI)			1666	1647	66.5%	0.87 [0.63, 1.19]	
Heterogeneity: Tau <sup>2</sup> =	0.10; Chi <sup>2</sup> = 51.61,	df = 3 (F	P < 0.00001)	; l² = 94	%		
Test for overall effect: 2	Z = 0.89 (P = 0.37)						
Total (95% CI)			2344	2301	100.0%	0.72 [0.56, 0.94]	
Heterogeneity: Tau <sup>2</sup> =	0.10; Chi <sup>2</sup> = 94.29,	df = 5 (F	o < 0.00001)	; l² = 95	%		
Test for overall effect: 2	Z = 2.41 (P = 0.02)					F	0.5 0.7 1 1.5 2 avours LABA/ICS Favours ICS

Figure 36: The effect of LABA/ICS versus ICS monotherapy on total number of exacerbations

A subgroup analysis based on comparison ICS dose indicated a statistically significant difference favouring LABA/ICS for the low (Rate ration = 0.51; 95% CI: 0.38 to 0.67;  $I^2 = 85\%$ ) dose comparison, but not for the medium (Rate ratio = 0.87; 95% CI: 0.63 to 1.19;  $I^2 = 94\%$ ) dose comparison.

One trial<sup>101</sup> involving 265 participants (LABA/ICS = 132, ICS = 133) receiving either LABA/ICS combination or ICS monotherapy at run-in provided data for a comparison of the effects of LABA/ICS combination therapy compared with higher-dose ICS monotherapy on the number of exacerbations. The result indicated a statistically significant difference favouring LABA/ICS (WMD = -0.13; 95% CI: -0.23 to -0.03).

*Number participants experiencing*  $\geq 1$  *exacerbations:* Twenty trials<sup>76,104,106,110-113,115-118</sup> involving 10,726 participants (LABA/ICS = 5,324, ICS = 5,402) provided data for a metaanalysis of the effects of LABA/ICS combination therapy compared with higher-dose ICS monotherapy on the percent participants with one or more exacerbations (%) (Figure 37). The pooled result indicated a statistically significant difference favouring LABA/ICS (RR = 0.82; 95% CI: 0.73 to 0.91; I<sup>2</sup> = 40%).

exacerbations							
	LABA/	ICS	ICS			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.16.1 Low dose							
Lalloo 2003	110	230	136	237	11.1%	0.83 [0.70, 0.99]	-
Peters 2007	78	162	78	168	9.2%	1.04 [0.83, 1.30]	+
Rabe 2006	28	355	55	342	4.5%	0.49 [0.32, 0.75]	- <b>-</b> -
Subtotal (95% CI)		747		747	24.7%	0.79 [0.57, 1.09]	•
Total events	216		269				
Heterogeneity: Tau <sup>2</sup> =	0.06; Chi <sup>2</sup>	= 9.60,	df = 2 (P	9 = 0.00	8); l <sup>2</sup> = 79	%	
Test for overall effect: 2	Z = 1.42 (I	P = 0.10	6)				
1.16.2 Medium dose							
Bateman 2003	50	168	74	176	7.3%	0.71 [0.53, 0.95]	-
Bouros 1999	8	68	3	64	0.7%	2.51 [0.70, 9.05]	+
Condemi 1999	21	221	31	216	3.4%	0.66 [0.39, 1.12]	
Greening 1994	84	220	76	206	8.6%	1.03 [0.81, 1.32]	+
Johansson 2001	24	176	25	173	3.4%	0.94 [0.56, 1.59]	-+-
Kelsen 1999	38	239	44	244	5.0%	0.88 [0.59, 1.31]	-
Murray 1999	43	260	45	254	5.3%	0.93 [0.64, 1.37]	-+
O'Byrne 2005	27	909	28	926	3.4%	0.98 [0.58, 1.65]	
Scicchitano 2004	170	947	259	943	11.2%	0.65 [0.55, 0.78]	-
van Noord 1999	16	139	15	135	2.3%	1.04 [0.53, 2.01]	
Vermetten 1999 Subtotal (95% CI)	9	113 <b>3460</b>	17	120 <b>3457</b>	1.8% <b>52.3%</b>	0.56 [0.26, 1.21] 0.83 [0.71, 0.97]	•
Total events	490		617				
Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: 2	,		,	(P = 0.	07); l <sup>2</sup> = 4	1%	
1.16.3 High dose							
Bergmann 2004	0	170	1	177	0.1%	0.35 [0.01, 8.46]	
Ind 2003	58	171	124	325	8.4%	0.89 [0.69, 1.14]	-
Mitchell 2003	34	100	51	101	6.2%	0.67 [0.48, 0.94]	
SLGQ97 2005	5	171	22	325	1.2%	0.43 [0.17, 1.12]	
Wallin 2003	1	18	2	19	0.2%	0.53 [0.05, 5.33]	
Woolcock 1996	88	487	50	251	6.8%	0.91 [0.66, 1.24]	-+
Subtotal (95% CI)		1117		1198	23.0%	0.81 [0.69, 0.96]	•
Total events	186		250				
Heterogeneity: Tau <sup>2</sup> =	-		•	9 = 0.51	); l² = 0%		
Test for overall effect: 2	Z = 2.45 (I	P = 0.0	1)				
Total (95% CI)		5324		5402	100.0%	0.82 [0.73, 0.91]	♦
Total events	892		1136				
Heterogeneity: Tau <sup>2</sup> =	0.02; Chi²	= 31.5	8, df = 19	(P = 0.	03); l <sup>2</sup> = 40	0% -	1 + + + + + + + + + + + + + + + + + + +
Test for overall effect: 2	•		,				vours LABA/ICS Favours ICS
Test for subgroup diffe	rences: N	ot appli	cable				

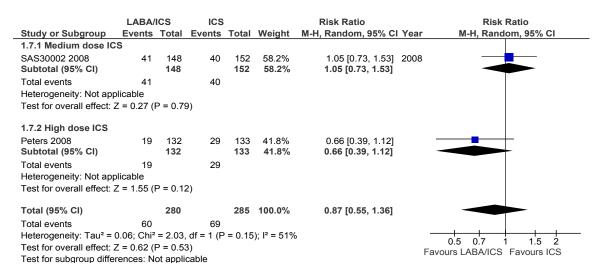
**Figure 37:** The effect of LABA/ICS versus higher dose ICS on % participants experiencing ≥1 exacerbations

A subgroup analysis based on comparison ICS dose failed to indicate a different between the treatments for the low (RR = 0.79; 95% CI: 0.57 to 1.09;  $I^2 = 79\%$ ) dose comparison. However,

LABA/iCS was favoured for medium (RR = 0.83; 95% CI: 0.71 to 0.97;  $I^2 = 41\%$ ), and high (RR = 0.81; 95% CI: 0.69 to 0.96;  $I^2 = 0\%$ ) dose comparisons.

Two trials<sup>101,124</sup> involving 565 participants (LABA/ICS = 280, ICS = 285) receiving either LABA/ICS combination or ICS monotherapy at run-in provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on number of participants with  $\geq$ 1 exacerbation (Figure 38). The result failed to indicate a statistically significant difference between the two treatments (RR = 0.87; 95% CI: 0.55 to 1.36; I<sup>2</sup> = 51%).

**Figure 38:** The effect of LABA/ICS versus higher dose ICS on % participants experiencing ≥1 exacerbations (mixed LABA/ICS use at baseline)



A subgroup analysis based on comparison ICS dose failed to indicate a statistically significant difference between the two treatments for the medium<sup>124</sup> (RR = 1.05; 95% CI: 0.73 to 1.53) and high <sup>101</sup> (RR = 0.66; 95% CI: 0.39 to 1.12) dose comparisons.

*Number of patients with severe exacerbations:* Seven trials<sup>76,105,106,111,115,119,122</sup> involving 5889 participants (LABA/ICS = 2,870, ICS = 3,019) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with higher-dose ICS monotherapy on the number of patients with severe exacerbations (Figure 39). The pooled results indicated a statistically significant difference favouring LABA/ICS (RR = 0.65; 95% CI: 0.57 to 0.75;  $I^2 = 0\%$ ).

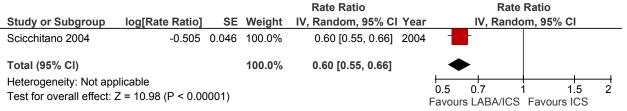
Figure 39: The effect of LABA/ICS versus ICS monotherapy on the number of patients with	
severe exacerbations	

	LABA/	ICS	ICS			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.18.1 Low dose							
Rabe 2006	28	355	55	342	9.7%	0.49 [0.32, 0.75]	
Subtotal (95% CI)		355		342	9.7%	0.49 [0.32, 0.75]	$\bullet$
Total events	28		55				
Heterogeneity: Not app	plicable						
Test for overall effect:	Z = 3.25 (	P = 0.0	01)				
1.18.2 Medium dose							
Bateman 2003	13	168	19	176	4.0%	0.72 [0.37, 1.41]	+
Greening 1994	1	220	0	206	0.2%	2.81 [0.12, 68.59]	
O'Byrne 2005	27	909	28	926	6.6%	0.98 [0.58, 1.65]	- <b>+</b> -
Scicchitano 2004	170	947	259	943	61.4%	0.65 [0.55, 0.78]	
Subtotal (95% CI)		2244		2251	72.2%	0.68 [0.58, 0.80]	♦
Total events	211		306				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 2.91	df = 3 (F	9 = 0.41	); l² = 0%		
Test for overall effect:	Z = 4.71 (	P < 0.0	0001)				
1.18.3 High dose							
Ind 2003	5	171	22	325	2.0%	0.43 [0.17, 1.12]	
Mitchell 2003	34	100	51	101	16.1%	0.67 [0.48, 0.94]	
Subtotal (95% CI)		271		426	18.1%	0.64 [0.47, 0.88]	
Total events	39		73				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 0.80	df = 1 (F	9 = 0.37	); l <sup>2</sup> = 0%		
Test for overall effect:	Z = 2.76 (	P = 0.0	06)				
Total (95% CI)		2870		3019	100.0%	0.65 [0.57, 0.75]	♦
Total events	278		434				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 5.69	df = 6 (F	9 = 0.46	); l <sup>2</sup> = 0%		
Test for overall effect:			•		,	0.0	02 0.1 1 10 50 ours LABA/ICS Favours ICS
Test for subgroup diffe	•		,			Fav	DUIS LABANCS Favours ICS

A subgroup analysis based on comparison ICS dose indicated a statistically significant difference favouring LABA/ICS for low (RR = 0.49; 95% CI: 0.32 to 0.75) medium (RR = 0.68; 95% CI: 0.58 to 0.80;  $I^2 = 0\%$ ), and high (RR = 0.64; 95% CI: 0.47 to 0.88;  $I^2 = 0\%$ ) dose comparisons.

*Number of severe exacerbations:* One trial<sup>119</sup> involving 2,760 participants (LABA/ICS = 1,834, ICS = 926) provided data for an analysis of the effects of LABA/ICS combination therapy compared with higher-dose ICS monotherapy on the number of severe exacerbations (Figure 40). The result indicated a statistically significant difference favouring LABA/ICS (Rate ratio = 0.60; 95% CI: 0.55 to 0.66).

Figure 40: The effect of LABA/ICS versus ICS monotherapy on no. severe exacerbations



*Number of patients with mild exacerbations:* Four trials<sup>76,106,111,115</sup> involving 1,467 participants (LABA/ICS = 659, ICS = 808) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with higher-dose ICS monotherapy on the number of patients with mild exacerbations (Figure 41). The pooled result failed to indicate a statistically significant difference between the two treatments (RR = 0.84; 95% CI: 0.64 to 1.11; I<sup>2</sup> = 51%).

CAUCCIDATIONS							
	LABA/	ICS	ICS			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
1.20.2 Medium dose							
Bateman 2003	35	168	54	176	26.3%	0.68 [0.47, 0.98]	
Greening 1994	66	220	57	206	31.4%	1.08 [0.80, 1.46]	
Subtotal (95% CI)		388		382	57.7%	0.87 [0.55, 1.37]	
Total events	101		111				
Heterogeneity: Tau <sup>2</sup> = 0	0.08; Chi²	= 3.73,	, df = 1 (P	= 0.05	); l² = 73%	)	
Test for overall effect: 2	Z = 0.60 (F	P = 0.5	5)				
1.20.3 High dose							
Ind 2003	21	171	39	325	19.1%	1.02 [0.62, 1.68]	
Mitchell 2003	25	100	39	101	23.2%	0.65 [0.43, 0.98]	
Subtotal (95% CI)		271		426	42.3%	0.80 [0.51, 1.25]	
Total events	46		78				
Heterogeneity: Tau <sup>2</sup> = (	0.05; Chi²	= 1.92,	, df = 1 (P	= 0.17	); l <sup>2</sup> = 48%	)	
Test for overall effect: 2	z = 0.99 (f	<sup>o</sup> = 0.32	2)				
Total (95% CI)		659		808	100.0%	0.84 [0.64, 1.11]	
Total events	147		189				
Heterogeneity: Tau <sup>2</sup> = (	0.04; Chi²	= 6.11,	, df = 3 (P	= 0.11	); l² = 51%	)	
Test for overall effect: 2	Z = 1.23 (F	<sup>D</sup> = 0.22	2)			1	Favours LABA/ICS Favours ICS
Test for subgroup differ	ences: No	ot appli	cable			'	

**Figure 41:** The effect of LABA/ICS versus ICS monotherapy on number of patients with mild exacerbations

A subgroup analysis based on comparison ICS dose failed to identify a difference between the medium (RR = 0.87; 95% CI: 0.55 to 1.37;  $I^2 = 73\%$ ) and high (RR = 0.80; 95% CI: 0.51 to 1.25;  $I^2 = 48\%$ ) dose comparisons. Heterogeneity among the medium dose comparisons may be explained by variations in patient disease severity. One study<sup>106</sup> included only participants with moderate disease severity, while the other study<sup>111</sup> included a range of severity from intermittent to severe. Heterogeneity in the high dose comparisons may be explained by variations in study treatment: one study<sup>76</sup> compared SAL/FP versus FP, while the other study<sup>115</sup> compared FORM/BDP to BDP.

*Number of mild exacerbations:* One trial<sup>111</sup> involving 426 participants (LABA/ICS = 220, ICS = 206) provided data for an analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on the number of mild exacerbations. The result failed to demonstrate a statistically significant difference between the treatments (WMD = 0.06; 95% CI: -0.22 to 0.35).

*Exacerbations requiring hospitalization:* Six trials<sup>76,111,112,114,115,117</sup> involving 2,469 participants (LABA/ICS = 1,166, ICS = 1,303) provided data for an analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on the number of exacerbations requiring hospitalization (Figure 42). The pooled result failed to indicate a statistically significant difference between the two treatments (RR = 0.80; 95% CI: 0.51 to 1.24;  $I^2 = 0\%$ ).

·	LABA/	ICS	ICS			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.22.2 Medium dose							
Greening 1994	1	220	0	206	1.9%	2.81 [0.12, 68.59]	
Johansson 2001	24	176	25	173	72.2%	0.94 [0.56, 1.59]	
Kelsen 1999	1	239	1	244	2.5%	1.02 [0.06, 16.23]	
Murray 1999	0	260	1	254	1.9%	0.33 [0.01, 7.96] 👘	
Subtotal (95% CI)		895		877	78.6%	0.95 [0.58, 1.56]	•
Total events	26		27				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi²	= 0.88	, df = 3 (P	9 = 0.83	); l² = 0%		
Test for overall effect: 2	Z = 0.22 (F	<b>&gt;</b> = 0.8	3)				
1.22.3 High dose							
Ind 2003	5	171	22	325	21.4%	0.43 [0.17, 1.12]	
Mitchell 2003	0	100	0	101		Not estimable	
Subtotal (95% CI)		271		426	21.4%	0.43 [0.17, 1.12]	
Total events	5		22				
Heterogeneity: Not app	olicable						
Test for overall effect: 2	Z = 1.73 (F	<sup>D</sup> = 0.08	8)				
Total (95% CI)		1166		1303	100.0%	0.80 [0.51, 1.24]	•
Total events	31		49				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi²	= 2.96	, df = 4 (P	9 = 0.57	); l <sup>2</sup> = 0%		$20.1$ 1 10 $\frac{1}{5}$
Test for overall effect: 2	Z = 0.99 (F	<b>-</b> = 0.32	2)			0.0 Favr	02 0.1 1 10 5 ours LABA/ICS Favours ICS
Test for subgroup diffe	rences: N	ot appli	cable			Favo	

**Figure 42:** The effect of LABA/ICS versus ICS monotherapy on no. exacerbations requiring hospitalization

A subgroup analysis based on comparison ICS dose failed to indicate a statistically significant difference between the two treatment for medium (RR = 0.95; 95% CI: 0.58 to 1.56;  $I^2 = 0\%$ ) and high (RR = 0.43; 95% CI: 0.17 to 1.12;  $I^2 = 0\%$ ) dose comparisons.

*Exacerbations requiring OCS:* Seven trials<sup>76,110-112,114,115,117</sup> involving 2,906 participants (LABA/ICS = 1,387, ICS = 1,519) provided data for an analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on the number of exacerbations requiring OCS (Figure 43). The pooled result failed to indicate a statistically significant difference between the two treatments (RR = 0.85; 95% CI: 0.72 to 1.00; I<sup>2</sup> = 0%)

LABA/	ICS	ICS			Risk Ratio	Risk Ratio
Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
21	221	31	216	10.0%	0.66 [0.39, 1.12]	
18	220	19	206	7.2%	0.89 [0.48, 1.64]	
24	176	25	173	10.1%	0.94 [0.56, 1.59]	
38	239	44	244	17.4%	0.88 [0.59, 1.31]	
43	260 <b>1116</b>	45	254 <b>1093</b>	18.8% <b>63.4%</b>	0.93 [0.64, 1.37] <b>0.87 [0.70, 1.07]</b>	•
144		164				
0.00; Chi <sup>2</sup>	= 1.29,	df = 4 (P	= 0.86	); l <sup>2</sup> = 0%		
z = 1.35 (F	⊃ = 0.18	3)				
47	171	107	325	32.6%	0.83 [0.63, 1.11]	-
9	100	12	101	4.1%	0.76 [0.33, 1.72]	_ <b>-</b> +-
	271		426	36.6%	0.83 [0.63, 1.08]	•
56		119				
).00; Chi²	= 0.05,	df = 1 (P	= 0.83	); l <sup>2</sup> = 0%		
-		•		,,		
	1387		1519	100.0%	0.85 [0.72, 1.00]	•
200		283				
0.00; Chi <sup>2</sup>	= 1.41,	df = 6 (P	= 0.97	); l <sup>2</sup> = 0%		
				,,	-	0.02 0.1 1 10 50
		,			F	avours LABA/ICS Favours ICS
	Events 21 18 24 38 43 144 0.00; Chi <sup>2</sup> 2 = 1.35 (F 47 9 56 0.00; Chi <sup>2</sup> 2 = 1.38 (F 200 0.00; Chi <sup>2</sup> 2 = 1.91 (F	21 221 18 220 24 176 38 239 43 260 1116 144 0.00; Chi <sup>2</sup> = 1.29, 2 = 1.35 (P = 0.18 47 171 9 100 271 56 0.00; Chi <sup>2</sup> = 0.05, 2 = 1.38 (P = 0.17) 1387 200 0.00; Chi <sup>2</sup> = 1.41, 2 = 1.91 (P = 0.00)	Events         Total         Events           21         221         31           18         220         19           24         176         25           38         239         44           43         260         45           1116         144         164           0.00; Chi <sup>2</sup> = 1.29, df = 4 (P         2           47         171         107           9         100         12           271         56         119           0.00; Chi <sup>2</sup> = 0.05, df = 1 (P         2         1.387           200         283         283	Events         Total         Events         Total           21         221         31         216           18         220         19         206           24         176         25         173           38         239         44         244           43         260         45         254           1116         1093         144         164           0.00; Chi <sup>2</sup> = 1.29, df = 4 (P = 0.86         2         1116         1093           47         171         107         325         9         100         12         101           271         426         56         119         100         12         101         271         426           56         119         0.00; Chi <sup>2</sup> = 0.05, df = 1 (P = 0.83         2         1.38 (P = 0.17)         1387         1519           200         283         0.00; Chi <sup>2</sup> = 1.41, df = 6 (P = 0.97         2         1.519         1.519           200         283         0.00; Chi <sup>2</sup> = 1.41, df = 6 (P = 0.97         2         1.91 (P = 0.06)	Events         Total         Events         Total         Weight           21         221         31         216         10.0%           18         220         19         206         7.2%           24         176         25         173         10.1%           38         239         44         244         17.4%           43         260         45         254         18.8%           1116         1093         63.4%           144         164           0.00; Chi <sup>2</sup> = 1.29, df = 4 (P = 0.86); l <sup>2</sup> = 0%         2           2         1.35 (P = 0.18)         101         4.1%           271         426         36.6%         56           56         119         0.00; Chi <sup>2</sup> = 0.05, df = 1 (P = 0.83); l <sup>2</sup> = 0%         2           2         1.38 (P = 0.17)         1387         1519         100.0%           200         283         0.00; Chi <sup>2</sup> = 1.41, df = 6 (P = 0.97); l <sup>2</sup> = 0%         2         1.91 (P = 0.06)	Events         Total         Events         Total         Weight         M-H, Random, 95% CI           21         221         31         216         10.0%         0.66 [0.39, 1.12]           18         220         19         206         7.2%         0.89 [0.48, 1.64]           24         176         25         173         10.1%         0.94 [0.56, 1.59]           38         239         44         244         17.4%         0.88 [0.59, 1.31]           43         260         45         254         18.8%         0.93 [0.64, 1.37]           1116         1093         63.4%         0.87 [0.70, 1.07]         144           144         164         0.00; Chi² = 1.29, df = 4 (P = 0.86); I² = 0%         271         426         36.6%         0.83 [0.63, 1.11]           9         100         12         101         4.1%         0.76 [0.33, 1.72]         271         426         36.6%         0.83 [0.63, 1.08]         56         119           0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%         2         1.38 (P = 0.17)         0.85 [0.72, 1.00]         200         283         0.00; Chi² = 1.41, df = 6 (P = 0.97); I² = 0%         2         1.91 (P = 0.06)         F

**Figure 43:** The effect of LABA/ICS versus ICS monotherapy on no. exacerbations requiring OCS

A subgroup analysis based on comparison ICS dose failed to indicate a statistically significant difference between the two treatment for medium (RR = 0.87; 95% CI: 0.70 to 1.07;  $I^2 = 0\%$ ) and high (RR = 0.83; 95% CI: 0.63 to 1.08;  $I^2 = 0\%$ ) dose comparisons.

*Short-acting beta*<sub>2</sub>*-agonist (SABA) use:* Seventeen trials<sup>58,65,104-111,113-115,117,119,121,122</sup> involving 10,823 participants (LABA/ICS = 5,806, ICS = 5,017) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with higher-dose ICS monotherapy on SABA use (Figure 44). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = -0.43; 95% CI: -0.55 to -0.30; I<sup>2</sup> = 79%). Heterogeneity may be explained by variations in disease severity as those studies that indicated more modest treatment benefit included patients with mild or intermittent disease severity.

	LAB	BA/ICS		1	CS			Mean Difference	Mean Difference
Study or Subgroup	Mean [puff/sday]	SD [puff/sday]	Total	Mean [puff/sday]	SD [puff/sday]	Total	Weight	IV, Random, 95% CI [puff/sday]	IV, Random, 95% CI [puff/sda
.10.1 Low dose ICS									
alloo 2003	-0.33	1.11	230	-0.1	1.11	237	8.2%	-0.23 [-0.43, -0.03]	-
Byrne 2001	0.66	0.83	323	0.75	0.83	312	9.3%	-0.09 [-0.22, 0.04]	+
abe 2006	-0.62	1.15	355	-0.28	1.15	342	8.7%	-0.34 [-0.51, -0.17]	-
AM40036 2004	-1	2.53	270	-1	2.55	273	4.6%	0.00 [-0.43, 0.43]	
ubtotal (95% CI)			1178			1164	30.8%	-0.19 [-0.33, -0.05]	•
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi <sup>2</sup> = 6.15, df	= 3 (P = 0.10); I <sup>2</sup>	= 51%						
est for overall effect:	Z = 2.64 (P = 0.008)								
.10.2 Medium dose I	CS								
araniuk 1999	-2.9	3.04	231	-2.4	2.99	223	3.4%	-0.50 [-1.05, 0.05]	
ateman 2003	-0.31	0.8	168	-0.13	0.8	176	8.7%	-0.18 [-0.35, -0.01]	-
Souros 1999	-0.7	1.37	68	-0.37	1.37	64	4.2%	-0.33 [-0.80, 0.14]	
Condemi 1999	-2.51	2.53	221	-1.55	2.2	216	4.4%	-0.96 [-1.40, -0.52]	
Greening 1994	-0.9	4	132	-0.9	4	126	1.4%	0.00 [-0.98, 0.98]	
elsen 1999	-1.98	2.32	239	-1.19	2.19	244	5.0%	-0.79 [-1.19, -0.39]	
lurray 1999	-1.96	2.26	260	-0.89	2.07	254	5.3%	-1.07 [-1.44, -0.70]	-
)'Byrne 2005	0.785	0.5	1834	1.03	0.5	926	10.3%	-0.24 [-0.28, -0.21]	-
cicchitano 2004	0.9	2.53	947	1.42	2.55	943	7.7%	-0.52 [-0.75, -0.29]	+
/ermetten 1999 Subtotal (95% CI)	-0.4	0.87	113 4213	-0.23	1.04	120 3292	7.4% 57.7%	-0.17 [-0.42, 0.08] -0.46 [-0.64, -0.29]	•
leterogeneity: Tau <sup>2</sup> =			1); l² =	79%					
est for overall effect:	Z = 5.17 (P < 0.0000	1)							
.10.3 High dose ICS									
ergmann 2004	-1.6	1.9	170	-1	2.2	177	4.6%	-0.60 [-1.03, -0.17]	
litchell 2003	-2.27	2.03	100	-0.89	2.55	101	2.8%	-1.38 [-2.02, -0.74]	
LGQ97 2005	1	2.4	145	2	2.4	283	4.1%	-1.00 [-1.48, -0.52]	<b>T</b>
ubtotal (95% CI)			415			561	11.4%	-0.95 [-1.37, -0.52]	•
eterogeneity: Tau <sup>2</sup> =			= 52%						
est for overall effect:	Z = 4.35 (P < 0.0001	)							
Total (95% CI)			5806			5017	100.0%	-0.43 [-0.55, -0.30]	•
Heterogeneity: Tau <sup>2</sup> =	0.04; Chi <sup>2</sup> = 74.48, d	f = 16 (P < 0.000	01); I² =	79%					-4 -2 0 2 4
est for overall effect:	Z = 6.74 (P < 0.0000	1)						E/	-4 -2 0 2 4 avours LABA/ICS Favours ICS
act for subgroup diffe	rences: Chi <sup>2</sup> = 22.10	df = 2 (P < 0.00)	)1) l <sup>2</sup> =	91.0%				16	

#### Figure 44: The effect of LABA/ICS versus ICS monotherapy on SABA use

A subgroup analysis based on comparison ICS dose failed to identify a difference between the low (WMD = -0.19; 95% CI: -0.33 to -0.05;  $I^2 = 51\%$ ), medium (WMD = -0.46; 95% CI: -0.64 to -0.29;  $I^2 = 79\%$ ) and high (WMD = -0.95; 95% CI: -1.37 to -0.52;  $I^2 = 52\%$ ) dose comparisons. Moreover, the precision of the 95% CIs for all differences suggest that the three treatments are clinically equivalent (MCID = ±0.81).

Three trials<sup>79,101,124</sup> involving 708 participants (LABA/ICS = 352, ICS = 356) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with higher-dose ICS monotherapy on SABA use (Figure 45). The pooled result failed to identify a statistically or clinically significant difference between the two treatments (WMD = -0.27; 95% CI: -0.72 to 0.19;  $I^2 = 77\%$ ). Moreover, the precision of the 95% CI suggests that the two treatments are clinically equivalent (MCID = ±0.81).

A subgroup analysis based on comparison ICS dose failed to indicate a statistically significant difference for the low (WMD = -0.30; 95% CI: -1.11 to 0.51) and medium (WMD = 0.00; 95% CI: -0.11 to 0.11) dose comparisons. The result for the high dose comparison indicated statistically significant difference favouring LABA/ICS (WMD = -0.59; 95% CI: -0.97 to -0.21)

## Figure 45: The effect of LABA/ICS versus ICS monotherapy on SABA use (mixed LABA/ICS use at baseline)

	LABA/ICS			1	ICS			Mean Difference	Mean Difference	
Study or Subgroup	Mean [puff/sday]	SD [puff/sday]	Total	Mean [puff/sday]	SD [puff/sday]	Total	Weight	IV, Random, 95% CI [puff/sday] Year	IV, Random, 95% CI [puff/sday]	
1.10.1 Low dose ICS										
Lemanske 2001	-1	2.5	74	-0.7	2.5	74	19.0%	-0.30 [-1.11, 0.51]		
Subtotal (95% CI)			74			74	19.0%	-0.30 [-1.11, 0.51]		
Heterogeneity: Not app										
Test for overall effect: 2	Z = 0.73 (P = 0.47)									
1.10.2 Medium dose l	cs									
SAS30002 2008	0	0.38	148	0	0.58	152	45.7%	0.00 [-0.11, 0.11] 2008		
Subtotal (95% CI)			148			152	45.7%	0.00 [-0.11, 0.11]	•	
Heterogeneity: Not app										
Test for overall effect: 2	Z = 0.00 (P = 1.00)									
1.10.3 High dose ICS										
Peters 2008	-0.74	1.79	130	-0.15	1.33	130	35.3%	-0.59 [-0.97, -0.21]		
Subtotal (95% CI)			130			130	35.3%	-0.59 [-0.97, -0.21]		
Heterogeneity: Not app										
Test for overall effect: 2	Z = 3.02 (P = 0.003)									
Total (95% CI)			352			356	100.0%	-0.27 [-0.72, 0.19]	-	
Heterogeneity: Tau <sup>2</sup> = 0	0.11; Chi <sup>2</sup> = 8.78, df	= 2 (P = 0.01); I <sup>2</sup>	= 77%						-1 -0.5 0 0.5 1	
Test for overall effect: 2	Z = 1.14 (P = 0.25)								-1 -0.5 0 0.5 1 Favours LABA/ICS Favours ICS	
Test for subgroup differ	rences: Chi <sup>2</sup> = 8.78,	df = 2 (P = 0.01),	l <sup>2</sup> = 77.	.2%				'	210013 EADATOS 1 210013 103	

Symptom free days (SFD): Sixteen trials<sup>53,58,76,104-106,109,111-114,117-119,122,123</sup> involving 10,702 participants (LABA/ICS = 5,869, ICS = 4,833) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on symptom free days (SFD) (Figure 46). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 8.37; 95% CI: 4.68 to 12.06;  $I^2 = 87\%$ ). Heterogeneity may be explained by variations in disease severity: studies with results strongly favouring LABA/ICS tended to include participants with moderate to severe asthma, while those showing more modest treatment benefits included participants with mild to moderate asthma.

		A/ICS			CS			Mean Difference	Mean Difference
Study or Subgroup	Mean [median %]	SD [median %]	Total	Mean [median %]	SD [median %]	Total	Weight	IV, Random, 95% CI [median %]	IV, Random, 95% CI [median
1.13.1 Low dose ICS									
alloo 2003	16	24.8	230	10	24.8	237	6.9%	6.00 [1.50, 10.50]	
)'Byrne 2001	72.6	25	323	70.3	25	312	7.1%	2.30 [-1.59, 6.19]	+
Peters 2007	82.7	25.2	160	85.8	24.9	165	6.6%	-3.10 [-8.55, 2.35]	-+
labe 2006	26.3	30.3	355	19.8	30.3		6.9%	6.50 [2.00, 11.00]	
Subtotal (95% CI)			1068			1056	27.6%	3.12 [-0.79, 7.02]	•
	10.46; Chi <sup>2</sup> = 8.88, df	= 3 (P = 0.03); I <sup>2</sup>	= 66%						
est for overall effect:	Z = 1.56 (P = 0.12)								
.13.2 Medium dose I	CS								
araniuk 1999	29.2	44.08	231	22.6	38.83	223	5.8%	6.60 [-1.03, 14.23]	+
ateman 2003	60.4	28.4	168	55.5	28.4	176	6.4%	4.90 [-1.10, 10.90]	+
Greening 1994	31	52.6	132	29	49.6	127	4.1%	2.00 [-10.45, 14.45]	_ <del>_</del>
ohansson 2001	53	38	176	55	38	173	5.7%	-2.00 [-9.97, 5.97]	
elsen 1999	23.6	30.9	239	12.5	25	244	6.8%	11.10 [6.08, 16.12]	<del>-</del>
lurray 1999	24.5	33.9	260	9.1	25.5	254	6.7%	15.40 [10.22, 20.58]	
Byrne 2005	53.5	39	1834	46	39	926	7.3%	7.50 [4.42, 10.58]	-
AM40120 2005	0	5.19	6	1.2	5.19	9	6.6%	-1.20 [-6.56, 4.16]	-+
cicchitano 2004	31.9	32.7	947	24.3	32.7	943	7.4%	7.60 [4.65, 10.55]	17
ubtotal (95% CI)			3993			3075	56.7%	6.44 [3.17, 9.70]	•
	15.94; Chi <sup>2</sup> = 27.86, d	f = 8 (P = 0.0005	); I <sup>2</sup> = 7	1%					
est for overall effect:	Z = 3.86 (P = 0.0001)								
.13.3 High dose ICS									
nd 2003	21	60	171	0.8	60	160	4.0%	20.20 [7.27, 33.13]	— <u> </u>
LGQ97 2005	18.5	28	150	2.03	30.82	291	6.5%	16.47 [10.76, 22.18]	
Voolcock 1996	85	60	487	43	60	251	5.2%	42.00 [32.86, 51.14]	
ubtotal (95% CI)			808			702	15.7%	26.20 [9.22, 43.17]	
	201.43; Chi <sup>2</sup> = 21.80,	df = 2 (P < 0.000	1); l² =	91%					
est for overall effect:	Z = 3.02 (P = 0.002)								
otal (95% CI)			5869			4833	100.0%	8.37 [4.68, 12.06]	•
leterogeneity: Tau <sup>2</sup> =	45.94; Chi <sup>2</sup> = 117.78,	df = 15 (P < 0.00	001); l²	= 87%					
	Z = 4.45 (P < 0.00001								-50 -25 0 25 5 Favours ICS Favours LABA
	rences: Chi2 = 59.23,		01) I <sup>2</sup> =	96.6%					Favours ICS Favours LAB

Figure 46: The effect of LABA/ICS versus ICS monotherapy on SFD

A subgroup analysis based on comparison ICS dose failed to indicate a statistically significant difference between the two treatments for the low dose (WMD = 3.12; 95% CI: -0.79 to 7.02; I<sup>2</sup> = 66%) comparison. There was a decrease in the magnitude and precision of the treatment effect for the medium dose (WMD = 6.44; 95% CI: 3.17 to 9.70; I<sup>2</sup> = 71%) comparison. There was little change in the magnitude and precision of the treatment effect for the high dose (WMD = 26.20; 95% CI: 9.22 to 43.17; I<sup>2</sup> = 91%) comparisons.

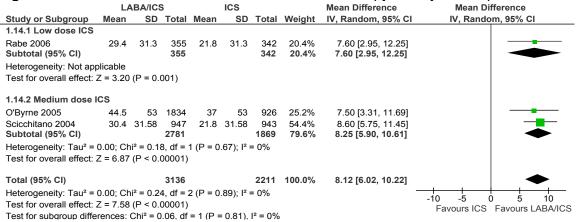
Two trials<sup>101,124</sup> involving 562 participants (LABA/ICS = 278, ICS = 284) receiving either LABA/ICS combination or higher-dose ICS monotherapy at run-in provided data for a metaanalysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on SFD (Figure 47). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 15.66; 95% CI: 11.85 to 19.48;  $I^2 = 0\%$ ).

**Figure 47:** The effect of LABA/ICS versus ICS monotherapy on SFD (mixed LABA/ICS use at baseline)

	LAE	BA/ICS		1	cs			Mean Difference	Mean Difference
Study or Subgroup	Mean [median %]	SD [median %] To	otal	Mean [median %]	SD [median %]	Total	Weight	IV, Random, 95% CI [median %] Year	IV, Random, 95% CI [median %]
1.13.1 Medium dose	ICS								
SAS30002 2008	79.8	20 1	148	64.9	20	152	70.9%	14.90 [10.37, 19.43] 2008	
Subtotal (95% CI)		1	48			152	70.9%	14.90 [10.37, 19.43]	
Heterogeneity: Not a	pplicable								
Test for overall effect	:: Z = 6.45 (P < 0.00001	1)							
1.13.2 High dose IC	s								
Peters 2008	23.46		130	5.93	24.07	132	29.1%	17.53 [10.46, 24.60]	
Subtotal (95% CI)		1	30			132	29.1%	17.53 [10.46, 24.60]	
Heterogeneity: Not a									
Test for overall effect	:: Z = 4.86 (P < 0.00001	1)							
Total (95% CI)		2	78			284	100.0%	15.66 [11.85, 19.48]	•
Heterogeneity: Tau <sup>2</sup>	= 0.00; Chi <sup>2</sup> = 0.38, df =	= 1 (P = 0.54); l <sup>2</sup> = 0%	ó						-20 -10 0 10 20
Test for overall effect	:: Z = 8.05 (P < 0.00001	1)							Favours ICS Favours LABA/ICS
Test for subgroup diff	ferences: Chi <sup>2</sup> = 0.38, c	$df = 1 (P = 0.54), I^2 = 0$	0%						

**Days with optimal control (OC):** Three trials<sup>105,119,122</sup> involving 5,347 participants (LABA/ICS = 3,136, ICS = 2,211) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with higher-dose ICS monotherapy on days with optimal control (OC) (Figure 48). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 8.12; 95% CI: 6.02 to 10.22;  $I^2 = 0\%$ ).

Figure 48: The effect of LABA/ICS versus ICS monotherapy on days with optimal control



A subgroup analysis based on comparison ICS dose failed to identify a difference between low (WMD = 7.60; 95% CI: 2.95 to 12.25) and medium (WMD = 8.25; 95% CI: 5.90 to 10.61;  $I^2 = 0\%$ ) dose comparisons.

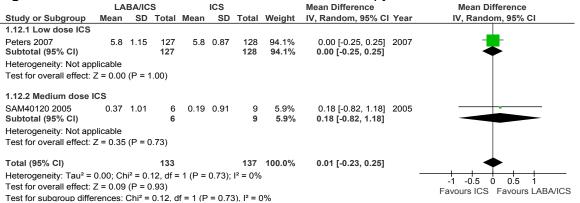
*Mean ICS dose:* One trial<sup>119</sup> involving 1,890 participants (LABA/ICS = 947, ICS = 943) provided data on the effects of LABA/ICS combination therapy compared with higher ICS monotherapy on mean ICS dose (Figure X). The result indicated a statistically significant decrease in ICS dose favouring LABA/ICS (SMD = -0.20; 95% CI: -0.30 to -0.11).

*Change in ICS dose:* One trial<sup>105</sup> involving 2,760 participants (LABA/ICS = 1,834, ICS = 926) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on change in ICS dose (Figure X). The result indicated a statistically significant difference favouring LABA/ICS (RR = 0.53; 95% CI: 0.43 to 0.64).

#### Health-related quality of life measures

Asthma quality of life questionnaire (AQLQ): Two trials<sup>53,123</sup> involving 270 participants (LABA/ICS = 133, ICS = 137) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with higher-dose ICS monotherapy on change in AQLQ score (Figure X). The pooled result failed to demonstrate a statistically significant difference between treatments (WMD = 0.01; 95% CI: -0.23 to 0.25;  $I^2 = 0\%$ ). Moreover, the precision of the 95% CI suggests that the two treatments are clinically equivalent (MCID = ±0.5).

#### Figure 49: The effect of LABA/ICS versus ICS monotherapy on AQLQ score

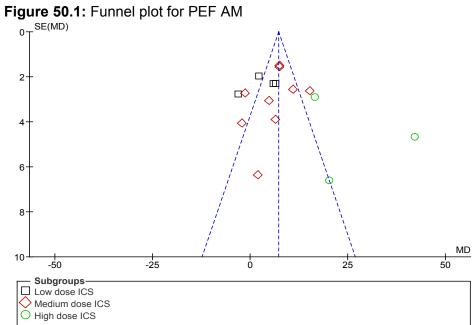


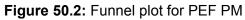
One trial<sup>79</sup> involving 148 participants (LABA/ICS = 74, ICS = 74) receiving either LABA/ICS combination or ICS monotherapy at run-in provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on the AQLQ. The result failed to indicate a difference between the two treatments that was statistically significant or clinically important (WMD = 0.08; 95% CI: -0.06 to 0.22).

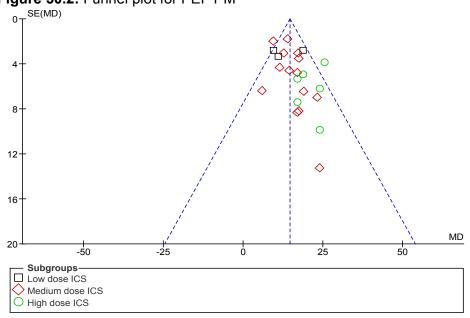
It was not considered appropriate to conduct subgroup analyses based on asthma severity as only a small proportion of studies (< 20% of available studies for any single outcome) reported results for populations restricted to a single asthma severity class.

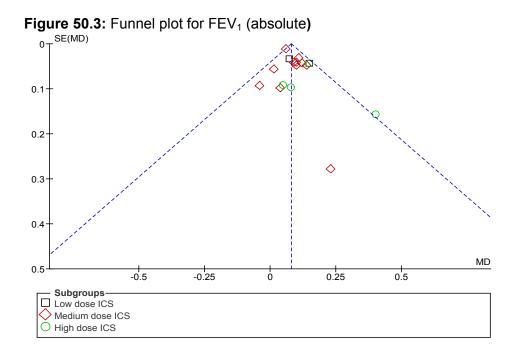
#### **Publication bias**

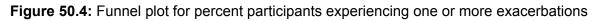
Meta-analyses for six measures (PEF AM, PEF PM, absolute FEV<sub>1</sub>, percent participants experiencing one or more exacerbations, SABA use, and SFD) contained enough studies of varying size to warrant an assessment of publication bias through funnel plot analysis (Figures 50.1-6). There was evidence of asymmetry in the funnel plot for PEF PM (Figure 50.2) indicating possible publication bias and an associated overestimation of the treatment effect. There was evidence of asymmetry in the funnel plots for PEF AM, absolute FEV<sub>1</sub>, % participants with  $\geq$ 1 exacerbations, SABA use, and SFD (Figure 50.1, Figure 50.3, Figure 50.4, Figure 50.5, Figure 50.6) indicating possible publication bias; however, the direction of the asymmetry suggested that the bias may serve to underestimate the treatment effect associated with LABA/ICS.

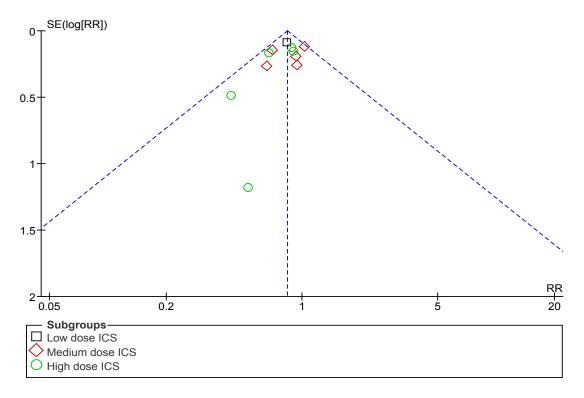












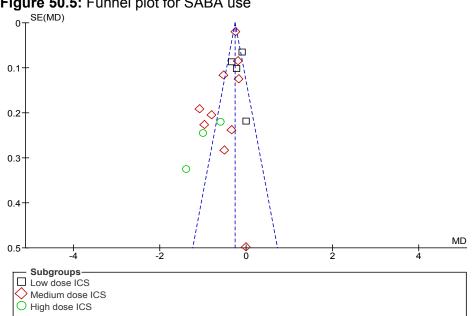
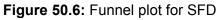
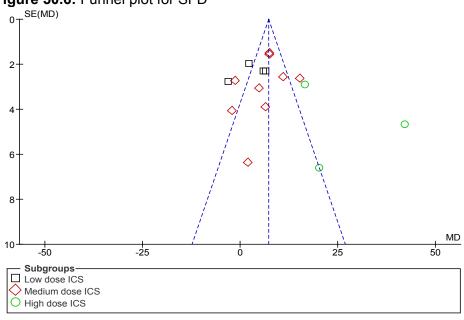


Figure 50.5: Funnel plot for SABA use





**Effectiveness of LABA/ICS therapy versus a different LABA/ICS therapy in adults** Twelve unique RCTs<sup>10,11,127-136</sup> were identified that assessed the comparative efficacy of LABA/ICS combination therapies for adult persistent asthma against one another. Nine trials<sup>10,11,127-131,133,136</sup> compared FORM/BUD vs SAL/FP, two compared FORM/BDP vs SAL/FP,<sup>134,135</sup> and one compared FORM/BUD vs FORM/BDP.<sup>132</sup> Eight trials<sup>10,128-130,132,134-136</sup> compared fixed dose vs fixed dose. Three trials<sup>127,131,133</sup> compared variable dose vs fixed dose. One trial<sup>131</sup> compared variable dose vs variable dose . LABA/ICS vs a similar dose of LABA/ICS was examined in 8 trials,<sup>11,127-129,131,133,134,136</sup> and the remaining four trials<sup>10,130,132,135</sup>

assessed LABA/ICS vs a higher dose (double or greater) of LABA/ICS (categorization of dose was based on the ICS dose). The age of included participants was  $\geq 18$  years in 4 (33.3%) studies.<sup>11,128,132,135</sup> In terms of asthma severity, two trials<sup>128,135</sup> included only participants with moderate asthma. The remaining trials examine participants covering a range of asthma severity: intermittent-moderate (2 trials),<sup>11,129</sup> intermittent-severe (2 trials),<sup>131,133</sup> mild-severe (2 trials),<sup>127,136</sup> and moderate-severe (4 trials).<sup>10,130,132,134</sup> The duration of the trials varied: 12 wk (6 trials),<sup>127,130,132,134-136</sup> 24 wk (2 trials),<sup>128,133</sup> 26 wk,<sup>10,129</sup> and 52 wk (2 trials).<sup>11,131</sup> The median treatment duration was 18 wk (IQR: 12, 26).

An additional seven RCTs<sup>105,186-191</sup> compared FORM/BUD fixed dosing versus FORM/BUD variable dosing and were retained for potential indirect comparison analysis.

### Methodological quality

Overall, the methodological quality of the twelve included studies was high (Table 6). The overall scores from the Jadad quality assessment tool ranged from 2-5 with a median score of 5 (IQR: 4 to 5). Only one trial<sup>133</sup> was considered to be low quality according to this scale (Jadad score < 3). Allocation concealment was considered adequate in 5 (41.7%) of studies and unclear in 7 (58.3%).

All included studies were randomized controlled trials; however, only 9 (75.0%) described the randomization method and were judged to have employed adequate randomization procedures. Double-blinding was reported in 10 (83.3%) trials, each explicitly describing the methods by which investigator and participants were blinded to the intervention. Withdrawals or dropouts, if any occurred, and the accounting of all participants was reported in all 12 trials. Due to the relatively high scores (Jadad score  $\geq$  3) of almost all studies, no sensitivity analyses based on quality were conducted.

Table 6: Methodological quality of combination head-to-	head LABA/ICS studies
Quality Components	No. Yes (%)
Randomization	12 (100)
Double-blinding	10 (83.3)
Description of withdrawals/dropouts	12 (100)
Appropriate method of randomization	9 (75.0)
Appropriate method of double-blinding	10 (83.3)
Inappropriate method of randomization	0 (0)
Inappropriate method of double-blinding	0 (0)
Adequate concealment of treatment allocation	5 (41.7)
Inadequate concealment of treatment allocation	0 (0)
Unclear concealment of treatment allocation	7 (58.3)

**Pulmonary function measures** *PEF AM:* Eight trials<sup>10,11,127-130,133,136</sup> involving 9,115 participants (FORM/BUD = 4,858; SAL/FP = 4,257) provided data for a meta-analysis of the effects of FORM/BUD compared with SAL/FP on PEF AM (L/min) (Figure 51). The combined result indicated a statistically significant difference favouring FORM/BUD (WMD = -1.89 L/min; 95% CI: -3.74 to -0.04; I<sup>2</sup> =

0%); however, the result did not meet our a priori criteria for clinical importance (MCID = 18.79 L/min).

	FOR	RM/BUD		SA	AL/FP			Mean Difference	Mean Difference
Study or Subgroup	Mean [L/min]		Total			Total	Weight	IV, Random, 95% CI [L/min]	
Aalbers 2004	24.3	32.5	434	24.9	32.5	224	12.5%	-0.60 [-5.84, 4.64]	
Bousquet 2007	29.5	43.9	1144	30.3	43.9	1145	26.5%	-0.80 [-4.40, 2.80]	
Busse 2008	32.754	44.59	793	33.59	44.02	391	12.0%	-0.84 [-6.19, 4.52]	
Dahl 2006	41.4	47.5	697	41.8	44.8	694	14.6%	-0.40 [-5.25, 4.45]	-+-
Fitzgerald 2005	390.6	45.5	344	400.1	45.5	344	7.4%	-9.50 [-16.30, -2.70]	<b>_</b>
Kuna 2007	26.8	44.6	1105	29.3	44.6	1123	25.0%	-2.50 [-6.20, 1.20]	
Ringdal 2002	41	101	167	43	101	157	0.7%	-2.00 [-24.01, 20.01]	
SAM40010 2004	29	80.71	174	37	79.9	179	1.2%	-8.00 [-24.76, 8.76]	· · · · ·
Total (95% CI)			4858			4257	100.0%	-1.89 [-3.74, -0.04]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> = 6.52	2, df = 7 (P =	0.48); l <sup>:</sup>	<sup>2</sup> = 0%					-20 -10 0 10 20
Test for overall effect:	Z = 2.00 (P = 0.0	05)							Favours SAL/FP Favours FORI

Figure 51: The effect of	FORM/BUD versus SAL/FP	on PEF AM (L/min)

Two trials<sup>134,135</sup> involving 469 participants (FORM/BDP = 240, SAL/FP = 229) provided data for a meta-analysis of the effects of FORM/BDP compared with SAL/FP on PEF AM (L/min). The combined result indicated a difference favouring SAL/FP (WMD=-8.11 L/min; 95% CI: - 20.24 to 4.02;  $I^2 = 0\%$ ); however, the result was neither statistically nor clinically important (MCID = 18.79 L/min).

One trial<sup>132</sup> involving 216 participants (FORM/BUD = 109, FORM/BDP = 107) provided data for an analysis on the effects of FORM/BDP therapy compared with FORM/BUD on PEF AM (L/min). The result indicated a difference favouring FORM/BDP (WMD=-0.80; 95% CI: -13.70 to 12.10); however, the result was neither statistically significant nor clinically important (MCID = 18.79 L/min).

**PEF PM:** Four trials<sup>10,127,129,136</sup> involving 5,531 participants (FORM/BUD = 2,857, SAL/FP = 2,674) provided data for a meta-analysis of the effects of FORM/BUD compared with SAL/FP on PEF PM (L/min) (Figure 52). The pooled result failed to identify a statistically significant difference between the treatments (WMD = -0.29; 95% CI: -2.51 to 1.93;  $I^2 = 0\%$ ). In addition, the precision of the confidence intervals suggest that any differences would not meet our a priori criteria for clinical importance (MCID=18.79 L/min).

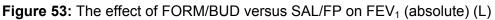
i igaio vai	1110 0110				101040	0, 1			
-	FOF	RM/BUD		SA	AL/FP			Mean Difference	Mean Difference
Study or Subgroup	Mean [L/min]	SD [L/min]	Total	Mean [L/min]	SD [L/min]	Total	Weight	IV, Random, 95% CI [L/min]	IV, Random, 95% CI [L/min]
Aalbers 2004	14.5	30.7	434	17.6	30.7	224	20.1%	-3.10 [-8.05, 1.85]	
Bousquet 2007	25.5	42.7	1144	24.1	42.7	1145	40.3%	1.40 [-2.10, 4.90]	
Kuna 2007	22.1	44	1105	22.8	44	1123	36.9%	-0.70 [-4.35, 2.95]	
SAM40010 2004	1	64.64	174	0	64.76	182	2.7%	1.00 [-12.44, 14.44]	
Total (95% CI)			2857			2674	100.0%	-0.29 [-2.51, 1.93]	•
Heterogeneity: Tau <sup>2</sup> =	= 0.00; Chi <sup>2</sup> = 2.22	2, df = 3 (P =	0.53); l <sup>:</sup>	<sup>2</sup> = 0%					-20 -10 0 10 20
Test for overall effect	: Z = 0.26 (P = 0.8	30)							Favours SAL/FP Favours FORM/BUE

Figure 52: The effect of FORM/BUD versus SAL/FP on PEF PM (L/min)

Two trials<sup>134,135</sup> involving 469 participants (FORM/BDP = 240, SAL/FP = 229) provided data for a meta-analysis of the effects of FORM/BDP compared with SAL/FP on PEF PM (L/min). The pooled result failed to identify a statistically significant difference between the treatments (WMD=-6.01; 95% CI: -19.89 to 7.87;  $I^2 = 21\%$ ). Due to small sample size, the 95% CIs of the pooled result include a possible value that would meet our a priori criteria for clinical importance (MCID = 18.79 L/min).

One trial<sup>132</sup> involving 216 participants (FORM/BUD = 109, FORM/BDP = 107) provided data for an analysis on the effects of FORM/BDP therapy compared with FORM/BUD on PEF PM (L/min). This study failed to identify a statistically significant difference between the treatments (WMD = -0.07; 95% CI: -12.59 to 12.45). In addition, the precision of the confidence intervals suggest that any differences would not meet our a priori criteria for clinical importance (MCID = 18.79 L/min).

*FEV*<sub>1</sub> (*absolute*): Eight trials<sup>10,127-131,133,136</sup> involving 11,119 participants (FORM/BUD = 5,851, SAL/FP = 5,268) provided data for a meta-analysis of the effects of FORM/BUD compared to SAL/FP on absolute FEV<sub>1</sub> (L) (Figure 53). The pooled result failed to identify a statistically significant difference between the treatments (WMD=0.01; 95% CI: -0.01 to 0.03; I<sup>2</sup> = 22%). In addition, the precision of the confidence intervals suggest that any differences would not meet our a priori criteria for clinical importance (MCID=0.23 L).



	FO	RM/BU	D	S	SAL/FP			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Aalbers 2004	0.18	0.3	434	0.13	0.3	224	11.5%	0.05 [0.00, 0.10]	
Bousquet 2007	0.23	0.528	1144	0.22	0.528	1145	13.7%	0.01 [-0.03, 0.05]	
Busse 2008	0.14	0.266	783	0.16	0.31	391	17.9%	-0.02 [-0.06, 0.02]	
Dahl 2006	0.27	0.528	697	0.29	0.527	694	9.2%	-0.02 [-0.08, 0.04]	
Kuna 2007	0.24	0.4	1105	0.24	0.4	1123	19.9%	0.00 [-0.03, 0.03]	
Ringdal 2002	0.26	0.4	194	0.27	0.4	189	4.8%	-0.01 [-0.09, 0.07]	
SAM40010 2004	2.491	0.389	78	2.528	0.379	90	2.4%	-0.04 [-0.15, 0.08]	
Vogelmeier 2005	0.17	0.38	1067	0.14	0.38	1076	20.8%	0.03 [-0.00, 0.06]	
Total (95% CI)			5502			4932	100.0%	0.01 [-0.01, 0.02]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Ch	ni² = 8.9	9, df = <sup>-</sup>	7 (P = 0	.25); l² :	= 22%			-0.2 -0.1 0 0.1 0.2
Test for overall effect:	Z = 0.70	(P = 0.	48)						Favours SAL/FP Favours FORM/BU

Two trials<sup>134,135</sup> involving 469 participants (FORM/BDP = 240, SAL/FP = 229) provided data for a meta-analysis of the effects of FORM/BDP compared with SAL/FP on FEV<sub>1</sub> (L). The pooled result failed to identify a statistically significant difference between the treatments (WMD = 0.01; 95% CI: -0.18 to 0.15;  $I^2 = 75\%$ ). In addition, the precision of the confidence intervals suggest that any differences would not meet our a priori criteria for clinical importance (MCID = 0.23 L).

One trial<sup>132</sup> involving 216 participants (FORM/BUD = 109, FORM/BDP = 107) provided data for an analysis on the effects of FORM/BDP compared with FORM/BUD on FEV<sub>1</sub> (L). This study did not identify a statistically significant difference between the treatments (WMD = 0.05; 95% CI: -0.07 to 0.17). In addition, the precision of the confidence intervals suggest that any differences would not meet our a priori criteria for clinical importance (MCID = 0.23 L).

*FEV*<sub>1</sub> % *predicted:* One trial<sup>135</sup> involving 241 participants (FORM/BDP = 125, SAL/FP =116) provided data for an analysis on the effects of FORM/BDP therapy compared with SAL/FP on FEV<sub>1</sub> % predicted (Figure 54). The result did not identify a statistically significant difference between the treatments (WMD=-3.10; 95% CI: -6.89 to 0.69). In addition, the precision of the confidence intervals suggest that any differences would not meet our a priori criteria for clinical importance (MCID = 12%).

#### Asthma symptom control measure

**Total number of exacerbations:** Six trials<sup>10,11,127,128,130,133</sup> involving 6,682 participants (FORM/BUD = 3,652, SAL/FP = 3,030) provided data for a meta-analysis on the effects of FORM/BUD compared with SAL/FP on the total number of exacerbations during the study period (Figure 54). The study periods ranged from 3 to 12 months follow-up. The pooled result failed to identify a statistically significant difference between the treatments (WMD = 0.06; 95% CI: -0.02 to 0.15; I<sup>2</sup> = 95%). In addition, the precision of the confidence intervals suggest that any differences would not meet our a priori criteria for clinical importance.

**Figure 54:** The effect of FORM/BUD versus SAL/FP on total number of exacerbations during study period

Mean	RM/BU SD	-	-	SAL/FP SD	Total	Weight	Mean Difference IV, Random, 95% Cl	Mean Diff IV, Randon	
0.196	0.157	434	0.263	0.194	224	17.5%	-0.07 [-0.10, -0.04]		,
0.119	0.324	1151	0.15	0.357	1153	17.5%	-0.03 [-0.06, -0.00]		
0.219	0.414	811	0.189	0.392	404	16.9%	0.03 [-0.02, 0.08]	+	-
0.223	0.67	697	0.155	0.67	694	15.8%	0.07 [-0.00, 0.14]	F	
0.279	0.449	344	0.145	0.352	344	16.3%	0.13 [0.07, 0.19]		<b>_</b>
0.735	0.35	215	0.472	0.35	211	16.0%	0.26 [0.20, 0.33]		
		3652			3030	100.0%	0.06 [-0.02, 0.15]		
,		,	= 5 (P <	< 0.000	01); l² =	95%		-0.2 -0.1 0	0.1 0.2
	0.196 0.119 0.219 0.223 0.279 0.735	0.196 0.157 0.119 0.324 0.219 0.414 0.223 0.67 0.279 0.449 0.735 0.35 0.01; Chi <sup>2</sup> = 108	0.196         0.157         434           0.119         0.324         1151           0.219         0.414         811           0.223         0.67         697           0.279         0.449         344           0.735         0.35         215           3652	0.196 0.157 434 0.263 0.119 0.324 1151 0.15 0.219 0.414 811 0.189 0.223 0.67 697 0.155 0.279 0.449 344 0.145 0.735 0.35 215 0.472 3652 0.01; Chi <sup>2</sup> = 108.91, df = 5 (P -	0.196 0.157 434 0.263 0.194 0.119 0.324 1151 0.15 0.357 0.219 0.414 811 0.189 0.392 0.223 0.67 697 0.155 0.67 0.279 0.449 344 0.145 0.352 0.735 0.35 215 0.472 0.35 3652 0.01; Chi <sup>2</sup> = 108.91, df = 5 (P < 0.0000	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$            0.196  0.157  434  0.263  0.194  224  17.5\%  -0.07 \ [-0.10, -0.04] \\ 0.119  0.324  1151  0.15  0.357  1153  17.5\%  -0.03 \ [-0.06, -0.00] \\ 0.219  0.414  811  0.189  0.392  404  16.9\%  0.03 \ [-0.02, 0.08] \\ 0.223  0.67  697  0.155  0.67  694  15.8\%  0.07 \ [-0.00, 0.14] \\ 0.279  0.449  344  0.145  0.352  344  16.3\%  0.13 \ [0.07, 0.19] \\ 0.735  0.35  215  0.472  0.35  211  16.0\%  0.26 \ [0.20, 0.33] \\ \hline 3652 \qquad 3030  100.0\%  0.06 \ [-0.02, 0.15] \\ 0.01; \ Chi^2 = 108.91, \ df = 5 \ (P < 0.00001); \ l^2 = 95\%  -7 \\ \hline $	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

*Time to first exacerbation:* Four trials<sup>10,129,131,133</sup> involving 7,470 participants (FORM/BUD = 3,712, SAL/FP = 3,758) provided data for a meta-analysis of the effects of FORM/BUD compared with SAL/FP on the time to first exacerbation (Figure 55). The combined result indicated a statistically significant difference favouring FORM/BUD (Hazard Ratio=0.82; 95% CI: 0.72 to 0.93).

Figure 55: The effect of FORM/BUD versus SAL/FP on time to first exacerbation

Study or Subgroup	log[Hazard Ratio]	SE	FORM/BUD Total		Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Bousquet 2007	-0.198	0.128	1151	1153	26.8%	0.82 [0.64, 1.05]	
Busse 2008	-0.166	0.245	389	406	7.3%	0.85 [0.52, 1.37]	
Kuna 2007	-0.0943	0.125	1105	1123	28.1%	0.91 [0.71, 1.16]	
Vogelmeier 2005	-0.2877	0.108	1067	1076	37.7%	0.75 [0.61, 0.93]	
Total (95% CI)			3712	3758	100.0%	0.82 [0.72, 0.93]	•
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:		= 3 (P =	0.71); l² = 0%	•		Fa	0.5 0.7 1 1.5 2 vours FORM/BUD Favours SAL/FP

One trial<sup>134</sup> involving 228 participants (FORM/BDP = 115, SAL/FP = 113) provided data on the effects of FORM/BDP compared with SAL/FP on time to first exacerbation. This study did not identify a statistically significant difference between the treatments (Hazard Ratio=0.67; 95% CI: 0.28 to 1.58). Due to small sample size, the 95% CIs of the estimate include possible values that would meet our a priori criteria for clinical importance.

One trial<sup>132</sup> involving 216 participants (FORM/BUD = 109, FORM/BDP = 107) provided data on the effects of FORM/BDP compared with FORM/BUD on time to first exacerbation. This study did not identify a statistically significant difference between the treatments (Hazard Ratio=0.83; 95% CI: 0.56 to 1.23). Due to small sample size, the 95% CIs of the estimate include possible values that would meet our a priori criteria for clinical importance.

**Proportion of participants with**  $\geq 1$  or more exacerbations: Three trials<sup>128,133,136</sup> involving 2,979 participants (FORM/BUD = 1,691, SAL/FP = 1,288) provided data for a meta-analysis on the effects of FORM/BUD compared to SAL/FP on the proportion of participants with  $\geq 1$  exacerbations (Figure 56). The combined result did not identify a statistically significant difference between the treatments (RR=1.03; 95% CI: 0.95 to 1.11; I<sup>2</sup> = 0%); however, the 95% CIs of the pooled estimate include possible values that would meet our a priori criteria for clinical importance.

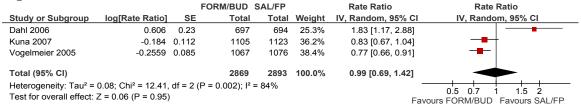
Figure 56: The effect of FORM/BUD versus SAL/FP on % participants with ≥1 exacerbations



One trial<sup>134</sup> involving 228 participants (FORM/BDP = 115, SAL/FP = 113) provided data on the effects of FORM/BDP compared with SAL/FP on the percentage of participants with  $\geq 1$  exacerbations. This study did not identify a statistically significant difference between the treatments (RR=0.66; 95% CI: 0.28 to 1.54); however, 95% CIs include possible values that would meet our a priori criteria for clinical importance.

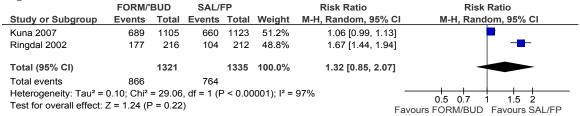
One trial<sup>132</sup> involving 216 participants (FORM/BUD = 109, FORM/BDP = 107) provided data on the effects of FORM/BDP compared with FORM/BUD on the percentage of participants with  $\geq$ 1 exacerbations. This study did not identify a statistically significant difference between the treatments (RR=0.69; 95% CI: 0.35 to 1.38); however, the 95% CIs include possible values that would meet our a priori criteria for clinical importance.

*Number of severe exacerbations:* Three trials<sup>128,129,131</sup> involving 5,762 participants (FORM/BUD = 2,869, SAL/FP = 2,893) provided data for a meta-analysis on the effects of FORM/BUD compared to SAL/FP on the number of severe exacerbations (Figure 57). The combined result did not identify a statistically significant difference between the treatments (RR=0.99; 95% CI: 0.69 to 1.42; I<sup>2</sup>=84%); however, the 95% CIs of the pooled estimate include possible values that would meet our a priori criteria for clinical importance. Dahl 2006<sup>128</sup> only included participants with moderate asthma, while the other two studies<sup>129,131</sup> included participants with intermittent-moderate asthma<sup>129</sup> and intermittent-severe asthma<sup>131</sup>.



*Number of mild exacerbations:* Two trials<sup>129,130</sup> involving 2,656 participants (FORM/BUD = 1,321, SAL/FP = 1,335) provided data for a meta-analysis on the effects of FORM/BUD compared with SAL/FP on the number of mild exacerbations. (Figure 58) The combined results did not identify a statistically significant difference between the treatments (RR=1.32; 95% CI: 0.85 to 2.07;  $I^2 = 97\%$ ). Heterogeneity may be explained by variations in study patient selection; Kuna 2007<sup>129</sup> included participants with intermittent-moderately severe asthma, while Ringdal 2002<sup>130</sup> included participants with moderate-severe asthma.

Eiguro EQ. The	offect of EORM/RUD ver	aug SAL/ED on numbo	r of mild overerbetions
rigure so. The	effect of FORM/BUD ver	SUS SAL/FF ON NUMBE	



One trial<sup>132</sup> involving 216 participants (FORM/BUD = 109, FORM/BDP = 107) provided data on the effects of FORM/BDP compared with FORM/BUD on the number of mild exacerbations. This study did not identify a statistically significant difference between the treatments (RR=0.65; 95% CI: 0.31 to 1.39); however, the 95% CIs of the pooled estimate include possible values that would meet our a priori criteria for clinical importance.

**SABA use (puffs/day):** Six trials<sup>10,11,127,129,131,133</sup> involving 9,210 participants (FORM/BUD = 4,894, SAL/FP = 4,316) provided data for a meta-analysis on the effects of FORM/BUD compared to SAL/FP on SABA use (puffs/day) (Figure 59). The combined result failed to demonstrate a statistically significant difference between the two groups (WMD=-0.03; 95% CI: -0.12 to 0.07;  $I^2$ =77%). In addition, the precision of the confidence intervals suggest that any differences would not meet our a priori criteria for clinical importance (MCID = -0.81 puffs/day). Heterogeneity may be explained by variations in study treatments; Vogelmeier 2005<sup>131</sup> was the only study that used a variable versus variable dosing strategy.

#### Figure 59: The effect of FORM/BUD versus SAL/FP on SABA use (puffs/day)

	FOF	RM/BUD		SA	AL/FP			Mean Difference	Mean Difference
Study or Subgroup	Mean [puff/sday]	SD [puff/sday]	Total	Mean [puff/sday]	SD [puff/sday]	Total	Weight	IV, Random, 95% CI [puff/sday]	IV, Random, 95% CI [puff/sday]
Aalbers 2004	-0.86	1.04	434	-0.81	1.04	224	13.7%	-0.05 [-0.22, 0.12]	
Bousquet 2007	-1.3	1	1151	-1.26	1	1153	20.7%	-0.04 [-0.12, 0.04]	
Busse 2008	-1.369	1.838	793	-1.3	1.62	396	11.3%	-0.07 [-0.27, 0.14]	
Fitzgerald 2005	0.18	0.407	344	0.11	0.304	344	22.8%	0.07 [0.02, 0.12]	
Kuna 2007	-1.27	1.05	1105	-1.37	1.05	1123	20.3%	0.10 [0.01, 0.19]	
Vogelmeier 2005	0.58	2.45	1067	0.93	2.45	1076	11.1%	-0.35 [-0.56, -0.14]	
Total (95% CI)			4894			4316	100.0%	-0.03 [-0.12, 0.07]	•
Heterogeneity: Tau <sup>2</sup> =	0.01; Chi <sup>2</sup> = 22.08, d	f = 5 (P = 0.0005)	); l <sup>2</sup> = 7	7%				-	
Test for overall effect:	Z = 0.54 (P = 0.59)							Fav	-0.5 -0.25 0 0.25 0.5 rours FORM/BUD Favours SAL/FP

One trial<sup>134</sup> involving 228 participants (FORM/BDP = 115, SAL/FP = 113) provided data on the effects of FORM/BDP compared with SAL/FP on SABA use (puffs/day). The combined results failed to demonstrate a statistically significant difference between the two groups (WMD = -0.19; 95% CI: -0.04 to 0.42). In addition, the precision of the confidence intervals suggest that any differences would not meet our a priori criteria for clinical importance (MCID = -0.81 puffs/day).

One trial<sup>132</sup> involving 216 participants (FORM/BUD = 109, FORM/BDP = 107) provided data for an analysis on the effects of FORM/BDP therapy compared with FORM/BUD on SABA use (puffs/day). This study failed to demonstrate a statistically significant difference between the two groups (WMD=-0.01; 95% CI: -0.33 to 0.31). In addition, the precision of the confidence intervals suggest that any differences would not meet our a priori criteria for clinical importance (MCID = -0.81 puffs/day).

Symptom free days (SFD): Six trials<sup>10,11,128,129,133,136</sup> involving 8,167 participants (FORM/BUD = 4,268, SAL/FP = 3,899) provided data for a meta-analysis on the effects of FORM/BUD compared to SAL/FP on symptom free days (SFD) as measured by median % SFD (Figure 60). The combined result indicated a statistically significant difference between SAL/FP and FORM/BUD (WMD=-1.60; 95% CI: -3.03 to -0.17;  $I^2 = 0\%$ ).

Figure 60: The effect of FORM/BUD versus SAL/FP on symptom free days (SFD) (median %)

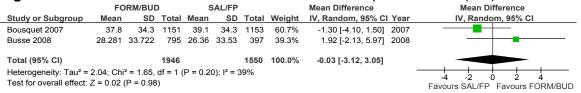
	FOR	M/BUD		SA	L/FP			Mean Difference	Mean Difference
Study or Subgroup	Mean [median %]	SD [median %]	Total	Mean [median %]	SD [median %]	Total	Weight	IV, Random, 95% CI [median %]	IV, Random, 95% CI [median %]
Bousquet 2007	36.4	34.3	1151	36.9	34.3	1153	26.1%	-0.50 [-3.30, 2.30]	
Busse 2008	26.185	34.569	789	25.39	33.41	395	12.3%	0.79 [-3.29, 4.88]	
Dahl 2006	60	25	697	63	25	694	29.7%	-3.00 [-5.63, -0.37]	
Fitzgerald 2005	52.1	61.9	344	58.8	66	344	2.2%	-6.70 [-16.26, 2.86]	
Kuna 2007	35.8	33.7	1105	37.4	33.7	1123	26.2%	-1.60 [-4.40, 1.20]	
SAM40010 2004	38.6	36.5	182	41.6	38.7	190	3.5%	-3.00 [-10.64, 4.64]	<del></del>
Total (95% CI)			4268			3899	100.0%	-1.60 [-3.03, -0.17]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup> = 4.23, df =	= 5 (P = 0.52); I <sup>2</sup> =	0%						-20 -10 0 10 20
Test for overall effect:	Z = 2.19 (P = 0.03)								Favours SAL/FP Favours FORM/BUI
									Favours SAL/FP Favours FORM/B

Two trials<sup>134,135</sup> involving 469 participants (FORM/BDP = 240, SAL/FP = 229) provided data for a meta-analysis of the effects of FORM/BDP compared with SAL/FP on median % SFD. The combined result failed to demonstrate a statistically significant difference between the two groups (WMD = -1.07; 95% CI: -6.22 to 8.35;  $I^2 = 0\%$ ).

One trial<sup>132</sup> involving 216 participants (FORM/BUD = 109, FORM/BDP = 107) provided data for an analysis on the effects of FORM/BDP therapy compared with FORM/BUD on median % SFD. The result failed to demonstrate a statistically significant difference between the two groups (WMD=-4.00; 95% CI: -21.60 to 13.60).

**Days with optimal control (OC):** Two trials<sup>10,133</sup> involving 3,496 participants (FORM/BUD = 1,946, SAL/FP = 1,550) provided data for an analysis on the effects of FORM/BUD therapy compared with SAL/FP on days with optimal control (OC). (Figure 61) The combined results did not identify a statistically significant difference between the treatments (WMD=-0.03; 95% CI: - 3.12 to 3.05;  $I^2 = 39\%$ ).

Figure 61: The effect of FORM/BUD versus SAL/FP on optimal control	$(\Omega C)$
<b>Figure 61.</b> The effect of FORM/BOD versus SAL/FF of optimal control	(UU)



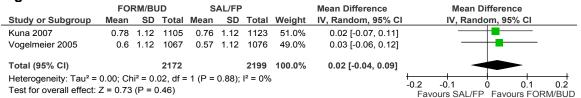
% participants stepping down their dose: One trial<sup>131</sup> involving 2143 participants (FORM/BUD = 1067, SAL/FP = 1076) provided data for an analysis on the effects of FORM/BUD therapy compared with SAL/FP on the % of participants stepping down their dose. The result favoured

FORM/BUD over SAL/FP (RR=1.22; 95% CI: 1.09 to 1.37). This difference was statistically significant.

**Proportion symptom free days (SFD):** One trial<sup>127</sup> involving 658 participants (FORM/BUD = 434, SAL/FP = 224) provided data for an analysis on the effects of FORM/BUD therapy compared with SAL/FP on the proportion of SFD. The result did not identify a statistically significant difference between the treatments (RR=1.00; 95% CI: 0.87 to 1.15).

**AQLQ:** Two trials<sup>129,131</sup> involving 4,371 participants (FORM/BUD = 2,172, SAL/FP = 2,199) provided data for an analysis on the effects of FORM/BUD therapy compared with SAL/FP on health-related quality of life as measured by the AQLQ score. (Figure 62) The combined results did not identify a statistically significant difference between the treatments (WMD=0.02; 95% CI: -0.04 to 0.09; I<sup>2</sup> = 0%). In addition, the precision of the confidence intervals suggest that any differences would not meet our a priori criteria for clinical importance (MCID = 0.5/q).

#### Figure 62: The effect of FORM/BUD versus SAL/FP on AQLQ



It was not considered appropriate to conduct subgroup analyses based on asthma severity as only a small proportion of studies (< 20% of available studies for any single outcome) reported results for populations restricted to a single asthma severity class.

### Potential steroid sparing effect of LABA/ICS maintenance therapy

Twelve unique RCTs<sup>49,137-147</sup> were identified that assessed the potential steroid sparing effects of LABA/ICS combination therapy versus ICS monotherapy. Seven trials<sup>49,137,138,140,141,144,147</sup> used an abrupt dose-reduction design in which asymptomatic patients receiving ICS monotherapy were randomized to the run-in dose of ICS monotherapy or half the run-in dose and a the addition of a LABA. One trial<sup>142</sup> used the abrupt dose-reduction design with patients symptomatic on ICS monotherapy. Four trials<sup>139,143,145,147</sup> used a dose tapering design in which asymptomatic patients receiving ICS monotherapy were randomized to either ICS alone or the same dose ICS and the addition of a LABA. Participants in both groups who achieved control were given the next dose down. This process was repeated until either treatment failure or until no drug was administered. These designs were sub-classified as Design 1 (e.g., abrupt reduction) and Design 2 (e.g., strep down reduction).

Six trials<sup>49,137,142,144-146</sup> compared SAL/FP vs FP alone, three<sup>138,140,141</sup> compared FORM/BUD vs BUD alone, one<sup>147</sup> compared SAL/BDP vs BDP alone, one<sup>139</sup> compared SAL/BUD vs BUD alone, and one<sup>143</sup> compared SAL/ICS vs ICS (unidentified) alone. A fixed dose of LABA/ICS was compared with a fixed dose of ICS in all trials. The age of included participants was  $\geq$ 18 years in 8 (66.7%) studies.<sup>138-141,143,145-147</sup> In terms of asthma severity, three trials<sup>49,137,146</sup> included only participants with moderate asthma and one<sup>145</sup> included only participants with severe asthma. The remaining trials examined participants covering a range of asthma severity: intermittent to mild (1 trial),<sup>147</sup> intermittent to severe (3 trials),<sup>138,140,141</sup> mild to moderate (1 trial),<sup>139</sup>, mild to severe (1 trial),<sup>144</sup> and moderate to severe (1 trial).<sup>143</sup> One trial<sup>142</sup> did not report the baseline severity of the study participants. Treatment duration also varied across studies: 12 wk (3 trials),<sup>49,142,144</sup> 20 wk (1 trial),<sup>141</sup> 24 wk (3 trials),<sup>137,145,146</sup> 26 wk (1 trial),<sup>147</sup> 48 wk (1 trial),<sup>143</sup> and 52 wk (2 trials).<sup>138,140</sup> The treatment duration in one trial<sup>139</sup> was unclear because it varied depending on participants' baseline ICS dose and asthma control. The median duration of treatment was 24 weeks (IQR: 16, 37).

#### Methodological quality

Overall, the methodological quality of included steroid sparing studies (n = 12) was moderate (Table 7). The Jadad quality assessment scores ranged from 2-5 with a median score of 3 (IQR, 3 to 3.5). All included studies were randomized controlled trials; however, only 2 (16.7%) adequately described their method for randomization and used an appropriate method of randomization. Double-blinding was reported in 12 (100) trials with 2 (16.7%) explicitly describing appropriate methods by which investigators and participants were blinded to the intervention. Withdrawals or dropouts, if any occurred, and the accounting of all participants was reported in 10 (83.3%) trials. Allocation concealment was considered adequate in 1 (8.3%) of studies and unclear in 11 (91.7%). Due to the relatively high scores (Jadad score  $\geq$ 3) of almost all studies, no sensitivity analyses were conducted.

Table 7: Methodological quality of steroid sparing studies (N = 12)									
Quality Components	No. Yes (%)								
Randomization	12 (100)								
Double-blinding	12 (100)								
Description of withdrawals/dropouts	10 (83.3)								
Appropriate method of randomization	2 (16.7)								
Appropriate method of double-blinding	3 (25.0)								
Inappropriate method of randomization	0 (0)								
Inappropriate method of double-blinding	0 (0)								
Adequate concealment of treatment allocation	1 (8.3)								
Inadequate concealment of treatment allocation	0 (0)								
Unclear concealment of treatment allocation	11 (91.7)								

### Pulmonary function measures

**PEF** AM: Ten trials<sup>49,137,139-142,144-147</sup> involving 2,660 participants (LABA/ICS =1,334, ICS = 1,326) provided data for a meta-analysis of the potential steroid sparing effects of LABA/ICS combination therapy compared with ICS monotherapy on morning PEF (L/min) (Figure 63). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 18.20 L/min; 95% CI: 14.24 to 22.16; I<sup>2</sup> = 0%). The lack of precision of the estimates prevents conclusions regarding the equivalence of the two treatments (MCID =  $\pm$ 18.79 L/min).

A subgroup analysis based on study design failed to indicate an important difference between treatment for Design 1 (WMD = 17.68 L/min; 95% CI: 13.25 to 21.90;  $I^2 = 0\%$ ) and a statistically significant and clinically important difference for Design 2 (WMD: 21.44 L/min; 95% CI: 21.44 to 31.28;  $I^2 = 0\%$ ) (MCID = 18.79 L/min).

Study or Subgroup         I           1.1.1 Design 1         Busse 2003           Pauwels 1997         Pohl 2005           SAM40090 2005         SAS40026 2006           Schermer 2007         SMS40012 2006		73.45 91 91 31.21 81.4 118	Total 155 425 63 234 178 69	Mean [L/min] 32.5 -4.5 398 1.9 33	84.11 84 84 30.97	Total 153 427 63 235	5.0% 11.3% 1.7%	Mean Difference IV, Random, 95% CI [L/min] 12.70 [-4.94, 30.34] 25.50 [13.74, 37.26] 9.00 [-21.58, 39.58]	Mean Difference IV, Random, 95% CI [L/min]
1.1.1 Design 1 Busse 2003 Pauwels 1997 Pohl 2005 SAM40090 2005 SAS40026 2006 Schermer 2007	45.2 21 407 19.3 52.2 54	73.45 91 91 31.21 81.4 118	155 425 63 234 178	32.5 -4.5 398 1.9	84.11 84 84 30.97	153 427 63	5.0% 11.3% 1.7%	12.70 [-4.94, 30.34] 25.50 [13.74, 37.26] 9.00 [-21.58, 39.58]	
Pauwels 1997 Pohl 2005 SAM40090 2005 SAS40026 2006 Schermer 2007	21 407 19.3 52.2 54	91 91 31.21 81.4 118	425 63 234 178	-4.5 398 1.9	84 84 30.97	427 63	11.3% 1.7%	25.50 [13.74, 37.26] 9.00 [-21.58, 39.58]	
Pohl 2005 SAM40090 2005 SAS40026 2006 Schermer 2007	407 19.3 52.2 54	91 31.21 81.4 118	425 63 234 178	398 1.9	84 30.97	63	1.7%	9.00 [-21.58, 39.58]	
SAM40090 2005 SAS40026 2006 Schermer 2007	19.3 52.2 54	31.21 81.4 118	234 178	1.9	30.97				-+
SAS40026 2006 Schermer 2007	52.2 54	81.4 118	178			235			
Schermer 2007	54	118		33			49.5%	17.40 [11.77, 23.03]	<b>=</b>
			60		91.3	170	4.7%	19.20 [1.00, 37.40]	———
SMS40012 2006	12.1	40.00	09	20	118	68	1.0%	34.00 [-5.52, 73.52]	
		40.09	83	0.8	40.57	85	10.5%	11.30 [-0.90, 23.50]	<b>⊢</b>
Subtotal (95% CI)			1207			1201	83.8%	17.58 [13.25, 21.90]	♦
1.1.2 Design 2									
Nielsen 1999	17.4	37.18	15	3.7	37.05	19	2.5%	13.70 [-11.43, 38.83]	
SAM 40008 2004	34.2	34.98	84	10.9	34.98	76	13.3%	23.30 [12.45, 34.15]	
SAM30007 2005	13.6	123.6	28	6.1	120.6	30	0.4%	7.50 [-55.42, 70.42]	
Subtotal (95% CI)			127			125	16.2%	21.44 [11.60, 31.28]	•
Heterogeneity: Tau <sup>2</sup> = 0.	.00; Chi <sup>2</sup> = 0.67	, df = 2 (P = 0	0.72); l <sup>a</sup>	2 = 0%					
Test for overall effect: Z	= 4.27 (P < 0.0	001)							
Total (95% CI)			1334			1326	100.0%	18.20 [14.24, 22.16]	•
Heterogeneity: Tau <sup>2</sup> = 0.	.00; Chi <sup>2</sup> = 5.22	, df = 9 (P = 0	0.82); l <sup>a</sup>	<sup>2</sup> = 0%				-	
Test for overall effect: Z	= 9.01 (P < 0.0	0001)	,.						-50 -25 0 25 50 Favours ICS Favours LABA

#### Figure 63: Potential steroid-sparing effect of LABA/ICS vs ICS on PEF AM

**PEF PM:** Seven trials<sup>137,139,141,144-147</sup> involving 1,323 participants (LABA/ICS =662, ICS = 661) provided data for a meta-analysis of the potential steroid sparing effects of LABA/ICS combination therapy compared with ICS monotherapy on morning PEF (Figure 64). The pooled result indicated a difference favouring LABA/ICS (WMD = 16.12 L/min; 95% CI: 11.71 to 20.53;  $I^2 = 0\%$ ); however, the differences failed to reach the a priori criteria for clinical importance (MCID = 18.79 L/min). Due to the imprecision of these results clinical equivalence cannot be claimed.

A subgroup analysis failed to indicate important differences between Design 1 (WMD = 15.70 L/min; 95% CI: 10.80 to 20.59;  $I^2 = 0\%$ ) and Design 2 (WMD: 17.94 L/min; 95% CI: 7.78 to 28.09;  $I^2 = 0\%$ ).

LABA/ICS ICS Mean Difference Mean	Mean Difference
study or Subgroup Mean [L/min] SD [L/min] Total Mean [L/min] SD [L/min] Total Weight IV, Random, 95% CI [L/min] IV, Random	n, 95% CI [L/min]
.2.1 Design 1	
Busse 2003 49.4 73.45 155 31.3 76.69 153 6.9% 18.10 [1.33, 34.87]	<b>—</b>
Pohl 2005 411 76 63 404 76 63 2.8% 7.00 [-19.54, 33.54]	+
SAM40090 2005 19.2 32.28 234 1.6 32.04 235 57.3% 17.60 [11.78, 23.42]	- <b>-</b>
SMS40012 2006 10.3 42.8 83 1.8 34.1 85 14.1% 8.50 [-3.22, 20.22]	+
Subtotal (95% Cl) 535 536 81.2% 15.70 [10.80, 20.59]	•
leterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.35, df = 3 (P = 0.50); l <sup>2</sup> = 0%	
est for overall effect: Z = 6.29 (P < 0.00001)	
.2.2 Design 2	
lielsen 1999 14.1 41.44 15 3.2 41.85 19 2.4% 10.90 [-17.28, 39.08] —	+
SAM 40008 2004 26.8 35.6 84 7.2 35.6 76 15.9% 19.60 [8.55, 30.65]	
SAM30007 2005 5.1 125.7 28 6.6 122.1 30 0.5% -1.50 [-65.35, 62.35]	-
Subtotal (95% CI) 127 125 18.8% 17.94 [7.78, 28.09]	-
leterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.68, df = 2 (P = 0.71); l <sup>2</sup> = 0%	
est for overall effect: Z = 3.46 (P = 0.0005)	
otal (95% CI) 662 661 100.0% 16.12 [11.71, 20.53]	•
leterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.19, df = 6 (P = 0.79); l <sup>2</sup> = 0%	
-50 - 25 (set or over a line of the original of the origina	0 25 50 S Favours LAB/
est for subgroup differences: Chi <sup>2</sup> = 0.15, df = 1 (P = 0.70), l <sup>2</sup> = 0%	5 Favouis LAD/

#### Figure 64: Potential steroid-sparing effect of LABA/ICS vs ICS on PEF PM

*FEV*<sub>1</sub> (*absolute*): Seven trials<sup>49,137,139,141,142,145,146</sup> involving 1,171 participants (LABA/ICS = 592, ICS = 579) provided data for a meta-analysis of the potential steroid sparing effects of LABA/ICS combination therapy compared with ICS monotherapy on absolute FEV<sub>1</sub> (Figure 65). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD =

0.09 L; 95% CI: 0.06 to 0.12;  $I^2 = 0\%$ ). Moreover, the precision of the 95% CI suggests that the two treatments are clinically equivalent (MCID = ±0.23 L).

A subgroup analysis failed to indicate a clinically important difference between treatments for Design 1 (WMD = 0.09 L; 95% CI: 0.05 to 0.12;  $I^2 = 0\%$ ) and Design 2 (WMD: 0.15 L; 95% CI: -0.02 to 0.31;  $I^2 = 0\%$ ) which suggests that the two treatments are clinically equivalent (MCID = ±18.79 L/min).

**Figure 65:** Potential steroid-sparing effect of LABA/ICS vs ICS on FEV<sub>1</sub> (absolute)

	LA	BA/ICS			ICS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.3.1 Design 1									
Busse 2003	0.1	0.25	155	0	0.25	153	37.9%	0.10 [0.04, 0.16]	
Pohl 2005	0.36	0.46	63	0.37	0.46	63	4.6%	-0.01 [-0.17, 0.15]	-+-
SAS40026 2006	0.08	0.27	178	-0.01	0.26	170	38.1%	0.09 [0.03, 0.15]	
Schermer 2007 Subtotal (95% CI)	0.0758	0.308	69 <b>465</b>	-0.0045	0.211	68 <b>454</b>	15.1% <b>95.6%</b>	0.08 [-0.01, 0.17] <b>0.09 [0.05, 0.12]</b>	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi	² = 1.64	, df = 3	(P = 0.65	); I <sup>2</sup> = 0	%			
Test for overall effect:	Z = 4.89 (	(P < 0.0	0001)						
1.3.2 Design 2									
Nielsen 1999	0.16	0.81	15	-0.04	0.74	19	0.4%	0.20 [-0.33, 0.73]	
SAM 40008 2004	0.17	0.62	84	0.02	0.62	76	3.2%	0.15 [-0.04, 0.34]	+
SAM30007 2005	0.1	0.8	28	0	0.75	30	0.7%	0.10 [-0.30, 0.50]	
Subtotal (95% CI)			127			125	4.4%	0.15 [-0.02, 0.31]	-
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi	<sup>2</sup> = 0.09	, df = 2	(P = 0.95	); I <sup>2</sup> = 0	%			
Test for overall effect:	Z = 1.74 (	(P = 0.0	8)						
Total (95% CI)			592			579	100.0%	0.09 [0.06, 0.12]	•
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi	² = 2.20	, df = 6	(P = 0.90	); I <sup>2</sup> = 0	%		-	
Test for overall effect:	Z = 5.15 (	(P < 0.0	0001)		-				-0.5 -0.25 0 0.25 0. Favours ICS Favours LA
Test for subgroup diffe	erences: C	Chi² = 0.4	47, df =	= 1 (P = 0.	49), l² =	• 0%			Favouisios Favouis LA

*FEV*<sub>1</sub> % *predicted:* Five trials<sup>138,140,142,143,147</sup> involving 1,241 participants (LABA/ICS =618, ICS = 623) provided data for a meta-analysis of the potential steroid sparing effects of LABA/ICS combination therapy compared with ICS monotherapy on % predicted PEF (Figure 66). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 4.75; 95% CI: 2.38 to 7.11; I<sup>2</sup> = 41%); the precision of the 95% CI suggests that the two treatments are clinically equivalent (MCID =  $\pm 12\%$ ).

A subgroup analysis indicated a clinically important difference between treatments for Design 1 (WMD = 4.25; 95% CI: 2.03 to 6.47;  $I^2 = 35\%$ ) and Design 2 (WMD = 9.70; 95% CI: 2.77 to 16.63). The lack of precision of the estimates prevents conclusions regarding the equivalence of the two treatments (MCID = ±12%).

## Figure 66: Potential steroid-sparing effect of LABA/ICS vs ICS on FEV<sub>1</sub> % predicted

	LAB	BA/ICS		1	CS			Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]	IV, Random, 95% CI [%]
1.4.1 Design 1									
Kips 2000	-2	27	29	0.5	27	31	2.8%	-2.50 [-16.17, 11.17]	
Pauwels 1997	86	14.7	425	80	21.9	427	33.6%	6.00 [3.50, 8.50]	_ <b>_</b>
Schermer 2007	2.6	8.3	69	0.01	6.6	68	33.5%	2.59 [0.08, 5.10]	
SMS40012 2006	4	13.3	83	-0.9	13.9	85	20.5%	4.90 [0.79, 9.01]	
Subtotal (95% CI)			606			611	90.4%	4.25 [2.03, 6.47]	•
Heterogeneity: Tau <sup>2</sup> =	1.71; Chi <sup>2</sup> =	4.59, df =	3 (P =	0.20); l <sup>2</sup> = 3	5%				
Test for overall effect:	Z = 3.76 (P =	= 0.0002)							
1.4.2 Design 2									
Self 1998	5.5	8.66	12	-4.2	8.66	12	9.6%	9.70 [2.77, 16.63]	
Subtotal (95% CI)			12			12	9.6%	9.70 [2.77, 16.63]	
Heterogeneity: Not app	plicable								
Test for overall effect:	Z = 2.74 (P =	= 0.006)							
Total (95% CI)			618			623	100.0%	4.75 [2.38, 7.11]	•
Heterogeneity: Tau <sup>2</sup> =	2.72; Chi <sup>2</sup> =	6.80, df =	4 (P =	$0.15$ ; $l^2 = 4$	1%				
Test for overall effect:		,	•	//					-20 -10 0 10 2
Test for subgroup diffe		,		P = 0.14),   <sup>2</sup> =	= 54.9%				Favours ICS Favours LABA/
		, .							

#### Asthma control measures

*No. participants with*  $\geq 1$  *exacerbations:* Two trials<sup>137,145</sup> involving 494 participants (LABA/ICS = 248, ICS = 246) provided data for a meta-analysis of the potential steroid sparing effects of LABA/ICS combination therapy compared with ICS monotherapy on the percent of participants with  $\geq$  asthma exacerbations (Figure 67). The pooled result failed to identify a statistically significant difference between the treatments (RR = 1.23; 95% CI: 0.59 to 2.56; I<sup>2</sup> = 0%). A subgroup analysis failed to indicate an important difference between Design 1 (RR = 1.65; 95% CI: 0.40 to 6.76) and Design 2 (RR = 1.11; 95% CI: 0.47 to 2.61).

Figure 67: Pote	ntial steroid-	sparing effect of L	_ABA/ICS vs ICS on no. p	articipants with $\geq 1$
exacerbation				
	LABA/ICS	ICS	Risk Ratio	Risk Ratio

	LABA/	ICS	ICS			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	Year	M-H, Random, 95% CI
1.7.1 Design 1								
Busse 2003 Subtotal (95% CI)	5	155 <b>155</b>	3	153 <b>153</b>	26.7% <b>26.7%</b>	1.65 [0.40, 6.76] <b>1.65 [0.40, 6.76]</b>	2003	
Total events	5		3		2011 /0			
Heterogeneity: Not app	olicable							
Test for overall effect:	Z = 0.69 (I	P = 0.49	9)					
1.7.2 Design 2								
SAM 40008 2004	10	93	9	93	73.3%	1.11 [0.47, 2.61]	2004	
Subtotal (95% CI)		93		93	73.3%	1.11 [0.47, 2.61]		
Total events	10		9					
Heterogeneity: Not app	olicable							
Test for overall effect:	Z = 0.24 (F	<b>P</b> = 0.8	1)					
Total (95% CI)		248		246	100.0%	1.23 [0.59, 2.56]		•
Total events	15		12					
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 0.22,	df = 1 (P	= 0.64	); I² = 0%			
Test for overall effect:	Z = 0.56 (F	P = 0.5	7)				ŗ	0.05 0.2 1 5 20 Favours LABA/ICS Favours ICS
Test for subgroup diffe	rences: N	ot appli	cable				1	

*No. severe exacerbations:* Two trials<sup>138,140</sup> involving 912 participants (LABA/ICS = 454, ICS = 458) provided data for a meta-analysis of the potential steroid sparing effects of LABA/ICS combination therapy compared with ICS monotherapy on the number of severe asthma exacerbations (Figure 68). Both trials used an abrupt-dose reduction design (Design 1). The

pooled result failed to identify a statistically significant difference between treatments (WMD = -0.18; 95% CI: -0.40 to 0.04;  $I^2 = 0$ %).

Figure 68: Potential steroid-sparing effect of LABA/ICS vs ICS on no. severe exacerbations

	LA	BA/IC	S		ICS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	I IV, Random, 95% CI
Kips 2000	0.29	0.75	29	0.47	1.34	31	16.4%	-0.18 [-0.72, 0.36]	<b>_</b> _
Pauwels 1997	0.51	1.8	425	0.69	1.8	427	83.6%	-0.18 [-0.42, 0.06]	· - <b>-</b> +
Total (95% CI)			454			458	100.0%	-0.18 [-0.40, 0.04]	-
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 2	,		'	= 1 (P =	1.00);	l² = 0%	)		-0.5 -0.25 0 0.25 0.5 Favours LABA/ICS Favours ICS

*No. mild exacerbations:* Two trials<sup>138,140</sup> involving 912 participants (LABA/ICS = 454, ICS = 458) provided data for a meta-analysis of the potential steroid sparing effects of LABA/ICS combination therapy compared with ICS monotherapy on the number of mild asthma exacerbations (Figure 69). Both trials used Design 1 methods and compared FORM/BUD vs BUD, included patients with intermittent to severe asthma, and were of the same duration (52 wk). The pooled result failed to identify a difference between treatments (WMD = 22.98; 95% CI: -12.84 to 58.79;  $I^2 = 94\%$ ).

Figure 69: Potential steroid-sparing effect of LABA/ICS vs ICS on no. mild exacerbations

0	LA	ABA/IC	S	•	ics			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	I IV, Random, 95% CI
Kips 2000	18.3	37.27	29	14.6	30.18	31	47.3%	3.70 [-13.53, 20.93]	
Pauwels 1997	57.7	38	425	17.4	31	427	52.7%	40.30 [35.64, 44.96]	
Total (95% CI)			454			458	100.0%	22.98 [-12.84, 58.79]	
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 2			6.15, d	lf = 1 (P	< 0.000			22.30 [-12.04, 30.73]	

*SABA use (puffs/day):* Six trials<sup>49,137,139,140,142,144</sup> involving 2,146 participants (LABA/ICS =1,074, ICS = 1,072) provided data for a meta-analysis of the potential steroid sparing effects of LABA/ICS combination therapy compared with ICS monotherapy on SABA use (Figure 70). The pooled result failed to identify a statistically significant difference between the two treatments (WMD = -0.17; 95% CI: -0.38 to 0.04; I<sup>2</sup> = 92%); however, the precision of the 95% CI suggests that LABA/ICS is clinically equivalent to ICS monotherapy (MCID = ±0.81).

A subgroup analysis based on design indicated a potential clinical equivalence between treatments for studies that employed Design 1 (WMD = -0.15; 95% CI: -0.35 to 0.05;  $I^2 = 93\%$ ; MCID = ±0.81). The result for the study that employed Design 2 indicated a statistically significant difference favouring LABA/ICS (WMD = -2.56; 95% CI: -4.82 to -0.30). In addition, the pooled estimate indicates a clinically important difference between the two treatments (MCID = -0.81). Heterogeneity may be explained by the study designs.

#### Figure 70: Potential steroid-sparing effect of LABA/ICS vs ICS on SABA use (puffs/day)

	LAI	BA/ICS		1	CS			Mean Difference	Mean Difference
Study or Subgroup	Mean [puff/sday]	SD [puff/sday]	Total	Mean [puff/sday]	SD [puff/sday]	Total	Weight	IV, Random, 95% CI [puff/sday]	IV, Random, 95% CI [puff/sday]
1.10.1 Design 1									
Busse 2003	-0.43	1.37	155	-0.21	0.87	153	17.8%	-0.22 [-0.48, 0.04]	-
Pauwels 1997	0.51	0.53	425	0.87	0.53	427	23.8%	-0.36 [-0.43, -0.29]	
SAM40090 2005	0	0.26	234	0.03	0.26	235	24.2%	-0.03 [-0.08, 0.02]	+
SAS40026 2006	-0.36	1.19	176	-0.37	1.43	170	17.0%	0.01 [-0.27, 0.29]	+
Schermer 2007 Subtotal (95% CI)	0.47	0.85	69 1 <b>059</b>	0.58	0.91	68 1053	16.3% <b>99.2%</b>	-0.11 [-0.40, 0.18] -0.15 [-0.35, 0.05]	•
Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 2 1.10.2 Design 2		f = 4 (P < 0.00001	);   <sup>2</sup> = 9	93%					
Nielsen 1999 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2		3.95	15 15	0.42	2.35	19 19	0.8% 0.8%	-2.56 [-4.82, -0.30] -2.56 [-4.82, -0.30]	-
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 2 Test for subgroup diffe	Z = 1.61 (P = 0.11)	,	<i>,</i> .			1072	100.0%	-0.17 [-0.38, 0.04] Fa	-4 -2 0 2 4 avours LABA/ICS Favours ICS

*Symptom-free days (SFD):* Six trials<sup>49,137,138,140,144,145</sup> involving 2,194 participants (LABA/ICS =1,104, ICS = 1,090) provided data for a meta-analysis of the potential steroid sparing effects of LABA/ICS combination therapy compared with ICS monotherapy on SFD (Figure 71). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 5.24; 95% CI: 1.26 to 9.21;  $I^2 = 52\%$ ).

Figure 71: Potential steroid-sparing effect of LABA/ICS vs ICS on symptom-free days (SFD)

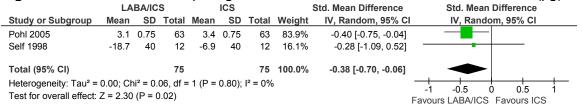
 LABA/ICS
 ICS
 Mean Difference
 Mean Difference

 Study or Subgroup
 Mean [median %]
 SD [median %]

olday of oubgroup	Mean [meanan 70]	OD [Incular 70]	Totul	Mean [meanan 70]	OD [Incular /0]	Total	weight	TV, Rundom, 5070 Or [median 70]	it, Rundom, 50% of [median /6]
1.13.1 Design 1									
Busse 2003	11.6	37.35	155	6.2	35.87	153	14.8%	5.40 [-2.78, 13.58]	+
Kips 2000	41.3	37.7	29	30.4	33.4	31	4.3%	10.90 [-7.17, 28.97]	- <del></del>
Pauwels 1997	53	27	425	43.7	27	427	29.9%	9.30 [5.67, 12.93]	
SAM40090 2005	4.1	17.1	234	2.2	17	234	32.1%	1.90 [-1.19, 4.99]	<b>+</b>
SAS40026 2006 Subtotal (95% CI)	14.8	37.25	177 1020	10.2	37.7	169 1014	15.5% 96.7%	4.60 [-3.30, 12.50] 5.57 [1.45, 9.70]	•
Heterogeneity: Tau <sup>2</sup> = 1 Test for overall effect: Z		f = 4 (P = 0.05); l <sup>2</sup>	= 59%						
1.13.2 Design 2									
SAM 40008 2004 Subtotal (95% CI)	78.9	68	84 84	83.3	68	76 76	3.3% 3.3%	-4.40 [-25.50, 16.70] -4.40 [-25.50, 16.70]	
Heterogeneity: Not app Test for overall effect: Z									
Total (95% CI) Heterogeneity: Tau <sup>2</sup> = 1	0.33; Chi <sup>2</sup> = 10.46, d	df = 5 (P = 0.06); I	1104 ² = 52%	5		1090	100.0%	5.24 [1.26, 9.21]	-50 -25 0 25 50
Test for overall effect: Z Test for subgroup differ		df = 1 (P = 0.38), I	² = 0%						Favours ICS Favours LABA/ICS

*Mean ICS dose:* Two trials<sup>141,143</sup> involving 150 participants (LABA/ICS =75, ICS = 75) provided data for a meta-analysis of the potential steroid sparing effects of LABA/ICS combination therapy compared with ICS monotherapy on mean ICS dose (Figure 72). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = -0.38  $\mu$ g; 95% CI: -0.70 to -0.06; I<sup>2</sup> = 0%).

Figure 72: Potential steroid-sparing effect of LABA/ICS vs ICS on mean ICS dose (µg)



Health-related quality of life measures *AQLQ:* Two trials<sup>142,143</sup> involving 161 participants (LABA/ICS = 81, ICS = 80) provided data for a meta-analysis of the potential steroid sparing effects of LABA/ICS combination therapy compared with ICS monotherapy on Asthma Quality of Life Questionnaire score (Figure 73). The pooled result failed to indicate a statistically significant difference between the treatments  $(WMD = 0.54; 95\% CI: -0.19 \text{ to } 1.27; I^2 = 76\%)$ . Moreover, the lack of precision of the estimates prevents conclusions regarding the equivalence of the two treatments (MCID =  $\pm 0.5$ ).

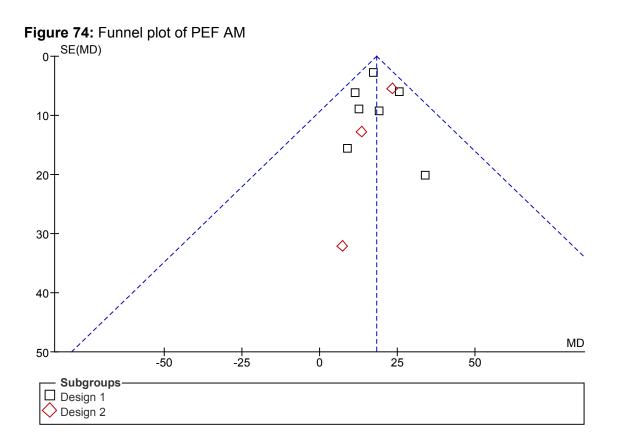
	LA	BA/IC	s		ICS			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
1.12.1 Design 1										
Schermer 2007 Subtotal (95% CI)	0.38	0.58	69 <b>69</b>	0.14	0.62	68 68	60.3% <b>60.3%</b>	0.24 [0.04, 0.44] <b>0.24 [0.04, 0.44]</b>	2007	<b>▲</b>
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 2.34	(P = 0	0.02)							
1.12.2 Design 2										
Self 1998 Subtotal (95% CI)	1.1	1.04	12 12	0.1	0.69	12 12	39.7% <b>39.7%</b>	1.00 [0.29, 1.71] <b>1.00 [0.29, 1.71]</b>	1998	
Heterogeneity: Not ap Test for overall effect:		(P = 0	).006)							
Total (95% CI)			81			80	100.0%	0.54 [-0.19, 1.27]		
Heterogeneity: Tau <sup>2</sup> = 0.22; Chi <sup>2</sup> = 4.12, df = 1 (P = 0.04); l <sup>2</sup> = 76% Test for overall effect: Z = 1.46 (P = 0.15) Test for subgroup differences: Chi <sup>2</sup> = 4.12, df = 1 (P = 0.04), l <sup>2</sup> = 75.7%										-1 -0.5 0 0.5 1 Favours ICS Favours LABA/IC

#### Eigune 72: Detential starsid sparing affect of LADA/ICS values on AOLO spare

The results of the clinical analysis are summarized in Table X. It was not considered appropriate to conduct subgroup analyses based on asthma severity as only a small proportion of studies (< 20% of available studies for any single outcome) reported results for populations restricted to a single asthma severity class.

#### **Publication bias**

Meta-analysis for one measure (PEF AM) contained sufficient studies to warrant an assessment of publication bias through funnel plot analysis. There was no obvious evidence of asymmetry (small study effects) (Figure 74).



**Comparative safety of LABA/ICS therapies for adults with persistent asthma** Seventy-nine trials (24 low dose,  $^{45-47,56,57,59,61-65,68,69,72,74,81,91,98,100,102,103,113,122,123}$  37 medium dose,  $^{29,49,53,60,66,67,70,82-85,87-90,92,94-96,99,105-107,109,110,112,114,117,119,121,124-126,137,140,144,147}$  and 18 high dose  $^{73,75,76,80,93,97,101,104,108,115,116,118,120,141-143,145,146}$ ) reported data that permitted the examination of the comparative safety of LABA/ICS combination therapy versus ICS monotherapy on 10 events considered clinically relevant and important: number of participants reporting  $\geq 1$  adverse event (AE) (61 trials), total serious adverse events (SAEs) (53 trials), headache (51 trials), withdrawal due to AE (49 trials), upper respiratory tract infection (39 trials), candidiasis (29 trials), treatment-related AEs (28 trials), worsening asthma (27 trials), death (fatal SAEs [26 trials] and all-cause mortality [4 trials]) and hoarseness (19 trials).

1 AE							
Study or Subgroup	LABA/		ICS		Woight	Risk Ratio	Risk Ratio
Study or Subgroup 1.12.1 Low dose	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bateman 2001	177	333	90	165	1.1%	0.97 [0.82, 1.16]	+
Boonsawat 2008	49	151	57	155	0.4%	0.88 [0.65, 1.20]	
Buhl 2003	131	352	78	171	0.8%	0.82 [0.66, 1.01]	
Chuchalin 2002	40	111	40	114	0.3%	1.03 [0.72, 1.46]	
Chuchalin 2008 Corren 2007	579	973	608	970	5.8%	0.95 [0.88, 1.02]	1
Kerwin 2007	84 254	130 420	77 112	127 212	0.9% 1.5%	1.07 [0.88, 1.29]	-
Kuna 2006	154	409	74	207	0.7%	1.14 [0.99, 1.33] 1.05 [0.84, 1.31]	_ <b>_</b> _
Lalloo 2003	90	230	94	237	0.7%	0.99 [0.79, 1.24]	<u> </u>
Murray 2004	48	88	51	89	0.5%	0.95 [0.73, 1.24]	_ <b>_</b>
Pearlman 2004	62	92	52	89	0.7%	1.15 [0.92, 1.45]	+
Rabe 2006	135	354	139	342	1.0%	0.94 [0.78, 1.13]	-
SAM40036 2004	74	288	96	289	0.5%	0.77 [0.60, 1.00]	
SAS30015 2004	47	78	38	78	0.4%	1.24 [0.93, 1.65]	
SAS40036 2005	100	172	77	159	0.8%	1.20 [0.98, 1.47]	L_
SAS40068 2005	207	262	212	270	4.0%	1.01 [0.92, 1.10]	
SFA103153 2007 Strand 2004	146 48	239 78	161 42	236 72	1.9% 0.5%	0.90 [0.78, 1.02] 1.05 [0.81, 1.37]	
Subtotal (95% CI)	40	4760	72	3982	22.4%	0.99 [0.94, 1.04]	•
Total events	2425		2098				
Heterogeneity: Tau <sup>2</sup> = 0	0.00; Chi <sup>2</sup> :	= 23.65,	df = 17 (F	= 0.13	); I <sup>2</sup> = 28%	, D	
Test for overall effect: 2							
1.12.2 Medium dose							
Baraniuk 1999	83	118	82	114	1.3%	0.98 [0.83, 1.15]	+
Bateman 2003	1051	1700	1022	1707	0.007	Not estimable	Ļ
Bateman 2004 Bouros 1999	1051 0	1709 0	1032 0	1707 0	9.0%	1.02 [0.96, 1.07]	ſ
Bouros 1999 Busse 2003	0 140	281	155	0 277	1.4%	Not estimable 0.89 [0.76, 1.04]	
Condemi 1999	140	201	186	216	5.2%	1.00 [0.93, 1.04]	+
Johansson 2001	67	176	65	173	0.5%	1.01 [0.77, 1.33]	<u> </u>
Kelsen 1999	0	0	0	0		Not estimable	
Kemp 1998	134	252	130	254	1.2%	1.04 [0.88, 1.23]	+
Langton Hewer 1995	10	11	9	12	0.2%	1.21 [0.83, 1.77]	
Lundback 2006	92	95	88	92	8.3%	1.01 [0.96, 1.07]	+
Molimard 2001	47	130	46	129	0.3%	1.01 [0.73, 1.40]	
Morice 2007	136	462	82	217	0.7%	0.78 [0.62, 0.97]	-
Murray 1999	168	260	183	254	2.3%	0.90 [0.80, 1.01]	1
Nathan 2006 Noonan 2006	65 149	94 239	63 64	91 109	0.9% 1.0%	1.00 [0.82, 1.21] 1.06 [0.88, 1.28]	
O'Byrne 2005	971	1834	528	926	5.8%	0.93 [0.87, 1.00]	-
Overbeek 2005	0	20	0	20	0.070	Not estimable	
SAM30013 2005	74	121	73	116	0.9%	0.97 [0.80, 1.19]	+
SAM40034 2004	47	75	59	79	0.7%	0.84 [0.68, 1.04]	
SAM40065 2007	118	150	235	299	3.0%	1.00 [0.90, 1.11]	+
SAM40090 2005	23	242	30	241	0.1%	0.76 [0.46, 1.28]	
SAM40120 2005	1	8	3	10	0.0%	0.42 [0.05, 3.28]	· · ·
SAS30002 2008	89	148	88	152	1.0%	1.04 [0.86, 1.25]	<u> </u>
SAS30039 2005 SAS40026 2006	47 172	182 321	35 170	180 315	0.2% 1.6%	1.33 [0.90, 1.95]	
Scicchitano 2004	526	947	533	943	4.7%	0.99 [0.86, 1.15] 0.98 [0.91, 1.06]	4
Shapiro 2000	58	81	67	81	1.2%	0.87 [0.73, 1.03]	
SLGA5021 2005	213	246	204	242	5.5%	1.03 [0.95, 1.11]	+
SLGF75 2005	4	14	5	32	0.0%	1.83 [0.58, 5.80]	
SMS40012 2006	34	93	41	95	0.3%	0.85 [0.59, 1.21]	
Subtotal (95% CI)		8530		7376	57.3%	0.98 [0.96, 1.01]	
Total events	4709	00.04	4256		. 12 00/		
Heterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: 2			ui = 26 (F	- = 0.35	<i>)</i> , ı− = 8%		
1.12.3 High dose							
Aubier 1999	243	338	116	165	2.3%	1.02 [0.91, 1.15]	+
Bergmann 2004	47	179	45	186	0.3%	1.09 [0.76, 1.55]	_ <del></del>
Boyd 1995	44	55	53	64	1.1%	0.97 [0.81, 1.15]	-+
Ind 2003	0	0	0	0		Not estimable	
Jenkins 2000	122	180	124	173	1.8%	0.95 [0.82, 1.09]	+
Jenkins 2006	99	341	27	115	0.3%	1.24 [0.85, 1.79]	
Mitchell 2003	69	102	71	101	1.0%	0.96 [0.80, 1.16]	1
Nielsen 1999	0	0	0	0	0.00/	Not estimable	Ţ
Peters 2008 Pohl 2005	505	575	118	133	6.2%	0.99 [0.93, 1.06]	1
SAM30007 2005	74 20	0 29	81 25	0 32	0.4%	Not estimable 0.88 [0.65, 1.20]	
SAM30007 2005 SAM40008 2004	20 51	29 93	25 45	32 93	0.4%	1.13 [0.86, 1.50]	- <b> -</b>
Schermer 2007	19	68	20	69	0.1%	0.96 [0.57, 1.64]	<u> </u>
Self 1998	0	12	5	12	0.0%	0.09 [0.01, 1.48]	←────
SLGQ97 2005	117	171	235	325	2.2%	0.95 [0.84, 1.07]	+
van Noord 2001	167	337	90	172	1.1%	0.95 [0.79, 1.13]	+
Wallin 2003	0	0	0	0		Not estimable	
Woolcock 1996	355	487	172	251	3.2%	1.06 [0.96, 1.18]	t
Subtotal (95% CI)		2967		1891	20.3%	1.00 [0.96, 1.04]	1
Total events Heterogeneity: Tau <sup>2</sup> = (				= 0.73);	I <sup>2</sup> = 0%		
Test for overall effect: 2	≤ = 0.24 (P	= 0.81)					
Total (95% CI)		16257		13249	100.0%	0.99 [0.97, 1.01]	
Total events	9066		7581				
Heterogeneity: Tau <sup>2</sup> = 0		= 61.17,		<b>-</b> = 0.36	); I² = 5%		0,2 0,5 1 2 5
Test for overall effect: 2							avours LABA/ICS Favours ICS
	Z = 1.31 (P	= 0.19)		- = 0.36	); I <sup>2</sup> = 5%		0.2 0.5 1 2 Favours LABA/ICS Favour

# Figure 75: The effect of LABA/ICS versus ICS monotherapy on no. participants experiencing ≥ 1 AE

Study or Subgroup	LABA/ Events		ICS Events		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% Cl
.14.1 Low dose							
Bateman 2001	6	333	3	165	1.0%	0.99 [0.25, 3.91]	
Boonsawat 2008	0	155	1	151	0.2%	0.32 [0.01, 7.91]	
Buhl 2003	3	352	2	171	0.6%	0.73 [0.12, 4.32]	
Chuchalin 2002	0	111	2	114	0.2%	0.21 [0.01, 4.23]	
Chuchalin 2008	27	973	26	970	6.7%	1.04 [0.61, 1.76]	
Corren 2007	2	130	0	127	0.2%	4.89 [0.24, 100.77]	
Kerwin 2007	5	420	0	212	0.2%	5.57 [0.31, 100.18]	
Kuna 2006	3	409	4	207	0.9%	0.38 [0.09, 1.68]	
Peters 2007	4	165	6	169	1.2%	0.68 [0.20, 2.38]	
Rabe 2006	6	354	8	342 289	1.7%	0.72 [0.25, 2.07]	
SAM40036 2004	1 0	288	3 1		0.4%	0.33 [0.03, 3.20]	
SAS30015 2004 SAS40068 2005	4	78 262	2	78 270	0.2%	0.33 [0.01, 8.06]	
	4	202	2 11	270	0.7% 2.0%	2.06 [0.38, 11.16]	
SFA103153 2007 Strand 2004	1	239 78	2	230	0.3%	0.54 [0.20, 1.43] 0.46 [0.04, 4.98]	
Subtotal (95% CI)	1	4347	2	3573	16.5%	0.82 [0.58, 1.15]	•
Total events	68	4041	71	00/0	10.070	0.02 [0.00, 1110]	•
		-015		- 0 02)	· 12 - 00/		
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:				- 0.02)	l, I = 0 %		
		0.20)					
1.14.2 Medium dose							
Baraniuk 1999	1	118	1	114	0.2%	0.97 [0.06, 15.26]	
Bateman 2003	2	168	3	176	0.6%	0.70 [0.12, 4.13]	
Bateman 2004	67	1709	53	1707	15.2%	1.26 [0.89, 1.80]	<b>†</b> ■-
Bouros 1999	1	69	1	65	0.3%	0.94 [0.06, 14.75]	
Busse 2003	1	281	3	277	0.4%	0.33 [0.03, 3.14]	
Condemi 1999	1	221	1	216	0.2%	0.98 [0.06, 15.53]	
Johansson 2001	3	176	0	173	0.2%	6.88 [0.36, 132.24]	
Kemp 1998	1	252	0	254	0.2%	3.02 [0.12, 73.87]	
Koenig 2008	1	156	9	310	0.4%	0.22 [0.03, 1.73]	
Murray 1999	7	260	7	254	1.8%	0.98 [0.35, 2.75]	-+
Noonan 2006	7	239	0	109	0.2%	6.88 [0.40, 119.31]	
O'Byrne 2005	108	1828	48	925	17.4%	1.14 [0.82, 1.58]	+
Rojas 2007	34	180	47	182	12.5%	0.73 [0.50, 1.08]	-=+
SAM30013 2005	1	121	1	116	0.2%	0.96 [0.06, 15.15]	
SAM40034 2004	1	75	1	79	0.3%	1.05 [0.07, 16.54]	
SAM40065 2007	2	150	4	299	0.7%	1.00 [0.18, 5.38]	
SAM40090 2005	1	242	1	241	0.2%	1.00 [0.06, 15.83]	
SAS30002 2008	4	148	2	152	0.7%	2.05 [0.38, 11.05]	
SAS30039 2005	2	182	1	180	0.3%	1.98 [0.18, 21.62]	<u> </u>
SAS40026 2006	3	321	3	315	0.7%	0.98 [0.20, 4.83]	
Scicchitano 2004	58	947	55	943	14.8%	1.05 [0.73, 1.50]	+
Shapiro 2000	0	81	1	81	0.2%	0.33 [0.01, 8.06]	
SLGA5021 2005	7	246	5	242	1.5%	1.38 [0.44, 4.28]	
SMS40012 2006	1	93	4	95	0.4%	0.26 [0.03, 2.24]	
Zetterstrom 2001	4	238	1	124	0.4%	2.08 [0.24, 18.45]	<u> </u>
Subtotal (95% CI)		8501		7629	70.1%	1.04 [0.89, 1.23]	•
Total events	318		252				
Heterogeneity: Tau <sup>2</sup> =				P = 0.9'	1); I² = 0%		
Test for overall effect:	Z = 0.51 (F	P = 0.61)					
1.14.3 High dose							
Aubier 1999	11	338	5	165	1.8%	1.07 [0.38, 3.04]	_ <b>_</b>
Bergmann 2004	2	179	2	186	0.5%	1.04 [0.15, 7.30]	
Boyd 1995	7	55	7	64	2.0%	1.16 [0.44, 3.11]	_ <b>_</b>
Jenkins 2000	6	180	6	173	1.5%	0.96 [0.32, 2.92]	<b>_</b>
Jenkins 2006	5	341	2	115	0.7%	0.84 [0.17, 4.29]	
Mitchell 2003	1	102	1	101	0.2%	0.99 [0.06, 15.62]	
Nielsen 1999	0	102	1	19	0.2%	0.42 [0.02, 9.55]	
Peters 2008	33	575	5	133	2.2%	1.53 [0.61, 3.84]	<b></b>
Pohl 2005	33 0	5/5 0	5 0	133	2.270	Not estimable	
SAM30007 2005	0	29	1	32	0.2%	0.37 [0.02, 8.66]	
	3	29 93	1	32 93	0.2%		
SAM40008 2004 SLGO97 2005	3	93 171	9	93 325	0.2% 2.3%	7.00 [0.37, 133.66]	<b></b>
SLGQ97 2005						1.90 [0.77, 4.70]	
van Noord 2001	8	337	2	172	0.8%	2.04 [0.44, 9.51]	
Woolcock 1996 Subtotal (95% CI)	6	487 2902	2	251 1829	0.7% 13.4%	1.55 [0.31, 7.61] <b>1.31 [0.90, 1.91]</b>	
Total events	91	2002	43	1023	· • · • /0	[0.00, 1.01]	
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>		df = 12 (P	9 = 0.98)	; l <sup>2</sup> = 0%		
Test for overall effect:	∠ = 1.42 (F	- = 0.16)					
		15750		13031	100.0%	1.03 [0.90, 1.19]	•
Total (95% CI)	477	15750	366	10001			
	477 0.00 <sup>.</sup> Chi <sup>2</sup>		366 df = 52 (				

## Figure 76: The effect of LABA/ICS versus ICS monotherapy on total SAEs

Study or Subgroup	LABA/		ICS		147.1.1.4	Risk Ratio	Risk Ratio
.13.1 Low dose	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
ateman 2001	28	333	10	165	1.3%	1.39 [0.69, 2.79]	
loonsawat 2008	7	151	13	155	0.8%	0.55 [0.23, 1.35]	
Buhl 2003	0	0	0	0	0.070	Not estimable	
Chuchalin 2008	152	973	153	970	15.2%	0.99 [0.81, 1.22]	<b>_</b>
Corren 2007	132	130	2	127	0.1%	0.49 [0.04, 5.32]	
avuru 2000	2	92	0	90	0.1%	4.89 [0.24, 100.51]	
Kerwin 2007	2 54	420	28	212	3.6%	0.97 [0.64, 1.49]	
(una 2006	8	409	20	207			
					0.3%	2.02 [0.43, 9.45]	
Aurray 2004	11	88	14	89	1.2%	0.79 [0.38, 1.65]	
lelson 2003	0	0	0	0	0.00/	Not estimable	_
Pearlman 2004	20	92	22	89	2.3%	0.88 [0.52, 1.50]	1
AS40036 2005	10	172	5	159	0.6%	1.85 [0.65, 5.29]	
AS40068 2005	56	262	55	270	5.9%	1.05 [0.75, 1.46]	T
SFA103153 2007	34	239	41	236	3.7%	0.82 [0.54, 1.24]	-
Strand 2004	17	78	23	72	2.2%	0.68 [0.40, 1.17]	
Subtotal (95% CI)		3439		2841	37.4%	0.96 [0.84, 1.09]	•
otal events	400		368				
leterogeneity: Tau <sup>2</sup> = 0 Test for overall effect: 2				= 0.69);	I <sup>2</sup> = 0%		
.13.2 Medium dose							
araniuk 1999	11	118	10	114	1.0%	1.06 [0.47, 2.41]	_ <del></del>
ateman 2003	0	0	0	0		Not estimable	
ateman 2004	92	1709	119	1707	9.3%	0.77 [0.59, 1.01]	-
usse 2003	14	281	9	277	1.0%	1.53 [0.67, 3.48]	+
ondemi 1999	27	221	26	216	2.5%	1.01 [0.61, 1.68]	- <del> </del> -
ohansson 2001	7	176	2	173	0.3%	3.44 [0.72, 16.33]	+
elsen 1999	20	239	17	244	1.7%	1.20 [0.65, 2.24]	- <del> -</del>
loenig 2008	34	156	49	310	4.2%	1.38 [0.93, 2.04]	+
angton Hewer 1995	0	0	0	0		Not estimable	
undback 2006	2	95	6	92	0.3%	0.32 [0.07, 1.56]	<u> </u>
Norice 2007	8	462	4	217	0.5%	0.94 [0.29, 3.09]	
Aurray 1999	24	260	26	254	2.3%	0.90 [0.53, 1.53]	
lathan 2006	14	200 94	15	91	1.4%	0.90 [0.46, 1.76]	
loonan 2006	2	239	0	109	0.1%	2.29 [0.11, 47.33]	
)'Byrne 2005	66	1828	42	925	4.5%	0.80 [0.54, 1.16]	-
Rojas 2007	5	180		182	0.4%	1.01 [0.30, 3.43]	
SAM30013 2005	8	121	8	116	0.7%	0.96 [0.37, 2.47]	
SAM40034 2004	6	75	3	79	0.4%	2.11 [0.55, 8.12]	
SAM40036 2004	18	288	26	289	1.9%	0.69 [0.39, 1.24]	
SAM40065 2007	30	150	65	299	4.4%	0.92 [0.63, 1.35]	
SAM40090 2005	2	242	1	241	0.1%	1.99 [0.18, 21.82]	
SAS30002 2008	11	148	13	152	1.1%	0.87 [0.40, 1.88]	
SAS30039 2005	5	182	5	180	0.4%	0.99 [0.29, 3.36]	
SAS40026 2006	17	321	12	315	1.2%	1.39 [0.68, 2.86]	
Shapiro 2000	11	81	7	81	0.8%	1.57 [0.64, 3.85]	
SLGA5021 2005	25	246	20	242	2.1%	1.23 [0.70, 2.15]	
/ermetten 1999	14	113	12	120	1.2%	1.24 [0.60, 2.56]	
Letterstrom 2001	6	238	5	124	0.5%	0.63 [0.19, 2.01]	
Subtotal (95% CI)		8263		7149	44.2%	0.97 [0.86, 1.10]	•
otal events	479	- 20 27	507 df = 25 (l	D - 0 70	). 12 - 00/		
leterogeneity: Tau <sup>2</sup> = 0 est for overall effect: 2				P = 0.73	); I- = 0%		
.13.3 High dose	~ /				4 = 0/	0.04/0.04	
which 1000	21	338	16	165	1.7%	0.64 [0.34, 1.19]	
	1	179	4	186	0.1%	0.26 [0.03, 2.30]	- <u>-</u>
ergmann 2004		55	17	64	2.0%	1.16 [0.66, 2.05]	<u> </u>
Bergmann 2004 Boyd 1995	17		0	0		Not estimable	
Bergmann 2004 Boyd 1995 nd 2003	17 0	0			1.3%	1.18 [0.59, 2.39]	- <del>-</del> -
Bergmann 2004 Boyd 1995 nd 2003 enkins 2000	17 0 16	0 180	13	173			
Bergmann 2004 Boyd 1995 nd 2003 Jenkins 2000 Jenkins 2006	17 0 16 3	0 180 341	13 5	115	0.3%	0.20 [0.05, 0.83]	
Bergmann 2004 Boyd 1995 Ind 2003 Ienkins 2000 Ienkins 2006 Peters 2008	17 0 16 3 39	0 180 341 575	13 5 10	115 133	0.3% 1.4%	0.20 [0.05, 0.83] 0.90 [0.46, 1.76]	
Aubier 1999 Bergmann 2004 Boyd 1995 nd 2003 Ienkins 2000 Ienkins 2006 Peters 2008 SAM30007 2005	17 0 16 3	0 180 341	13 5	115	0.3%	0.20 [0.05, 0.83]	
Bergmann 2004 Boyd 1995 nd 2003 lenkins 2000 eenkins 2006 Peters 2008 GAM30007 2005	17 0 16 3 39	0 180 341 575	13 5 10	115 133	0.3% 1.4%	0.20 [0.05, 0.83] 0.90 [0.46, 1.76]	
Bergmann 2004 Boyd 1995 nd 2003 lenkins 2000 enkins 2006 Peters 2008 SAM30007 2005 SAM40008 2004	17 0 16 3 39 7	0 180 341 575 29	13 5 10 13	115 133 32	0.3% 1.4% 1.1%	0.20 [0.05, 0.83] 0.90 [0.46, 1.76] 0.59 [0.28, 1.28]	
Jergmann 2004 Joyd 1995 nd 2003 enkins 2000 enkins 2006 Peters 2008 SAM30007 2005 SAM40008 2004 Schermer 2007	17 0 16 3 39 7 19	0 180 341 575 29 93	13 5 10 13 16	115 133 32 93	0.3% 1.4% 1.1% 1.8%	0.20 [0.05, 0.83] 0.90 [0.46, 1.76] 0.59 [0.28, 1.28] 1.19 [0.65, 2.16]	
Bergmann 2004 Joyd 1995 nd 2003 enkins 2000 enkins 2006 Peters 2008 SAM40008 2004 Schermer 2007 SLGQ97 2005	17 0 16 3 39 7 19 11	0 180 341 575 29 93 68	13 5 10 13 16 14	115 133 32 93 69	0.3% 1.4% 1.1% 1.8% 1.3%	0.20 [0.05, 0.83] 0.90 [0.46, 1.76] 0.59 [0.28, 1.28] 1.19 [0.65, 2.16] 0.80 [0.39, 1.63]	
Bergmann 2004 Soyd 1995 nd 2003 enkins 2000 Peters 2008 SAM30007 2005 SAM40008 2004 Schermer 2007 LGQ97 2005 ran Noord 2001	17 0 16 3 9 7 19 11 8 31	0 180 341 575 29 93 68 171 337	13 5 10 13 16 14 16 9	115 133 32 93 69 325 172	0.3% 1.4% 1.1% 1.8% 1.3% 0.9% 1.3%	0.20 [0.05, 0.83] 0.90 [0.46, 1.76] 0.59 [0.28, 1.28] 1.19 [0.65, 2.16] 0.80 [0.39, 1.63] 0.95 [0.42, 2.18] 1.76 [0.86, 3.61]	
Bergmann 2004 Joyd 1995 nd 2003 enkins 2000 enkins 2006 Peters 2008 SAM30007 2005 SAM40008 2004 Schermer 2007 LIGQP7 2005 an Noord 2001 Voolcock 1996	17 0 16 3 9 7 19 11 8	0 180 341 575 29 93 68 171	13 5 10 13 16 14 16	115 133 32 93 69 325	0.3% 1.4% 1.1% 1.8% 1.3% 0.9%	0.20 [0.05, 0.83] 0.90 [0.46, 1.76] 0.59 [0.28, 1.28] 1.19 [0.65, 2.16] 0.80 [0.39, 1.63] 0.95 [0.42, 2.18] 1.76 [0.86, 3.61] 0.77 [0.54, 1.09]	
Bergmann 2004 Joyd 1995 nd 2003 lenkins 2000 Peters 2008 SAM30007 2005 SAM40008 2004 Schermer 2007 SLGQ97 2005 ran Noord 2001 Voolcock 1996 Subtotal (95% Cl) Fotal events	17 0 16 3 9 7 19 11 8 31 64 237	0 180 341 575 29 93 68 171 337 487 <b>2853</b>	13 5 10 13 16 14 16 9 43	115 133 32 93 69 325 172 251 1778	0.3% 1.4% 1.1% 1.8% 1.3% 0.9% 1.3% 5.1% 18.4%	0.20 [0.05, 0.83] 0.90 [0.46, 1.76] 0.59 [0.28, 1.28] 1.19 [0.65, 2.16] 0.80 [0.39, 1.63] 0.95 [0.42, 2.18] 1.76 [0.86, 3.61] 0.77 [0.54, 1.09] 0.89 [0.71, 1.11]	
Bergmann 2004           Joyd 1995           nd 2003           enkins 2000           enkins 2006           Peters 2008           SAM30007 2005           SAM40008 2004           Schermer 2007           SLGQ97 2005           ran Noord 2001           Voolcock 1996           Subtotal (95% CI)	17 0 16 3 99 7 19 11 8 31 64 237 2.03; Chi <sup>2</sup> =	0 180 341 575 29 93 68 171 337 487 <b>2853</b> = 14.16,	13 5 10 13 16 14 16 9 43 176 df = 11 (I	115 133 32 93 69 325 172 251 1778	0.3% 1.4% 1.1% 1.8% 1.3% 0.9% 1.3% 5.1% 18.4%	0.20 [0.05, 0.83] 0.90 [0.46, 1.76] 0.59 [0.28, 1.28] 1.19 [0.65, 2.16] 0.80 [0.39, 1.63] 0.95 [0.42, 2.18] 1.76 [0.86, 3.61] 0.77 [0.54, 1.09] 0.89 [0.71, 1.11]	
Bergmann 2004           Joyd 1995           Ind 2003           enkins 2000           enkins 2006           Peters 2008           SAM30007 2005           SAM40008 2004           Schermer 2007           SLGQ97 2005           ran Noord 2001           Voolcock 1996           Subtotal (95% CI)           oral events           Heterogeneity: Tau <sup>2</sup> = 0           'est for overall effect: 2	17 0 16 3 39 7 19 11 8 31 64 237 0.03; Chi <sup>2</sup> = 2 = 1.06 (P	0 180 341 575 29 93 68 171 337 487 <b>2853</b> = 14.16,	13 5 10 13 16 14 16 9 43 176 df = 11 (I	115 133 32 93 69 325 172 251 1778 P = 0.22	0.3% 1.4% 1.1% 1.8% 1.3% 0.9% 1.3% 5.1% 18.4%	0.20 [0.05, 0.83] 0.90 [0.46, 1.76] 0.59 [0.28, 1.28] 1.19 [0.65, 2.16] 0.80 [0.39, 1.63] 0.95 [0.42, 2.18] 1.76 [0.86, 3.61] 0.77 [0.54, 1.09] 0.89 [0.71, 1.11]	
Bergmann 2004 Joyd 1995 nd 2003 enkins 2000 enkins 2006 Peters 2008 SAM30007 2005 SAM30007 2005 SAM40008 2004 Schermer 2007 SLGQ97 2005 an Noord 2001 Voolcock 1996 Subtotal (95% CI) Tau <sup>2</sup> = ( Test for overall effect: 2 Total (95% CI)	17 0 16 3 39 7 19 11 8 31 64 237 0.03; Chi <sup>2</sup> = 2.0.0; CP	0 180 341 575 29 93 68 171 337 487 2853 = 14.16, = 0.29)	13 5 10 13 16 14 16 9 43 176 df = 11 (I	115 133 32 93 69 325 172 251 1778 P = 0.22	0.3% 1.4% 1.1% 1.8% 1.3% 0.9% 1.3% 5.1% 18.4% );   <sup>2</sup> = 22%	0.20 [0.05, 0.83] 0.90 [0.46, 1.76] 0.59 [0.28, 1.28] 1.19 [0.65, 2.16] 0.80 [0.39, 1.63] 0.95 [0.42, 2.18] 1.76 [0.86, 3.61] 0.77 [0.54, 1.09] 0.89 [0.71, 1.11]	
Bergmann 2004           Joyd 1995           Ind 2003           enkins 2000           enkins 2006           Peters 2008           SAM30007 2005           SAM40008 2004           Schermer 2007           SLGQ97 2005           ran Noord 2001           Voolcock 1996           Subtotal (95% CI)           oral events           Heterogeneity: Tau <sup>2</sup> = 0           'est for overall effect: 2	17 0 16 3 39 7 19 11 8 31 64 237 0.03; Chi <sup>2</sup> = 2 = 1.06 (P	0 180 341 575 29 93 68 171 337 487 2853 = 14.16, = 0.29) 14555	13 5 10 13 16 14 16 9 43 176 df = 11 (I	115 133 32 93 69 325 172 251 1778 P = 0.22 11768	0.3% 1.4% 1.1% 1.8% 1.3% 0.9% 1.3% 5.1% 18.4% ); I <sup>2</sup> = 22%	0.20 [0.05, 0.83] 0.90 [0.46, 1.76] 0.59 [0.28, 1.28] 1.19 [0.65, 2.16] 0.80 [0.39, 1.63] 0.95 [0.42, 2.18] 1.76 [0.86, 3.61] 0.77 [0.54, 1.09] 0.89 [0.71, 1.11]	

## Figure 77: The effect of LABA/ICS versus ICS monotherapy on headache

Study or Subgroup	LABA/ Events		ICS Events		Weight	Risk Ratio M-H, Random, 95% C	Risk Ratio I M-H, Random, 95% CI
1.17.1 Low dose							
Bateman 2001	15	332	11	165	4.6%	0.68 [0.32, 1.44]	
Boonsawat 2008	2	151	1	155	0.5%	2.05 [0.19, 22.40]	<u> </u>
Busse 2003	2	281	4	277	0.9%	0.49 [0.09, 2.67]	
Chuchalin 2008	15	973	17	970	5.6%	0.88 [0.44, 1.75]	
Condemi 1999	0	221	5	216	0.3%	0.09 [0.00, 1.60]	
Corren 2007	4	130	3	127	1.2%	1.30 [0.30, 5.70]	
avuru 2000	0	92	1	90	0.3%	0.33 [0.01, 7.90]	
	11	420	1	212			
Cerwin 2007					0.6%	5.55 [0.72, 42.72]	
Aurray 2004	0	88	1	89	0.3%	0.34 [0.01, 8.16]	
AM40034 2004	1	75	2	79	0.5%	0.53 [0.05, 5.69]	
AM40036 2004	4	288	1	289	0.6%	4.01 [0.45, 35.69]	
AS30015 2004	2	78	3	78	0.9%	0.67 [0.11, 3.88]	
AS40036 2005	5	172	3	159	1.3%	1.54 [0.37, 6.34]	<del></del>
AS40068 2005	6	262	11	270	2.7%	0.56 [0.21, 1.50]	
FA103153 2007	5	239	6	236	1.9%	0.82 [0.25, 2.66]	
trand 2004	1	78	2	72	0.5%	0.46 [0.04, 4.98]	
ubtotal (95% CI)		3880		3484	22.6%	0.82 [0.58, 1.16]	•
otal events	73		72				•
leterogeneity: Tau <sup>2</sup> =		- 11 64		(D = 0.7)	1). 12 - 00/		
est for overall effect:				(F = 0.7	1), 1 – 0%		
.17.2 Medium dose							
Baraniuk 1999	6	118	1	114	0.6%	5.80 [0.71, 47.40]	<b></b>
ateman 2004	40	1709	39	1707	13.9%	1.02 [0.66, 1.58]	- <b>+</b> -
Greening 1994	0	0	0	0	2.270	Not estimable	
ohansson 2001	1	176	1	173	0.3%	0.98 [0.06, 15.59]	
elsen 1999	7	239	6	244	2.3%	1.19 [0.41, 3.49]	_ <b>_</b>
emp 1998	7	252	5	254	2.1%	1.41 [0.45, 4.39]	
loenig 2008	3	156	13	310	1.7%	0.46 [0.13, 1.59]	
Iolimard 2001	2	130	2	129	0.7%	0.99 [0.14, 6.94]	
lurray 1999	1	260	3	254	0.5%	0.33 [0.03, 3.11]	
lathan 2006	1	94	2	91	0.5%	0.48 [0.04, 5.25]	
oonan 2006	17	239	4	109	2.3%	1.94 [0.67, 5.62]	
auwels 1997	17	425	14	427	5.5%	1.22 [0.61, 2.44]	
lojas 2007	1	180	0	182	0.3%	3.03 [0.12, 73.97]	
AM30013 2005	2	121	0	116	0.3%	4.80 [0.23, 98.82]	
AM40065 2007	4	150	5	299	1.6%	1.59 [0.43, 5.85]	
	9	242	8	299	3.0%		
AM40090 2005					3.0%	1.12 [0.44, 2.86]	
AM40120 2005	0	0	0	0	0.00/	Not estimable	
AS30002 2008	5	148	1	152	0.6%	5.14 [0.61, 43.43]	
AS30039 2005	1	182	0	180	0.3%	2.97 [0.12, 72.36]	
AS40026 2006	3	321	2	315	0.8%	1.47 [0.25, 8.75]	
Scicchitano 2004	24	947	38	943	10.4%	0.63 [0.38, 1.04]	
Shapiro 2000	0	81	0	81		Not estimable	
LGA5021 2005	6	246	5	242	1.9%	1.18 [0.37, 3.82]	_ <b>_</b>
MS40012 2006	1	93	4	95	0.6%	0.26 [0.03, 2.24]	
an der Molen 1997	5	125	1	114	0.6%	4.56 [0.54, 38.45]	
ubtotal (95% CI)		6634	·	6772	50.7%	1.04 [0.82, 1.30]	•
otal events	163		154				
leterogeneity: Tau <sup>2</sup> = est for overall effect:				(P = 0.5	6); I <sup>2</sup> = 0%		
est for overall effect.	2 – 0.31 (r	- 0.70	)				
.17.3 High dose	^	~	~	~		Not a -time -t	
ubier 1999	0	0	0	0		Not estimable	
nd 2003	7	171	8	325	2.7%	1.66 [0.61, 4.51]	
enkins 2000	3	180	4	173	1.2%	0.72 [0.16, 3.17]	<del></del>
litchell 2003	2	102	4	101	0.9%	0.50 [0.09, 2.64]	
eters 2008	43	575	7	133	4.4%	1.42 [0.65, 3.09]	+
AM30007 2005	2	29	2	32	0.7%	1.10 [0.17, 7.34]	
AM40008 2004	4	93	2	93	0.9%	2.00 [0.38, 10.65]	- <b> -</b>
LGQ97 2005	7	173	8	329	2.7%	1.66 [0.61, 4.51]	- <b>-</b>
an Noord 1999	0	139	4	135	0.3%	0.11 [0.01, 1.99]	
an Noord 2001	20	337	14	172	6.1%	0.73 [0.38, 1.41]	_ <b>_</b>
Voolcock 1996	25	487	15	251	6.8%	0.86 [0.46, 1.60]	1
ubtotal (95% CI)		2286		1744	26.8%	1.01 [0.74, 1.38]	Ţ
otal events leterogeneity: Tau <sup>2</sup> =	113 0 00 <sup>.</sup> Chi²	= 7 69	68 df = 9 (P	= 0 57).	l² = 0%		
est for overall effect:				0.07),			
otal (95% CI)		12800		12000	100.0%	0.98 [0.83, 1.15]	
otal events	349		294				]
OTON EVENIES		- 30.00		(D - 0 7	S) · 12 - 00/		· · · · · ·
eterogeneity: Tou? -	0.00. 011	- 29.98	, ui ≓ 4/	(r <sup>2</sup> – 0.7)	∪,i = 0%		0.005 0.1 1 10 2
eterogeneity: Tau <sup>2</sup> = est for overall effect:			<b>`</b>				0.000 0

## Figure 78: The effect of LABA/ICS versus ICS monotherapy on withdrawal due to AE

	LABA/	ICS	ICS			Risk Ratio	Risk Ratio
tudy or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
.18.1 Low dose							
ateman 2001	48	333	21	165	2.2%	1.13 [0.70, 1.83]	+-
oonsawat 2008	7	151	3	155	0.3%	2.40 [0.63, 9.09]	
huchalin 2002	0	0	0	0		Not estimable	
Chuchalin 2008	109	973	115	970	8.4%	0.94 [0.74, 1.21]	+
Cerwin 2007	23	420	6	212	0.7%	1.93 [0.80, 4.68]	<b>—</b>
lurray 2004	10	88	11	89	0.8%	0.92 [0.41, 2.05]	
lelson 2003	0	0	0	0		Not estimable	
earlman 2004	15	92	12	89	1.0%	1.21 [0.60, 2.44]	
Peters 2007	64	165	63	169	6.8%	1.04 [0.79, 1.37]	Ť
AM40036 2004	8	288	6	289	0.5%	1.34 [0.47, 3.81]	
AS40036 2005	9	172	12	159	0.7%	0.69 [0.30, 1.60]	
AS40068 2005	33	262	32	270	2.5%	1.06 [0.67, 1.68]	+
FA103153 2007 Subtotal (95% CI)	32	239 <b>3183</b>	32	236 2803	2.4% <b>26.2%</b>	0.99 [0.63, 1.56] 1.03 [0.90, 1.19]	<b>→</b>
otal events	358		313				
eterogeneity: Tau <sup>2</sup> = 0	0.00; Chi²	= 5.56,	df = 10 (F	P = 0.85	5); l² = 0%		
est for overall effect: Z	2 = 0.47 (F	P = 0.64	)				
.18.2 Medium dose							
araniuk 1999	32	118	33	114	3.0%	0.94 [0.62, 1.42]	+
ateman 2004	222	1709	217	1707	16.7%	1.02 [0.86, 1.22]	+
Susse 2003	34	281	32	277	2.5%	1.05 [0.67, 1.65]	+
Condemi 1999	39	221	43	216	3.3%	0.89 [0.60, 1.31]	+
ohansson 2001	4	176	5	173	0.3%	0.79 [0.21, 2.88]	
Celsen 1999	66	239	71	244	6.3%	0.95 [0.71, 1.26]	+
loenig 2008	24	156	52	310	2.6%	0.92 [0.59, 1.43]	+
Iorice 2007	16	462	9	217	0.8%	0.84 [0.37, 1.86]	
lurray 1999	17	260	15	254	1.1%	1.11 [0.57, 2.17]	
lathan 2006	23	94	14	91	1.4%	1.59 [0.87, 2.89]	+
loonan 2006	0	0	0	0		Not estimable	
AM30013 2005	7	121	10	116	0.6%	0.67 [0.26, 1.70]	— <del>•</del> †
AM40034 2004	2	75	4	79	0.2%	0.53 [0.10, 2.79]	
AM40065 2007	13	150	32	299	1.3%	0.81 [0.44, 1.50]	
AM40090 2005	3	242	3	241	0.2%	1.00 [0.20, 4.89]	
AS30002 2008	36	148	39	152	3.3%	0.95 [0.64, 1.40]	+
AS30039 2005	2	182	0	180	0.1%	4.95 [0.24, 102.29]	
AS40026 2006	23	321	11	315	1.0%	2.05 [1.02, 4.14]	<b>⊢</b>
hapiro 2000	18	81	21	81	1.7%	0.86 [0.49, 1.48]	-
LGA5021 2005	60	246	55	242	5.0%	1.07 [0.78, 1.48]	+
ubtotal (95% CI)		5282		5308	51.4%	1.00 [0.91, 1.10]	•
otal events	641		666				
eterogeneity: Tau <sup>2</sup> = 0				(P = 0.9	90); l² = 0%	)	
est for overall effect: Z	z = 0.00 (F	P = 1.00	)				
.18.3 High dose							
ubier 1999	62	338	28	165	3.1%	1.08 [0.72, 1.62]	+
ergmann 2004					3.1% 0.1%		
loyd 1995	2 40	179 55	1 47	186 64	0.1% 10.6%	2.08 [0.19, 22.72] 0.99 [0.80, 1.23]	+
				64 173	0.6%		
enkins 2000 eters 2008	10 109	180 575	8 21	173 133	0.6% 2.8%	1.20 [0.49, 2.97]	<b>—</b>
AM40008 2004	109	575 93	21	93	2.8% 0.8%	1.20 [0.78, 1.84] 1.44 [0.65, 3.21]	<b></b>
LGQ97 2005	13	93 171	9 35	93 325	0.8 <i>%</i> 1.4%	0.71 [0.38, 1.30]	<del></del>
an Noord 2001	35	337	35 20	325 172	1.4% 1.9%	0.89 [0.53, 1.50]	<b>_</b>
oolcock 1996	35 25		20 12			0.89 [0.53, 1.50] 1.07 [0.55, 2.10]	<u> </u>
ubtotal (95% CI)	20	487 <b>2415</b>	12	251 <b>1562</b>	1.1% <b>22.4%</b>	1.07 [0.55, 2.10] 1.02 [0.88, 1.19]	4
otal events	309	2-713	181	1002	<b></b> 7/0	1.02 [0.00, 1.10]	Ţ
otal events leterogeneity: Tau <sup>2</sup> = 0		= 3.61		= 0 90)	· 12 = 00/		
est for overall effect: Z				- 0.09)	, 1 - 070		
Sector Overall Ellevi. Z	J.29 (F	- 0.11	,				
		10880		9673	100.0%	1.01 [0.94, 1.09]	
otal (95% CI)	1000		1160				
otal events	1308						
	0.00; Chi²		df = 38 (	(P = 0.9	99); l² = 0%	, <u> </u>	01 0.1 1 10 100

Figure 79: The effect of LABA/ICS versus ICS monotherapy on upper respiratory tract infection

<b>J</b>	LABA/	ICS	ICS			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
1.15.1 Low dose							
Boonsawat 2008	0	0	0	0		Not estimable	
Buhl 2003	0	0	0	0		Not estimable	
Chuchalin 2002	0	0	0	0		Not estimable	
Kavuru 2000	4	92	3	90	3.2%	1.30 [0.30, 5.66]	
Kerwin 2007	3	420	1	212	1.5%	1.51 [0.16, 14.47]	
Murray 2004	4	88	3	89	3.2%	1.35 [0.31, 5.85]	
Rabe 2006	0	354	2	342	0.8%	0.19 [0.01, 4.01]	
Strand 2004	2	78	1	72	1.3%	1.85 [0.17, 19.93]	
Subtotal (95% CI)		1032		805	10.0%	1.21 [0.52, 2.82]	<b>•</b>
Total events	13		10				
Heterogeneity: Tau <sup>2</sup> = (		= 1 62		= 0.81)	$ ^{2} = 0\%$		
Test for overall effect: Z	,	,		,	,		
1.15.2 Medium dose							
Bateman 2003	0	0	0	0		Not estimable	
Bateman 2004	3	683	1	820	1.5%	3.60 [0.38, 34.55]	
Busse 2003	2	281	5	277	2.7%	0.39 [0.08, 2.02]	
Condemi 1999	1	221	11	216	1.8%	0.09 [0.01, 0.68]	
DiFranco 1999	0	0	0	0		Not estimable	
Kelsen 1999	5	239	14	244	5.8%	0.36 [0.13, 1.00]	
Koenig 2008	7	156	7	310	5.6%	1.99 [0.71, 5.57]	
Langton Hewer 1995	0	0	0	0		Not estimable	
Lundback 2006	6	95	0	92	0.9%	12.59 [0.72, 220.41]	
Morice 2007	7	462	3	217	3.7%	1.10 [0.29, 4.20]	
Murray 1999	9	260	14	254	7.7%	0.63 [0.28, 1.42]	
Noonan 2006	5	239	0	109	0.9%	5.04 [0.28, 90.38]	
O'Byrne 2005	15	1828	10	925	8.0%	0.76 [0.34, 1.68]	<b>_</b> _
Rojas 2007	4	180	2	182	2.5%	2.02 [0.38, 10.90]	
SAM40034 2004	2	75	4	79	2.6%	0.53 [0.10, 2.79]	
SAM40090 2005	1	242	2	241	1.3%	0.50 [0.05, 5.45]	
SAS30039 2005	2	182	0	180	0.8%	4.95 [0.24, 102.29]	
SAS40026 2005	2	321	8	315	3.8%	0.37 [0.10, 1.37]	
Scicchitano 2004	11	947	13	943	3.0 <i>%</i> 8.0%		
Shapiro 2000	3	81	2	81	2.3%	0.84 [0.38, 1.87]	
•	6		18	242	2.3% 6.7%	1.50 [0.26, 8.74]	
SLGA5021 2005 Subtotal (95% CI)	0	246 6738	10	242 5727	66.6%	0.33 [0.13, 0.81] 0.76 [0.51, 1.14]	
	92	0/00	114	0121	00.070	0.70 [0.01, 1.14]	•
Total events Heterogeneity: Tau <sup>2</sup> = 0		= 26.02		$(\mathbf{P} = 0)$	)7)· I² = 35	%	
Test for overall effect: Z				(1 – 0.0	57), 1 = 55	70	
	- 1.52 (1	- 0.13	<i>'</i> )				
1.15.3 High dose							
Aubier 1999	0	0	0	0		Not estimable	
Ind 2003	0	0	0	0		Not estimable	
Jenkins 2000	6	180	6	173	5.0%	0.96 [0.32, 2.92]	
Peters 2008	66	575	12	133	11.2%	1.27 [0.71, 2.28]	
Pohl 2005			3			0.14 [0.01, 2.71]	
	0 1	63 20	3	63 32	0.9% 1.4%		
SAM30007 2005		29			1.4%	0.55 [0.05, 5.77]	
Schermer 2007	2	68 227	2	69	2.0%	1.01 [0.15, 7.00]	
van Noord 2001	8	337	2	172	2.9%	2.04 [0.44, 9.51]	
Woolcock 1996 Subtotal (95% CI)	0	0 1252	0	0 642	22 /0/	Not estimable	
Subtotal (95% CI)		1232	07	042	23.4%	1.15 [0.72, 1.82]	T
Total events	83		27	- 0.00	12 - 00/		
Heterogeneity: $Tau^2 = 0$				≓ 0.69)	i, i⁻ = 0%		
Test for overall effect: Z	L = U.58 (F	- = 0.56	))				
Total (95% CI)		9022		7174	100.0%	0.85 [0.64, 1.14]	
Total events	188		151			[010-1, 111-1]	•
Heterogeneity: Tau <sup>2</sup> = (		= 3/ 00		(P = 0 '	20)· l2 - 10	0/2	+ + + + +
Test for overall effect: Z				(i - 0.2		/0	0.005 0.1 1 10 200
Test for subgroup differ							Favours LABA/ICS Favours ICS
	CHCC3. NC	ν αρριί					

## Figure 80: The effect of LABA/ICS versus ICS monotherapy on candidiasis

•	LABA/	ICS	ICS			Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
1.16.1 Low dose							
Bateman 2001	31	333	14	165	0.2%	0.01 [-0.04, 0.06]	ł
Boonsawat 2008	0	155	0	151	2.9%	0.00 [-0.01, 0.01]	ł
3uhl 2003	0	352	0	171	5.9%	0.00 [-0.01, 0.01]	t t
Corren 2007	0	0	0	0		Not estimable	
Kerwin 2007	36	420	16	212	0.2%	0.01 [-0.03, 0.05]	ł
Murray 2004	15	88	12	89	0.0%	0.04 [-0.07, 0.14]	ł
Nelson 2003	16	95	16	97	0.0%	0.00 [-0.10, 0.11]	ł
Pearlman 2004	0	92	0	89	1.0%	0.00 [-0.02, 0.02]	ł
Rabe 2006	6	354	9	342	1.0%	-0.01 [-0.03, 0.01]	ł
Subtotal (95% CI)		1889		1316	11.4%	-0.00 [-0.01, 0.01]	
Total events	104		67				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 2.65,	df = 7 (P	= 0.92	); l² = 0%		
Test for overall effect:	Z = 0.11 (I	P = 0.92	2)				
1.16.2 Medium dose							
Baraniuk 1999	0	118	0	114	1.7%	0.00 [-0.02, 0.02]	t
Bateman 2003	0	168	0	176	3.7%	0.00 [-0.01, 0.01]	1
Bateman 2004	4	1709	3	1707	51.7%	0.00 [-0.00, 0.00]	<b>—</b>
Bouros 1999	0	0	0	0		Not estimable	
Busse 2003	0	281	0	277	9.7%	0.00 [-0.01, 0.01]	t
Condemi 1999	0	221	0	216	6.0%	0.00 [-0.01, 0.01]	t
Fitzgerald 1999	13	89	11	91	0.0%	0.03 [-0.07, 0.12]	t
Johansson 2001	1	176	0	173	1.9%	0.01 [-0.01, 0.02]	+
Kelsen 1999	26	239	34	244	0.1%	-0.03 [-0.09, 0.03]	t
Kemp 1998	11	252	13	254	0.3%	-0.01 [-0.04, 0.03]	t
Molimard 2001	5	130	4	129	0.2%	0.01 [-0.04, 0.05]	t
Morice 2007	27	462	9	217	0.4%	0.02 [-0.02, 0.05]	
Murray 1999	3	260	3	254	1.4%	-0.00 [-0.02, 0.02]	
Nathan 2006	9	94	5	91	0.1%	0.04 [-0.03, 0.12]	
Noonan 2006	0	0	0	0		Not estimable	
Rojas 2007	14	180	6	182	0.2%	0.04 [-0.00, 0.09]	t
SAM40120 2005	0	8	0	10	0.0%	0.00 [-0.19, 0.19]	t
Subtotal (95% CI)		4387		4135	77.6%	0.00 [-0.00, 0.00]	
Total events	113		88				
Heterogeneity: Tau <sup>2</sup> =	,		'	(P = 0.	71); l² = 0%	6	
Test for overall effect:	Z = 0.58 (I	P = 0.56	5)				
1.16.3 High dose							
Aubier 1999	0	338	0	165	5.5%	0.00 [-0.01, 0.01]	Ļ
Bergmann 2004	0	179	1	186	2.1%	-0.01 [-0.02, 0.01]	4
Peters 2008	144	575	26	133	0.1%	0.05 [-0.02, 0.13]	4
Pohl 2005	0	0	20	0	0.170	Not estimable	
van Noord 2001	41	337	23	172	0.1%	-0.01 [-0.07, 0.05]	1
Woolcock 1996	2	487	23	251	3.1%	-0.00 [-0.02, 0.01]	1
Subtotal (95% CI)	2	407 1916	2	907	11.0%	-0.00 [-0.02, 0.01]	
Total events	187		52				
Heterogeneity: Tau <sup>2</sup> =		= 7 95		= 0.09	);   <sup>2</sup> = 50%		
Test for overall effect: 2	,	,		0.00	,,. 0070		
			,				
Total (95% CI)		8192		6358	100.0%	0.00 [-0.00, 0.00]	
Total events	404		207				
	0 00 <sup>.</sup> Chi <sup>2</sup>	= 20.60	). df = 27	(P = 0.	80); l <sup>2</sup> = 0%	6	
Heterogeneity: Tau <sup>2</sup> =	0.00, 011		- , -	•			-100 -50 0 50 1

## Figure 81: The effect of LABA/ICS versus ICS monotherapy on treatment-related AEs

	LABA/	ICS	ICS			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.21.1 Low dose							
Bateman 2001	5	333	0	165	0.3%	5.47 [0.30, 98.28]	
Buhl 2003	12	352	7	171	2.8%	0.83 [0.33, 2.08]	
Chuchalin 2002	1	111	4	114	0.5%	0.26 [0.03, 2.26]	
Kavuru 2000	3	92	9	90	1.4%	0.33 [0.09, 1.17]	
Kuna 2006	18	409	10	207	4.0%	0.91 [0.43, 1.94]	
Lalloo 2003	6	230	8	237	2.1%	0.77 [0.27, 2.19]	
Nelson 2003	0	0	0	0		Not estimable	
Price 2002	4	332	20	331	2.1%	0.20 [0.07, 0.58]	
Rabe 2006	1	354	5	342	0.5%	0.19 [0.02, 1.65]	
Subtotal (95% CI)		2213		1657	13.7%	0.55 [0.31, 0.95]	$\bullet$
Fotal events	50		63				
-leterogeneity: Tau <sup>2</sup> = (	0.21; Chi <sup>2</sup>	= 10.85	, df = 7 (F	) = 0.15	5); l² = 35%	/ 0	
Test for overall effect: 2	Z = 2.14 (F	° = 0.03	5)				
1.21.2 Medium dose							
Bouros 1999	1	69	1	65	0.3%	0.94 [0.06, 14.75]	
Fitzgerald 1999	16	89	17	91	5.8%	0.96 [0.52, 1.78]	- <del>+</del> -
Johansson 2001	7	176	10	173	2.6%	0.69 [0.27, 1.77]	— <del></del> +-
Kemp 1998	53	252	59	254	17.5%	0.91 [0.65, 1.26]	-+
Koenig 2008	23	156	70	310	11.1%	0.65 [0.42, 1.00]	
angton Hewer 1995	1	11	0	12	0.2%	3.25 [0.15, 72.36]	
Volimard 2001	17	130	20	129	6.2%	0.84 [0.46, 1.54]	
Morice 2007	3	462	7	217	1.3%	0.20 [0.05, 0.77]	
SAM40034 2004	3	75	1	79	0.5%	3.16 [0.34, 29.71]	
Scicchitano 2004	28	947	43	943	9.6%	0.65 [0.41, 1.03]	
/ermetten 1999	8	113	14	120	3.3%	0.61 [0.26, 1.39]	
Zetterstrom 2001 Subtotal (95% CI)	16	238 <b>2718</b>	5	124 <b>2517</b>	2.4% 60.9%	1.67 [0.63, 4.44] 0.79 [0.65, 0.96]	•
Total events	176		247				
Heterogeneity: Tau <sup>2</sup> = (	-		-	(P = 0.4	10); l² = 4%	6	
Test for overall effect: 2	<u>×</u> = 2.41 (F	<sup>7</sup> = 0.02	.)				
21.2 High doco							
	0	0	0	0		Not optimoble	
nd 2003	0	0	0	0	1 10/	Not estimable	
nd 2003 Ienkins 2000	3	180	4	173	1.1%	0.72 [0.16, 3.17]	
nd 2003 Ienkins 2000 SAM30007 2005	3 0	180 29	4 1	173 32	0.2%	0.72 [0.16, 3.17] 0.37 [0.02, 8.66]	
nd 2003 Ienkins 2000 SAM30007 2005 SAM40008 2004	3 0 1	180 29 93	4 1 0	173 32 93	0.2% 0.2%	0.72 [0.16, 3.17] 0.37 [0.02, 8.66] 3.00 [0.12, 72.71]	
nd 2003 Jenkins 2000 SAM30007 2005 SAM40008 2004 SLGQ97 2005	3 0 1 1	180 29 93 171	4 1 0 3	173 32 93 325	0.2% 0.2% 0.5%	0.72 [0.16, 3.17] 0.37 [0.02, 8.66] 3.00 [0.12, 72.71] 0.63 [0.07, 6.04]	
nd 2003 Jenkins 2000 SAM30007 2005 SAM40008 2004 SLGQ97 2005 van Noord 2001	3 0 1 1 17	180 29 93 171 337	4 1 0 3 10	173 32 93 325 172	0.2% 0.2% 0.5% 3.9%	0.72 [0.16, 3.17] 0.37 [0.02, 8.66] 3.00 [0.12, 72.71] 0.63 [0.07, 6.04] 0.87 [0.41, 1.85]	
nd 2003 Jenkins 2000 SAM30007 2005 SAM40008 2004 SLGQ97 2005 van Noord 2001 Wallin 2003	3 0 1 1 17 17	180 29 93 171 337 18	4 1 3 10 7	173 32 93 325 172 38	0.2% 0.2% 0.5% 3.9% 0.6%	0.72 [0.16, 3.17] 0.37 [0.02, 8.66] 3.00 [0.12, 72.71] 0.63 [0.07, 6.04] 0.87 [0.41, 1.85] 0.30 [0.04, 2.27]	
nd 2003 Jenkins 2000 SAM30007 2005 SAM40008 2004 SLGQ97 2005 van Noord 2001 Wallin 2003 Woolcock 1996 Subtotal (95% CI)	3 0 1 1 17 17 89	180 29 93 171 337	4 1 3 10 7 50	173 32 93 325 172	0.2% 0.2% 0.5% 3.9%	0.72 [0.16, 3.17] 0.37 [0.02, 8.66] 3.00 [0.12, 72.71] 0.63 [0.07, 6.04] 0.87 [0.41, 1.85]	
nd 2003 Jenkins 2000 SAM30007 2005 SAM40008 2004 SLGQ97 2005 van Noord 2001 Wallin 2003 Woolcock 1996 Subtotal (95% CI) Fotal events	3 0 1 17 17 89 112	180 29 93 171 337 18 487 <b>1315</b>	4 1 3 10 7 50 75	173 32 93 325 172 38 251 <b>1084</b>	0.2% 0.2% 0.5% 3.9% 0.6% 18.9% <b>25.4%</b>	0.72 [0.16, 3.17] 0.37 [0.02, 8.66] 3.00 [0.12, 72.71] 0.63 [0.07, 6.04] 0.87 [0.41, 1.85] 0.30 [0.04, 2.27] 0.92 [0.67, 1.25]	
nd 2003 Jenkins 2000 SAM30007 2005 SAM40008 2004 SLGQ97 2005 van Noord 2001 Wallin 2003 Woolcock 1996 Subtotal (95% CI) Fotal events Heterogeneity: Tau <sup>2</sup> = (	3 0 1 17 17 89 112 0.00; Chi <sup>2</sup>	180 29 93 171 337 18 487 <b>1315</b> = 2.18,	4 1 0 3 10 7 50 75 df = 6 (P	173 32 93 325 172 38 251 <b>1084</b>	0.2% 0.2% 0.5% 3.9% 0.6% 18.9% <b>25.4%</b>	0.72 [0.16, 3.17] 0.37 [0.02, 8.66] 3.00 [0.12, 72.71] 0.63 [0.07, 6.04] 0.87 [0.41, 1.85] 0.30 [0.04, 2.27] 0.92 [0.67, 1.25]	
nd 2003 Jenkins 2000 SAM30007 2005 SAM40008 2004 SLGQ97 2005 van Noord 2001 Wallin 2003 Woolcock 1996 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2	3 0 1 17 17 89 112 0.00; Chi <sup>2</sup>	180 29 93 171 337 18 487 <b>1315</b> = 2.18,	4 1 0 3 10 7 50 75 df = 6 (P	173 32 93 325 172 38 251 <b>1084</b> = 0.90)	0.2% 0.2% 0.5% 3.9% 0.6% 18.9% 25.4%	0.72 [0.16, 3.17] 0.37 [0.02, 8.66] 3.00 [0.12, 72.71] 0.63 [0.07, 6.04] 0.87 [0.41, 1.85] 0.30 [0.04, 2.27] 0.92 [0.67, 1.25]	
1.21.3 High dose nd 2003 Jenkins 2000 SAM30007 2005 SAM40008 2004 SLGQ97 2005 van Noord 2001 Wallin 2003 Woolcock 1996 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = ( Test for overall effect: 2 Total (95% CI)	3 0 1 17 1 89 112 0.00; Chi <sup>2</sup> Z = 0.90 (F	180 29 93 171 337 18 487 <b>1315</b> = 2.18, P = 0.37	4 1 0 3 10 7 50 75 df = 6 (P	173 32 93 325 172 38 251 <b>1084</b> = 0.90)	0.2% 0.2% 0.5% 3.9% 0.6% 18.9% <b>25.4%</b>	0.72 [0.16, 3.17] 0.37 [0.02, 8.66] 3.00 [0.12, 72.71] 0.63 [0.07, 6.04] 0.87 [0.41, 1.85] 0.30 [0.04, 2.27] 0.92 [0.67, 1.25] <b>0.88 [0.67, 1.16]</b>	
nd 2003 Jenkins 2000 SAM30007 2005 SAM40008 2004 SLGQ97 2005 van Noord 2001 Wallin 2003 Woolcock 1996 Subtotal (95% CI) Fotal events Heterogeneity: Tau <sup>2</sup> = 0 Fest for overall effect: 2	3 0 1 17 1 89 112 0.00; Chi <sup>2</sup> Z = 0.90 (F 338	180 29 93 171 337 18 487 1315 = 2.18, 0 = 0.37 6246	4 1 0 3 10 7 50 75 df = 6 (P 7) 385	173 32 93 325 172 38 251 1084 = 0.90) 5258	0.2% 0.2% 0.5% 3.9% 0.6% 18.9% 25.4% ; l <sup>2</sup> = 0%	0.72 [0.16, 3.17] 0.37 [0.02, 8.66] 3.00 [0.12, 72.71] 0.63 [0.07, 6.04] 0.87 [0.41, 1.85] 0.30 [0.04, 2.27] 0.92 [0.67, 1.25] 0.88 [0.67, 1.16] 0.78 [0.66, 0.90]	

## Figure 82: The effect of LABA/ICS versus ICS monotherapy on worsening asthma

-	LABA/	CS	ICS			Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
.19.1 Low dose							
Bateman 2001	0	333	0	165	4.0%	0.00 [-0.01, 0.01]	+
Chuchalin 2008	0	973	2	970	28.4%	-0.00 [-0.01, 0.00]	<b>+</b>
Grutters 1999	0	12	0	13	0.0%	0.00 [-0.14, 0.14]	•
Pearlman 2004	0	92	0	89	0.8%	0.00 [-0.02, 0.02]	•
SAM40036 2004	0	288	0	289	7.6%	0.00 [-0.01, 0.01]	+
SAS30015 2004	0	78	0	78	0.6%	0.00 [-0.02, 0.02]	+
SAS40036 2005	0	172	0	159	2.5%	0.00 [-0.01, 0.01]	+
SAS40068 2005	0	262	1	270	3.3%	-0.00 [-0.01, 0.01]	+
SFA103153 2007	0	239	0	236	5.1%	0.00 [-0.01, 0.01]	+
SLGF75 2005	0	14	0	32	0.0%	0.00 [-0.10, 0.10]	+
Subtotal (95% CI)		2463		2301	52.3%	-0.00 [-0.00, 0.00]	
otal events	0		3				
Heterogeneity: Tau <sup>2</sup> = (		= 0.78.		= 1.00	): $ ^2 = 0\%$		
est for overall effect: 2					,,		
		0.00	- /				
.19.2 Medium dose							
Susse 2003	0	281	0	277	7.1%	0.00 [-0.01, 0.01]	+
Koenig 2008	0	156	1	310	2.5%	-0.00 [-0.01, 0.01]	+
AM40034 2004	0	75	0	79	0.6%	0.00 [-0.03, 0.03]	4
AM40065 2007	0	150	0	299	3.3%	0.00 [-0.01, 0.01]	+
AM40090 2005	0	242	0	241	5.3%	0.00 [-0.01, 0.01]	+
AM40120 2005	0	8	0	10	0.0%	0.00 [-0.19, 0.19]	•
AS30002 2008	0	148	0	152	2.1%	0.00 [-0.01, 0.01]	+
AS30039 2005	0	182	0	180	3.0%	0.00 [-0.01, 0.01]	+
AS40026 2006	0	321	0	315	9.2%	0.00 [-0.01, 0.01]	<b>+</b>
SLGA5021 2005	0	246	0	242	5.4%	0.00 [-0.01, 0.01]	+
SMS40012 2006	0	93	0	95	0.8%	0.00 [-0.02, 0.02]	
Subtotal (95% CI)	· ·	1902	· ·	2200	39.3%	-0.00 [-0.00, 0.00]	
otal events	0		1			• • •	
leterogeneity: Tau <sup>2</sup> = (		= 0.28	df = 10 (	P = 1.0	$(0)^{12} = 0\%$		
est for overall effect: 2					•),. •,		
	(.	0.00	- )				
.19.3 High dose							
ubier 1999	1	338	0	165	2.9%	0.00 [-0.01, 0.01]	+
lielsen 1999	0	0	0	0		Not estimable	
AM30007 2005	0	29	0	32	0.1%	0.00 [-0.06, 0.06]	ł
AM40008 2004	0	93	0	93	0.8%	0.00 [-0.02, 0.02]	4
LGQ97 2005	1	171	0	325	1.6%	0.01 [-0.01, 0.02]	4
an Noord 2001	1	337	0	172	3.0%	0.00 [-0.01, 0.01]	+
Subtotal (95% CI)		968	5	787	8.5%	0.00 [-0.00, 0.01]	
otal events	3		0		-	- / .	
leterogeneity: Tau <sup>2</sup> = (	-	= 0.23	-	= 0.99	); $ ^2 = 0\%$		
est for overall effect: 2				0.00	,,. 0,0		
otal (95% CI)	(-	5333	,	5288	100.0%	-0.00 [-0.00, 0.00]	
	0	0000	A	J200	100.0%	-0.00 [-0.00, 0.00]	
otal events	3	- 2 15	4 df = 25 (	D = 4 0	0). 12 - 00/		
leterogeneity: Tau <sup>2</sup> = ( est for overall effect: 2				r = 1.0	∪), i <sup>_</sup> = 0%	)	-100 -50 0 50 100
	r = U 54 (F	- = 0.59	1)			_	avours LABA/ICS Favours ICS

## Figure 83: The effect of LABA/ICS versus ICS monotherapy on fatal SAEs

	LABA/	ICS	ICS			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% C
1.20.1 Low dose							
Chuchalin 2002	0	111	0	114		Not estimable	
Strand 2004	0	78	1	72	36.2%	0.31 [0.01, 7.44]	
Subtotal (95% CI)		189		186	36.2%	0.31 [0.01, 7.44]	
Total events	0		1				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 0.72 (I	⊃ = 0.4	7)				
1.20.2 Medium dose							
Morice 2007	0	462	0	217		Not estimable	
Scicchitano 2004	1	947	2	943	63.8%	0.50 [0.05, 5.48]	
Subtotal (95% CI)		1409		1160	63.8%	0.50 [0.05, 5.48]	
Total events	1		2				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 0.57 (I	⊃ = 0.5	7)				
Total (95% CI)		1598		1346	100.0%	0.42 [0.06, 2.84]	
Total events	1		3				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 0.06	, df = 1 (F	9 = 0.81	); l² = 0%		0.01 0.1 1 10
Test for overall effect:	Z = 0.89 (I	⊃ = 0.3 <sup>°</sup>	7)				Favours LABA/ICS Favours IC
Test for subgroup diffe	rences: N	ot appli	cable			· · · · · · · · · · · · · · · · · · ·	

#### Figure 84: The effect of LABA/ICS versus ICS monotherapy on all-cause mortality

	LABA/	ICS	ICS			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.22.1 Low dose							
Bateman 2001	7	333	3	165	3.2%	1.16 [0.30, 4.41]	
Boonsawat 2008	1	155	1	151	0.8%	0.97 [0.06, 15.43]	
Jenkins 2000	6	180	9	173	5.6%	0.64 [0.23, 1.76]	
Kavuru 2000	3	92	1	90	1.1%	2.93 [0.31, 27.69]	
Kerwin 2007	3	420	0	212	0.7%	3.54 [0.18, 68.25]	
Nelson 2003	0	0	0	0		Not estimable	
SAM40036 2004 Subtotal (95% CI)	4	288 <b>1468</b>	2	289 <b>1080</b>	2.0% <b>13.4%</b>	2.01 [0.37, 10.87] 1.11 <b>[0.58, 2.14]</b>	•
Total events	24		16				
Heterogeneity: Tau <sup>2</sup> =	0.00; Chi <sup>2</sup>	= 2.95	df = 5 (P	= 0.71	); l² = 0%		
Test for overall effect:	Z = 0.31 (F	<sup>&gt;</sup> = 0.7	5)				
1.22.2 Medium dose							
Baraniuk 1999	6	118	5	114	4.3%	1.16 [0.36, 3.69]	
Bateman 2003	0	0	0	0		Not estimable	<u> </u>
Bateman 2004	62	1709	45	1707	40.2%	1.38 [0.94, 2.01]	†■-
Condemi 1999	9	221	12	216	8.1%	0.73 [0.32, 1.70]	
Lundback 2006	10	95	8	92	7.3%	1.21 [0.50, 2.93]	- <b>-</b>
O'Byrne 2005	0	0	0	0		Not estimable	
Rojas 2007	2	180	1	182	1.0%	2.02 [0.18, 22.10]	
SAM40034 2004	6	75	8	79	5.6%	0.79 [0.29, 2.17]	
SAM40090 2005	0	242	4	241	0.7%	0.11 [0.01, 2.04] —	
SAS30039 2005	2	182	2	180	1.5%	0.99 [0.14, 6.95]	
SLGA5021 2005 Subtotal (95% CI)	11	246 <b>3068</b>	11	242 <b>3053</b>	8.6% 77.4%	0.98 [0.43, 2.23] 1.14 <b>[0.87, 1.50]</b>	•
Total events	108		96				
Heterogeneity: Tau <sup>2</sup> =				= 0.72	); l <sup>2</sup> = 0%		
		0.3;	5)				
	Z = 0.94 (I						
Test for overall effect: 1.22.3 High dose		-	-	-		<b>.</b>	
1.22.3 High dose Aubier 1999	0	0	0	0		Not estimable	
<b>1.22.3 High dose</b> Aubier 1999 Boyd 1995	0 0	0	0	0		Not estimable	
<b>1.22.3 High dose</b> Aubier 1999 Boyd 1995 Ind 2003	0 0 0	0 0	0 0	0 0		Not estimable Not estimable	
<b>1.22.3 High dose</b> Aubier 1999 Boyd 1995 Ind 2003 SAM30007 2005	0 0 0 0	0 0 29	0 0 1	0 0 32	0.6%	Not estimable Not estimable 0.37 [0.02, 8.66]	
<b>1.22.3 High dose</b> Aubier 1999 Boyd 1995 Ind 2003 SAM30007 2005 Schermer 2007	0 0 0 1	0 0 29 68	0 0 1 2	0 0 32 69	1.0%	Not estimable Not estimable 0.37 [0.02, 8.66] 0.51 [0.05, 5.47]	
<b>1.22.3 High dose</b> Aubier 1999 Boyd 1995 Ind 2003 SAM30007 2005 Schermer 2007 SLGQ97 2005	0 0 0 1 5	0 0 29 68 171	0 0 1 2 5	0 0 32 69 325	1.0% 3.8%	Not estimable Not estimable 0.37 [0.02, 8.66] 0.51 [0.05, 5.47] 1.90 [0.56, 6.47]	
<b>1.22.3 High dose</b> Aubier 1999 Boyd 1995 Ind 2003 SAM30007 2005 Schermer 2007	0 0 0 1	0 0 29 68	0 0 1 2	0 0 32 69	1.0%	Not estimable Not estimable 0.37 [0.02, 8.66] 0.51 [0.05, 5.47]	
<b>1.22.3 High dose</b> Aubier 1999 Boyd 1995 Ind 2003 SAM30007 2005 Schermer 2007 SLGQ97 2005 van Noord 2001	0 0 0 1 5	0 29 68 171 337	0 0 1 2 5	0 0 32 69 325 172	1.0% 3.8% 3.8%	Not estimable Not estimable 0.37 [0.02, 8.66] 0.51 [0.05, 5.47] 1.90 [0.56, 6.47] 2.55 [0.75, 8.70]	
<b>1.22.3 High dose</b> Aubier 1999 Boyd 1995 Ind 2003 SAM30007 2005 Schermer 2007 SLGQ97 2005 van Noord 2001 <b>Subtotal (95% CI)</b>	0 0 1 5 15 21 : 0.00; Chi <sup>2</sup>	0 29 68 171 337 <b>605</b> = 2.35,	0 0 1 2 5 3 11 df = 3 (P	0 0 32 69 325 172 <b>598</b>	1.0% 3.8% 3.8% <b>9.2%</b>	Not estimable Not estimable 0.37 [0.02, 8.66] 0.51 [0.05, 5.47] 1.90 [0.56, 6.47] 2.55 [0.75, 8.70]	
<b>1.22.3 High dose</b> Aubier 1999 Boyd 1995 Ind 2003 SAM30007 2005 Schermer 2007 SLGQ97 2005 van Noord 2001 <b>Subtotal (95% CI)</b> Total events Heterogeneity: Tau <sup>2</sup> =	0 0 1 5 15 21 : 0.00; Chi <sup>2</sup>	0 29 68 171 337 <b>605</b> = 2.35,	0 0 1 2 5 3 11 df = 3 (P	0 0 32 69 325 172 <b>598</b> = 0.50	1.0% 3.8% 3.8% <b>9.2%</b>	Not estimable Not estimable 0.37 [0.02, 8.66] 0.51 [0.05, 5.47] 1.90 [0.56, 6.47] 2.55 [0.75, 8.70]	
1.22.3 High dose Aubier 1999 Boyd 1995 Ind 2003 SAM30007 2005 Schermer 2007 SLGQ97 2005 van Noord 2001 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	0 0 1 5 15 21 : 0.00; Chi <sup>2</sup>	0 29 68 171 337 <b>605</b> = 2.35, P = 0.20	0 0 1 2 5 3 11 df = 3 (P	0 0 32 69 325 172 <b>598</b> = 0.50	1.0% 3.8% 3.8% <b>9.2%</b> );   <sup>2</sup> = 0%	Not estimable Not estimable 0.37 [0.02, 8.66] 0.51 [0.05, 5.47] 1.90 [0.56, 6.47] 2.55 [0.75, 8.70] <b>1.68 [0.76, 3.69]</b>	
1.22.3 High dose Aubier 1999 Boyd 1995 Ind 2003 SAM30007 2005 Schermer 2007 SLGQ97 2005 van Noord 2001 Subtotal (95% CI) Total events Heterogeneity: Tau <sup>2</sup> = Test for overall effect: Total (95% CI)	0 0 0 1 5 15 21 20.00; Chi <sup>2</sup> Z = 1.28 (f	0 29 68 171 337 <b>605</b> = 2.35, P = 0.20 <b>5141</b>	0 0 1 2 5 3 11 df = 3 (P 0) 123	0 0 32 69 325 172 <b>598</b> = 0.50 <b>4731</b>	1.0% 3.8% 3.8% 9.2% ); I <sup>2</sup> = 0% 100.0%	Not estimable Not estimable 0.37 [0.02, 8.66] 0.51 [0.05, 5.47] 1.90 [0.56, 6.47] 2.55 [0.75, 8.70] <b>1.68 [0.76, 3.69]</b>	

## Figure 85: The effect of LABA/ICS versus ICS monotherapy on hoarseness

## APPENDIX 8: APPRAISAL OF CANADIAN, NORTH AMERICAN, AND INTERNATIONAL CLINICAL PRACTICE GUIDELINES FOR THE USE OF LONG-ACTING BETA<sub>2</sub>-AGONIST AND INHALED CORTICOSTEROID COMBINATION THERAPY FOR PERSISTENT ASTHMA

## 1 **OBJECTIVES**

The objective of this study was to identify the recommendations regarding the use of LABA plus ICS for the management of asthma within three main guidelines. These guidelines were selected for this CADTH report because they were the most respected and widely cited Canadian (Canadian Thoracic Society; CTS), North American (National Asthma Education and Prevention Program - NAEPP), and International (Global Initiative for Asthma (GINA) guidelines. We examined these reports to evaluate the strength of evidence upon which the recommendations are based. Specifically, the study examined whether the guidelines provided evidence-based recommendations for the use of CT with newly diagnosed and ICS stabilized patients according to disease stage, therapy type, and the need to switch patients from one form of therapy (fixed vs. variable dose) to another and the strength of evidence upon which these recommendations were based.

## 2 METHODS

## 2.1.1 Study selection and inclusion/exclusion criteria

The full-texts of current CTS, NAEPP, and GINA guidelines were retrieved. In the case of the CTS guidelines, preliminary evaluation showed that the most recent update was incomplete due to the lack of description of guideline development and frequent references to previous versions of the guideline. Therefore, the original 1999 CTS guideline and all published updates covering a 6-year period (1999-2005) (1999, 2001 and 2003 versions) were retrieved.

## 2.2 Guideline assessment

## 2.2.1 Assessment tools

The AGREE Instrument is a tool designed to evaluate both the quality of reporting and of the recommendations contained in the guidelines and is meant to be used by policy makers, guideline developers, health care providers, and educators.<sup>193,193</sup> The AGREE Instrument has been used to compare the quality of corresponding clinical practice guidelines,<sup>194,194</sup> to identify predictors of high quality for clinical practice guidelines,<sup>195,195</sup> and to evaluate existing guidelines and make recommendations for the development of new guidelines.<sup>196</sup>

The instrument consists of 23 Likert scale items organized in 6 domains intended to capture different dimensions of guideline quality (scope and purpose, stakeholder involvement, rigour of development, clarity, applicability, and editorial independence). Guidelines are given an overall score from 0 to 100 on each component of the domain and a qualitative summary statement describing the strength of the guideline to inform practice.

#### 2.2.2 Assessment methods

Three reviewers independently assessed the CTS, NAEPP, and GINA guidelines using the AGREE instrument. Differences in scores were resolved through discussion and consensus. When consensus could not be reached, the Research Team referred to a experienced clinician for adjudication of the final score.

#### 2.2.3 Data handling

Data on the level of evidence and strength of recommendations contained within the text of each guideline were extracted by one reviewer using a standardized form based on the study research questions. Extracted data was verified by a second reviewer. The data was entered into a Word<sup>TM</sup> table (Microsoft Corp. 2003) for qualitative analysis.

## 2.2.4 Data synthesis and analysis

Data elements describing recommendations and evidence to support respective recommendations were extracted and entered into an Excel<sup>TM</sup> database. Evidence profiles of the three guidelines were constructed to summarize the management recommendations and evidence used. These summaries allowed three-way comparisons of the guidelines to be made. Similarities and differences in the respective management recommendations and available evidence were summarized qualitatively in text and tables. Guidelines were given an overall score as a percentage of the maximum possible score for that domain and a qualitative summary statement describing the strength of the guideline to inform practice. The six domain scores were not aggregated into an overall quality score.<sup>193,193</sup>

In addition, the level of evidence and strength of recommendations was assessed by extracting the evidence hierarchies used by the individual guidelines. Specific recommendations made by the guidelines were entered into a Word<sup>TM</sup> table (Microsoft Corp. 2003) by a single reviewer and then verified by a second reviewer. The level of evidence for each recommendation was identified and entered into the table. The item scores and comments from the AGREE tool were entered into a Word<sup>TM</sup> table (Microsoft Corp. 2003) for analysis. Standardized domain scores were calculated for each guideline as described in the AGREE manual.<sup>193</sup> These summaries allowed for three-way comparisons of the guidelines. Similarities and differences in the respective management recommendations and available evidence were summarized qualitatively in text and tables.

## 3 RESULTS

## 3.1 Description of Guidelines

The aim of each guideline was to provide current, evidence-based information to physicians on the control and management of asthma. The content for guidelines was selected and reviewed by teams of physicians and other asthma experts, e.g. asthma educators. All three guidelines were updates of previous versions of the guidelines.

The CTS guideline was a joint report by several Canadian respiratory health societies and physicians from varying disciplines. The guideline was funded through unrestricted grants from several pharmaceutical companies. Recommendations were graded according to five levels of evidence (Appendix A - Table 1). The group convened to update the guideline in 2003, and the updated guideline was released in 2004.

The GINA guideline was created by an international team of physicians and academic researchers. The guideline was funded through unrestricted educational grants from several pharmaceutical companies. Recommendations were graded according to four levels of evidence. The group convened to update the guideline in 2007, and the updated guideline was released in 2007.

The NAEPP guideline was a joint report created by a diverse team of stake holders (including physicians, researchers, and public health officials) working together with the National Heart, Lung, and Blood Institute (NHLBI) of the United States National Institutes of Health (NIH). Recommendations were graded according to four levels of evidence. The guideline and resource document were funded by the NHLBI. The group convened to update the guideline in 2005, and the updated guideline was released in 2007.

## 3.2 AGREE Results

The results of the assessment of the guidelines by component and domain are described below and in Figure 1 and Table 1.

**Scope and Purpose:** The score for this domain concerns the overall objectives of the guidelines, the specific clinical questions covered, and the target population the guidelines were designed for. All three guidelines scored >50% in this domain with NAEPP scoring the highest (89%).

**Stakeholder Involvement:** The score for this domain concerns the extent to which the guidelines represent the views of their intended users. Only the NAEPP guideline scored >50% in this domain with (67%). GINA received the lowest score of the evaluation in this domain (17%).

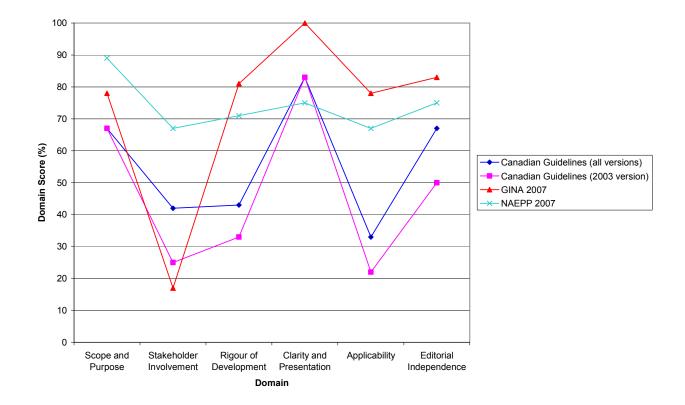
**Rigour of Development:** The score for this domain concerns the process used to gather the evidence, whether the methods to develop the recommendations and update the guidelines are clearly described. Two of the three guidelines (GINA and NAEPP) scored >50% on this domain.

**Clarity and Presentation:** The score for this domain reflects the clarity of the guidelines, specifically, the specificity of the recommendations, ease of identification of key points and recommendations, and the availability of supportive tools for application. All three guidelines scored >50% in this domain with GINA scoring the highest (100%).

**Applicability:** The score for this domain concerns the identification of the potential issues influencing guideline implementation (organizational, behavioral, and cost implications). Two guidelines scored >50% with GINA scoring the highest (78%).

**Editorial Independence:** The score for this domain reflects the independence of the development of the recommendations from funding bodies. All three guidelines scored >50% with GINA scoring the highest (83%).

Detailed descriptions of the scoring of the guidelines and comments are provided in Appendix A, Table 1.



AGREE Instrument: Domain Scores

## Figure 1: Domain scores for CACG, GINA and NAEPP guidelines

Table 1: AGREE instrument appraisal scores								
Domain and Item	CACG (all)	CACG (2003)	GINA (2007)	NAEPP (2007)				
	Total %	Total %	Total %	Total %				
Scope and Purpose								
1. The overall objective(s) of the guideline is (are) specifically described	75	75	100	100				
2. The clinical question(s) covered by the guideline is (are)	75	75	50%	75				
specifically described 3. The patients to whom the guideline is	75	75	100	100				
meant to apply are specifically described								
Domain Score	67	67	78	89				
Stakeholder Involvemer	nt							
4. The guideline development group includes individuals from all the relevant professional groups	75	75	50	100				
5. The patients' views and preferences have been sought	25	25	25	75				
6. The target users of the guideline are clearly defined	75	50	50	100				
7. The guideline has been piloted among target users	50	25	25	25				
Domain Score Rigour of Development	42	25	17	67				
8. Systematic methods were used to search for evidence	75	75	100	100				
9. The criteria for selecting the evidence are clearly described	25	25	75	50				
10. The methods used for formulating the recommendations are clearly described	75	50	75	75				
11. The health benefits, side-effects and risks have been considered in formulating the recommendations	75	75	100	100				
12. There is an explicit link between the recommendations	75	75	75	75				

Table 1: AGREE instrument appraisal scores								
Domain and Item	CACG (all)	CACG (2003)	GINA (2007)	NAEPP (2007)				
	Total %	Total %	Total %	Total %				
and the supporting evidence								
13. The guideline has been externally reviewed by experts prior to its publication	50	25	75	100				
14. A procedure for updating the guideline is provided	25	25	100	50				
Domain Score Clarity and Presentation	43	33	81	71				
15. The recommendations are specific and unambiguous	100	100	100	100				
16. The different options for management of the condition are clearly presented	100	100	100	100				
17. Key recommendations are easily identifiable	100	100	100	100				
18. The guideline is supported with tools for application	50	50	100	25				
Domain Score Applicability	83	83	100	75				
19. The potential organizational barriers in applying the recommendations have been discussed	50	25	100	50				
20. The potential cost implications of applying the recommendations have been considered	25	25	75	100				
21. The guideline presents key review criteria for monitoring and/or audit purposes	75	75	75	75				
Domain Score Editorial Independence	33	22	78	67				
22. The guideline is editorially independent from the	75	75	100	63				

Table 1: AGREE instrument appraisal scores										
Domain and Item	CACG (all)	CACG (2003)	GINA (2007)	NAEPP (2007)						
	Total %	Total %	Total %	Total %						
funding body										
23. Conflicts of interest of guideline development members have been recorded	75	50	75	100						
Domain Score	67	50	83	75						
Would you recommend	l these guidelines for u	se in practice?								
Recommendation Strongly recommend:	Number of Experts	Number of Experts	Number of Experts	Number of Experts 1						
Recommend	1	1	1							
(all)	– stakeholder involver		rigour of developmen	t low						

#### Guideline Recommendations

All three guidelines addressed the research questions regarding the clinical effectiveness and differences in safety of CT compared to ICS alone in treatment naïve adults and those stabilized on ICS, as well as addressing the research question regarding the comparative effectiveness of different drug combinations for maintenance therapy in adults.

Each guideline employed an evidence hierarchy to grade the levels of evidence that support the various recommendations. The CTS guideline used a 5-point scale (Level 1-5), with Level 1 being the highest rated evidence. Both the GINA and NAEPP guidelines used a 4-point scale (Category A-D), with Category A being the highest rated evidence (Appendix A – Table 2). Guidelines assessed the level of evidence of their recommendations based on study design and the body of data. Often the evidence hierarchies in each guideline were not assigned to the recommendations. For example, the CTS guidelines did not indicate the level of evidence for recommendations concerning the use of combination LABA/ICS therapies. In the GINA and NAEPP guidelines there were no levels of evidence for some of the recommendations concerning differences in safety between ICS and LABA combination therapy and ICS monotherapy.

As all guidelines recommend initiating the addition of LABA to ICS only after treatment with ICS monotherapy, none of the guidelines recommend the delivery of combination therapy to steroid naïve patients. None of the guidelines reported on the comparison the effectiveness of the two CT products (salmeterol/fluticasone versus formoterol budesonide) for maintenance therapy, though the benefits and potential harms of the combination therapies were discussed. Finally, there was no information in any of the guidelines that could answer the study questions pertaining to clinical benefit(s) to switching to variable from fixed-dose combination therapies. A summary of the guideline recommendations can be found in Table 3 (see Appendix A).

The most frequent level of evidence used to make recommendations was Level I or Category A (the highest level of evidence ratings for the respective guidelines). The three guidelines differed in ratings for question 2A concerning the clinical effectiveness of LABA and ICS combination therapy compared to ICS monotherapy in adults stabilized on ICS. The CTS guideline stated that LABAs are not recommended in the absence of inhaled anti-inflammatories (Level II). The GINA guideline stated that LABA (Formoterol) use as monotherapy for reliever medication is strongly discouraged since it must always be used in association with ICS (LoE not reported). The NAEPP guideline stated LABAs are not to be used as monotherapy for long-term control of asthma (Category A).

## 4 **DISCUSSION**

Overall, the guidelines vary in their quality of reporting, ranging from a score of 17% for a description of stakeholder involvement to 100% for clarity and presentation. All three guidelines scored lowest in the domain of stakeholder involvement, indicating a potential lack of engagement with future users of the guidelines. The NAEPP guideline received the highest rating for this domain (67%), due largely to the detailed information provided on the guideline development group, the soliciting of patients' views, and identification of target users. In general, investigators should be able to easily determine the process by which the guidelines were created and should find descriptions of appropriate and relevant health outcomes,

identification and synthesis of valid evidence to be included in the guidelines and how new information will impact the outcome of interest, harms and benefits, as well as estimates of cost (economic and non-economic) of implementing new guideline recommendations.<sup>194,194</sup> The guidelines investigated in this study scored very high in some domains, e.g. NAEPP received a domain score of 89% for Scope and Purpose, as they provided clear descriptions of overall objectives, clinical questions and patients. Both the GINA and CTS guidelines received their highest domain scores for Clarity and Presentation as their specific recommendations were specific, unambiguous and easily identifiable, and they provided detailed options for asthma management. As previously observed, the guidelines scored uniformly lower in the domain for Stakeholder Involvement, and would receive higher AGREE scores if that area was expanded in future updates. The wide range in domain scores may be due in part to different priorities for reporting on areas and their potential relevance to the end users of the guidelines, e.g. greater clarity on diagnosis and treatment options rather than on reporting on stakeholder involvement in the production of the guidelines.

Despite the wide range in scores across domains and the usefulness of the scores for comparing the guidelines, there is no set threshold for the domain scores to mark a "good" or "bad" guideline.<sup>193</sup> Thus, differences in domain scores cannot be assumed to indicate that one guideline is "bad" per se and the other "good".

With respect to the guideline recommendations, the three guidelines agreed that while LABAs should not be used as monotherapy for long-term control or as reliever medication, LABA is the preferred therapy to combine with ICS for patients who remain poorly controlled despite ICS monotherapy. For adult patients stabilized on ICS, the addition of LABA to low-dose ICS therapy should be considered to achieve clinical control. The evidence upon which the guidelines are based (RCTs) suggests that the use of LABAs in addition to ICSs was superior to higher-dose ICS alone,<sup>4,9</sup> and that the addition of LABAs can have a corticosteroid-sparing effect.<sup>4</sup> Both the CTS and GINA guidelines state that fixed combination inhalers, those delivering both ICS and LABA (salmeterol/fluticasone or formoterol/budesonide) in a single inhaler, are as effective as giving each drug separately. The NAEPP guidelines did not comment on the effectiveness of fixed combination inhalers vs. separate drugs.

While the Canadian guideline suggests that neither salmeterol nor formoterol combined with ICSs have shown major adverse effects, <sup>197,197</sup> a possible increased risk of asthma-related deaths associated with salmeterol use has led to advisories by the US FDA and Health Canada that LABAs are not a substitute for ICS or OCS. <sup>8,9,9</sup> According to the NAEPP guideline, the established beneficial effects of LABA and ICS combination therapy should be weighed against the uncommon risk for severe exacerbations associated with daily LABA use. Differences in recommendations between guidelines may be due to necessity of inferring recommendations from the available data. The content for guideline is debated by the guideline development groups, which could lead to differences in recommendations and the resulting differences in quality scores.

		Table	1: Det	ailed AGREE	assess	sment			
AGREE Instrument <sup>193</sup>	Conse	Canadian Asthma Consensus Guidelines <sup>4,197-</sup> <sup>200</sup> (all versions)		idian Asthma Consensus elines <sup>4</sup> (2003 version)	GINA Guidelines <sup>8</sup> 2007		NAEPP Guidelines <sup>9</sup> 2007		
	Score	Comments	Score	Comments	Score	Comments	Score	Comments	
Scope and Pur									
1. Overall Objective(s)	3	Abstract of original guidelines outline the objectives set out by the group. Updates indicate new objectives added & which old ones have been updated. (1999, S1) Comments on benefits/harms/costs (2003, 9A)	3	Guidelines for diagnosis and management of asthma (9A) No description of particular health benefits being aimed for. Not very	4	To disseminate information on patient care and incorporate new research into asthma care (ii)(vi) Pricing of asthma medication (x)	4	Recommendations for managing asthma (long term and exacerbations) around 4 essential components of asthma care with subtopics developed for each of 4 categories (p.xxii and 1-2).	
2. Clinical Question(s)	3	Partially answered – vague and pertains to ICS only. Nothing in '99 or '01 guidelines. (2003, 11A)	3	explicit. Questions for ICS alone, ICS + LABA combinations and LRTAs (11A) Does not have specific questions for add-on therapy.	2	No section describing specific clinical goals. Issues to be addressed are stated but not in question form.	3	Components of effective asthma management. (1-4) Not in question format.	

3. Patients Described	3		Objectives: Adults/children with asthma as defined. Could be more specific about age group and degree of asthma. (1999, S1)	3	7%	Related to adults with mild asthma. (10A,12A) Not very specific.	4	Ď	Adults. No age ranges. (28) Most age groups are for children (57) Patient and physician groups at national, district, local levels. Could be more specific	89%		Sections 4-5 Children 0-4 yrs; children 5-11 yrs; youths ≥12 years and adults. Categorized as intermittent or persistent asthma.
Score	0770			0	/ /0		/0/	5		0970	,	
Stakeholder In	volve	mer	nt									
4. Guideline Development Group		3	Physicians only.	3	incl affil Rele prof fron	hor list does not ude group iation. evant cessions inferred n author list.	2	cc re cc di pi gi re	Diversity of ountries epresented (50 ountries), but no iversity rofessional roups epresented. (i)			Wide range of involvement (physicians, researchers, nurses, consumers [representative from Mothers of Asthmatics], public health officials, etc. (xi)
5. Patients' Vi	ews	1	No indication patients' views canvassed.	1	pati cons Pati allo trea	statement re: ent views being sulted. ent preference wed in tment ommendation 2A)	1	pa	lo comments re: atient iews/preference			<ul> <li>p.xi – Draft posted</li> <li>online for public</li> <li>review and comments</li> <li>before guidelines</li> <li>finalized and released</li> <li>→ not clear that</li> <li>patients were the ones</li> <li>who responded. (xi)</li> <li>Some input from</li> <li>stakeholders.</li> </ul>

6. Target Users	3	General statements of users outlined; no specialties mentioned (objectives, dissemination, & implementation) (1999, S1)	2	By physicians for physicians. (13A) Not specified. Family physicians (9A)	2	Vague references to physician use, public health officials (x) Preface – dissemination paragraphs mention using guidelines to influence local doctors, national opinion leaders, educate families and health care professionals	4	Primary care clinicians, health care delivery organizations, 3 <sup>rd</sup> - party payers. (xi, 2)
7. Guideline Piloted	2	Validation by peer groups and regular updates. Comparisons to similar documents from other countries. No mention of pre-testing.	1	Though previous versions have been used, no mention of pilot program.	1	Though previous versions have been used, no mention of pilot program.	1	No statement of process, just that it was reviewed by expert panel. Posted for revision, but no pilot program described.
Domain Score	42		25	0/	17	0/0	67	0/
Rigour of Develop			25	/0	17	/0	07	/0
8. Systematic Methods	3	Systematic review of English language studies (2003, 10A) Reported search for add-on therapies only. (2003, 13A) Critical review of scientific literature (1999, S2) No information on sources or search terms.	3	Systematic review mentioned for add- on therapies. (13A) Specific search description for each section.	4	PubMed search using search fields established by committee. Two members completed questionnaires for abstracts. If information deemed appropriate for addition to report then followed by discussion and consensus (vi-xi)	4	Medline search; timeline given; MeSH terms available on NHLBI website; librarian involved with developing the search strategy with panel members. (3) English language studies only

9. Evidence Selection	1	Not reported. Partial information on kind of literature reviewed. Excluded non- English language studies.	1	Level of evidence – hierarchy (10A) Not clear what process was for inclusion/exclusion. (13A)	3	Members evaluated abstracts and/or full publications. Specific questionnaire for impact on report. No sample of questionnaire given. No explicit statement of the criteria used (vi- xi)	2	Independent review and voting system to determine inclusion. (3) Overall summaries of selection process. Too general. (4, 6) No inclusion/exclusion criteria described.
10. Formulating Recommendations	3	Small group discussion and consensus (1999, S1) Levels of evidence outlined. No specific methods described.	2	Group-based recommendations on critical review of literature and assigned level based on strength of supporting evidence. (10A) Comments and consensus. No details of consensus process.	3	Committee meetings to discuss publications indicated to have impact by at least one member. Consensus for changes to the report. (vi) No methodology. Disagreements decided on by vote. No mention of voting threshold.	3	<ul> <li>p.7-8 – Evidence ranked to justify recommendations being made. Also specified strength of recommendations. (7- 8)</li> <li>Findings discussed in small groups. Larger meetings to discuss findings, voting for consensus on final decision. No thresholds described for voting process.</li> </ul>
11. Health Benefits, Side Effects, and Risks	3	1999 (S24-27) coverage of ICS and LABA health benefits, side effects, etc. but could be more detailed for LABA. (1999, S24-27) Needs more specific recommendations.	3	Statements re: benefits of ICS and LABA (12A-13A) Statement of AEs in descriptions: low rate of AEs for all medications except at high doses. Could be more explicit	4	Health benefits and side effects of LABA use. (30)	4	Risks/AEs, and prevention and treatment are given in detail with evidence grade. (51-56) LABA-specific health benefits and risks (230-234)

12. Linking	3	Body of evidence links the recommendations to evidence in some cases; not in the summaries of recommendations. (1999, S29-30) Some recommendations are unclear as to the source of evidence. i.e. 1999 (S28) SABA 2 <sup>nd</sup> recommendation.	3	Links in general body of text but not in recommendation boxes.	3	Links in general body of text but not for final recommendations. Not all given. (viii, 60-61)	3	Recommendations have levels of evidence but not linked to supporting evidence. Some of the key points are linked to references. Within the text references are linked. (230-234)
13. External Review	2	Recommendations distributed to various committees, collaborating groups to validate recommendations. Discussed at Canadian regional meeting. (S1) No patient responses. All peer reviewers were authors (Pediatric Guideline). Not reported in updates.	1	No mention in text.	3	No list of reviewers and their affiliations. (xi) GINA Assembly invited to submit comments on draft documents and several individuals invited to serve as reviewers.	4	External review by end-users. Draft posted for comments by NAEPP Coordinating Committee and public comments. (xi)
14. Update Procedure Domain Score	43	Recommendations for future research questions (12A) Guidelines are updated, but no specifics on update process.	33	Process/timeline not clearly stated. No description.	81	Methodology A: Preparation of Yearly Updates (x) Process for producing updates: PubMed search using established search fields. Evaluations in teams of two; open to all members. Modifications to GINA through consensus by committee. (xi)	2	Periodical meetings of committee to determine if new publications are out. No procedure for future updates made available.

Clarity and Presenta	atior	1						
15. Specific Recommendations	4	General statements re: ICS treatment (1999, S24) Good specificity of recommendations. (2003, 12A)	4	Continuum of Asthma Management (11A) Clear statements; levels of evidence.	4	Brief statements outlining treatment options, strengths, definitions, etc. All components begin with keypoints then explanation with references reported and grade of evidence assessed. Grade of evidence assessed.	4	Clear description of drugs, population, safety issues, etc. (230)
16. Options for Management	4	2003 (12A) Different strategies assessed (LABA, LTR, increased dose) (2003, 12A) Good generalized comparisons. Different age groups and/or severities not specified.	4	Continuum treatment based on control. Add-on treatments discussed. Figures and discussion for each option (detailed).	4	Clear headings for different sections identifying different drugs and/or therapies.	4	Different chapters outlining different treatment options. Clear summaries of key points. Multiple points of care: e.g. clinic/office, ED/hospital-based. (96)
17. Identifiable Recommendations	4	All key recommendations in boxes & bold text separate from other text.	4	Boxed separately within the body of text. (12A) Not conveniently located. Could put all summaries up front in one location.	4	Key points separated and boxed with shading. Easy to find.	4	<ul> <li>p.230 – Expert Panel conclusions – bold text, separate page.</li> <li>(230)</li> <li>Key Points: Safety of LABA – boxed and bulleted. (231)</li> <li>Size of document with recommendations buried in text makes them hard to locate.</li> <li>Could summarize all in one location.</li> </ul>

18. Supported by Tools	2	No description of tools to support application. Summary document available.	2	No description of tools to support application. Summary document available.	4	Variety of educational materials, e.g. pocket guide for physicians, patients, and families. (90) Website access since 1995 to GINA documents, educational material, and updates re: activities and collaborating groups worldwide.	750	No description of tools to support application.
Domain Score	839	/0	839	/0	10	0%	75%	0
Applicability	2	Dance of	1	No montion i	A	Cuidaline	2	Can anal as formers
19. Organizational Barriers	2	Range of implementation suggestions, e.g. small groups and workshops, engaging key opinion leaders and facilitators for workshops. (1999, S60) General comments on the poor uptake of guidelines and suggestions for improving dissemination. (2003 11A)		No mention in text.	4	GuidelineImplementationStrategies, e.g.goal setting,strategies forasthma care,collaborationsamongprofessionalgroups. (88)Strategy forlow-incomecountries.Multipleformats todisseminate inmultiplevenues.Designed forbroadapplication.	2	General references to barriers. Examples of studies that implemented different strategies to improve dissemination of asthma education. (141)

20. Potential Cost	1	Reduced patient costs can be achieved through adherence to guideline (1999,S1) Stable funding for programs recommended from provincial and regional health authorities (2001,8A) No mention of comparative costs of management. about them.	1	No indication.	3	Discussion of cost- effectiveness evaluation for asthma care. (89) Could give samples of potential cost implications in some countries, e.g. industrialized vs. developing countries with examples	4	Studies examining the cost effectiveness of asthma education programs. (114)
21. Monitoring/Audit	3	Recommendations on asthma education & monitoring; items that could be used for auditing purposes. (2003, 18A) Continuum of asthma management (2003,11A) No link to statement of use for auditing purposes.	3	Definition of asthma control (10A) Assessing and adjusting treatment (11A) Could highlight information in more obvious fashion.	3	Monitoring by physician and communication with patient (61) System and parameters to evaluate effectiveness and quality of care is important, e.g. morbidity and mortality. (89) Specific criteria for control (58-59)	3	Measures for periodic assessment and monitoring (56-57)
Domain Score	33%		22%		78%	control (38-39)	67%	
Editorial Independe								
22.   3     Independence		1999 (S1) Sponsored by organizations with pharmaceutical company support (n=7). (1999, S1) Editorial independence (1999 summary, back page) Not available on all versions. Unrestricted grants. (2003,18A)	3	p.18A – Unrestricted grants (n=5). (18A) No statement separating results from pharmaceutical companies.	4	Unrestricted grants (n=12). (ii) Statement of editorial independence	2-3	NHLBI, NIH funding. (xiii) No statement of editorial independence.

23. Conflicts of Interest	3	Not all members have a statement regarding conflict(s) of interest. (2003, S9)	3	Not all members have a statement regarding conflict(s) of interest. (2003, S9)	3	Descriptive list online. (i, footnote) Some members do not have statement of disclosure.	4	Expert Panel members disclosed financial interests (xiii). Statements given for those without financial interests.
Domain Score	67%				83%		75%	
Further Comments	of (4 sun dou rec ref ven for • in not • on dou pool • and sup pool • wa AC • spool eff • for • • and sup pool • • sup for • • • and sup for • • • • • • • • • • • • • • • • • • •	Assessment mplicated by number documents to review main docs, 2 mmary docs) No single cument with all commendations – all er back to earlier rsions of guidelines certain topics. Another guideline 1995 is available but t used. 2003 update the ly guideline veloped after the GREE tool plemented. Search strategy cumentation very orly described. Search strategy d summary of oporting results orly described. Search strategy d summary of oporting results orly described. No mention of ectific measures of ect? Recommendations t specifically linked patient group or erences. No specific tement of expected pact or measures of ect. Key search ategy, selection & mary poorly scribed.	m qu rec (ćć m • aq pu ac bu st rec tcc gu th sc c c	Methods nould be recorded for rigorously. Unsure about uality of commendations lue to lace of nethods). Overall opears to be ractical and courate guideline at are not ructured or oported according o AGREE uidelines nerefore does not core well on all omponents of the nol.	th st co ot	So much formation, but he guideline tates that it is heant to be omplete source f information, .g. p.2	g g ree d d e e d d s g - e d d d d g f e i e i g ree t e i e g d d d g ree t i e s f e e i e s f e e g ree i e s f e e s f e s f e e s f e e s f e e s f e e s f e s f e e s f e e s f e s f e s f e s f e s f e s f e s f e s f e s f e s f e s f e s f e s f e s f e s f e s f e s f e s f e s f e s f e s f e s f e s s f e s f e s f e s s f e s s f e s s f e s f e s s f e s s s f e s s s s	No meta-analytic ratement of results – eports on single rudies' results. Best overall uideline of the 3 eviewed – greatest etail on most lements. Only rawback was lack of pecificity on evidence reference to trials. Length of ocument a definite rawback. Why not ut all ecommendations at he end or beginning?

Table 2: Levels of evidenc	e defined by the guidelines
Canadian Asthma Consensus Guidelines (all versions)	GINA Guidelines 2007
	and NAEPP Guidelines 2007
	NALI I Guidennes 2007
Level I – Evidence is based on randomized, controlled trials (or meta-analysis of such trials) of adequate size to ensure a low risk of incorporating false-positive or false- negative results.	Evidence Category A – Randomized controlled trials (RCTs). Rich body of data. Evidence is from endpoints of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. This category requires substantial numbers of studies involving substantial numbers of participants.
Level II – Evidence is based on randomized, controlled trials that are too small to provide Level I evidence. They may show either positive trends that are not statistically significant or no trends and are associated with a high risk of false-negative results.	Evidence Category B – RCTs. Limited body of data. Evidence is from endpoints of intervention studies that include only a limited number of patients, posthoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, this category pertains when few randomized trial exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
Level III – Evidence is abased on nonrandomized, controlled or cohort studies, case series, case-control studies or cross-sectional studies.	Evidence Category C – Nonrandomized trials. Observational studies. Evidence is from outcomes of uncontrolled or nonrandomized trails or from observational studies.
Level IV – Evidence is based on the opinion of respected authorities or expert committees as indicated in published consensus conferences or guidelines.	Evidence Category D – Panel consensus judgment. This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories. The
Level V – Evidence is based on the opinions of those who have written and reviewed the guidelines, based on their experience, their knowledge of the relevant literature and discussion with their peers.	Panel Consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.

	Table 3 <sup>.</sup> Guideli	ne recommendations	
	Canadian Asthma Consensus Guidelines (all versions)	GINA Guidelines 2007	NAEPP Guidelines 2007
Research Questions	(LoE) Recommendation	(LoE) Recommendation	(LoE) Recommendation
1A. Clinical effectiveness of LABA + ICS compared to ICS monotherapy in treatment naïve adults	• (NR) Fig. 1 Continuum of asthma management: Add-on therapies are to be considered only if asthma is not adequately controlled by low doses of ICSs. (11A; Can 2003 Update)	• (NR) Fig. 4.3-2 Management approach based on control: LABA are not introduced into treatment plan unless ICS therapy and other controlled options have not attained adequate asthma control. (59; GINA)	• (NR) LABAs should be added to treatment for patients whose asthma is not well controlled on a low to medium dose of ICSs. (336; NAEPP)
1B. Clinical benefit to switching to variable from fixed-dose combination therapies	NR	NR	NR
2A. Clinical effectiveness of LABA + ICS compared to ICS monotherapy in adults stabilized on ICS	<ul> <li>(I) If asthma is not adequately controlled by low doses of ICSs, the addition of a LABA should be considered. (11A/15A; Can 2003 Update)</li> <li>(NR) Fig.1 Continuum of asthma management (11A; Can 2003 Update)</li> <li>(NR) " [for] patients who remain poorly controlled despite ICS, the addition of a LABA has been found to be better than doubling the dose of ICS." (11A; Can 2003 Update)</li> <li>(NR) The addition of a LABA to low-dose ICS therapy was superior to moderate- dose ICS use alone (13A; Can 2003 Update)</li> <li>(NR) "The use of LABAs seems to allow for a reduction in the dose of ICSs, but additional studies are needed to establish the magnitude of the corticosteroid-sparing</li> </ul>	<ul> <li>(NR) Addition of LABA to daily regimen of ICSs improves symptom scores, decreases nocturnal asthma, improves lung function, decreases the use of rapid-acting inhaled β<sub>2</sub>-agonists, reduces the number of exacerbations, and achieves clinical control of asthma in more patients, more rapidly, and at a lower dose of ICSs than ICSs alone. (30)</li> <li>(Category A) Fig. 4.3-2at Step 3 the recommended option for adolescents and adults is to combine a low-dose of ICS with inhaled LABA, either in a combination inhaler device or as separate components. (60)</li> <li>(Category A) Fig. 4.3-2at Step 4 the preferred treatment is to combine a med/high dose of ICS with a LABA. However in most patients, the</li> </ul>	<ul> <li>(Category A) LABAs are not to be used as monotherapy for long-term control of asthma. (213)</li> <li>(Category A for ≥12 years of age) LABAs are used in combination with ICSs for long-term control and prevention of symptoms in moderate or severe persistent asthma. (213)</li> <li>(Category A) Of the adjunctive therapies available, LABA is the preferred therapy to combine with ICS in youths ≥12 years of age and adults. (214)</li> <li>(NR) The beneficial effects of LABA in combination therapy for the great majority of patients who require more therapy than low-dose ICS alone to control asthma (i.e., require step 3 care or higher) should be weighed against the increased risk of severe exacerbations, although</li> </ul>

	effect and its clinical relevance." (14A; Can 2003 Update) • (II) LABAs are not recommended for relief of acute symptoms or in the absence of inhaled anti-inflammatory therapy (S8; Can 2001 Summary)	<ul> <li>increase from medium to high-dose ICS provides relatively little additional benefit. (60)</li> <li>(NR) [Formoterol] has been shown to be as effective as SABA in acute asthma exacerbations. (60)</li> <li>(NR) Use [of Formoterol] as monotherapy as a reliever medication is strongly discouraged since it must always be used in association with an ICS. (60)</li> </ul>	uncommon, associated with the daily use of LABAs (214) For patients ≥5 years with moderate persistent asthma or asthma inadequately controlled on low-dose ICS, increasing ICS dose should be given equal weight to adding LABA. For patients ≥5 years with moderate persistent asthma or asthma inadequately controlled on step 3 care, the combination of ICS and LABA is preferred. • (Category D) The use of LABA for the treatment of acute symptoms or exacerbations is not currently recommended (214)
2B. Clinical benefit to switching to variable from fixed-dose combination therapies	NR	NR	NR
3. Comparative effectiveness of salmeterol/fluticasone combo vs. formoterol/budesonide combo for maintenance therapy in adults	<ul> <li>(NR) Combination devices simplify therapy. No evidence of superior effect from the combination device. Potential for improved compliance. Potential disadvantages are lack of flexibility and high doses of both compounds delivered inappropriately if device not used as instructed. (18A; Can 2001 Update)</li> <li>(NR) No comparison between the two types of combination devices.</li> </ul>	<ul> <li>(Category A) Controlled studies have shown that delivering both ICS and LABA in a combination inhaler is as effective as giving each drug separately. (31, 62)</li> <li>(Category A) Combination inhalers containing formoterol and budesonide may be used for both rescue and maintenance. (31, 60)</li> <li>(NR) No statement comparing the two types of combination therapy.</li> </ul>	<ul> <li>(NR) One study examining a combination inhaler with budesonide and formoterol showed that use of a low dose of budesonide from this combination inhaler 2x daily (maintenance therapy) plus additional use for relief of symptoms (adjustable therapy) was associated with lower rate of asthma exacerbations and a lower cumulative dose of budesonide than was twice daily treatment with a fourfold greater dose of budesonide alone. (219)</li> </ul>
4A. Differences in safety between combination ICS/LABA and ICS monotherapy in treatment naïve adults	NR	NR	NR

4B. Differences in	1 (NID)		$(\mathbf{M}) \mathbf{M}_{-1} \mathbf{M}_{-1}$
	1 (NR) "Neither salmeterol	• (NR) Fewer	• (NR) Multiple
safety between combination	nor formoterol has	systemic adverse effects,	studies have shown that
ICS/LABA and ICS		e.g. cardiovascular	individuals homozygous
	been shown to	stimulation, skeletal	for Arg/Arg at position
monotherapy in adults	have major adverse	muscle tremor, and	16 of the protein have
stabilized on ICS	effects in patients	hypokalemia, for	about a 3% reduction in
	with asthma when	therapy with inhaled	peak flow when
	used in conjunction	LABA vs. oral therapy.	compared to Gly/Gly
	with ICSs." (17A;	(31)	homozygotes. Studies of
	Can 2001 Update)	• (NR) Possible	the influence of the
		increased risk of asthma-	homozygous Arg-16
		related death associated	genetic variant on
		with salmeterol use in	response to LABA are
		small group of	inconclusive. (66)
		individuals. US FDA	• (Category A) To
		and Health Canada	reduce the potential for
		advisories that LABAs	adverse effects, consider
		are not a substitute for	adding a LABA to a low
		ICS or OCS, and should	or medium dose of ICS
		be used in combination	rather than using a
		with appropriate	higher dose of ICS to
		clinically determined	achieve or maintain
		dose of ICS. (31)	control of asthma. (220)
		• (NR) Conflicting	• (NR) The
		results regarding effects	established, beneficial
		of regular use of	effects of LABA for the
		salmeterol with/without	great majority of
		use of ICSs on	patients whose asthma is
		deterioration of asthma	not well controlled with
		in individuals with	ICS alone should be
		unusual genotype for	weighed against the
		beta-adrenergic receptor.	increased risk for severe
		(31)	exacerbations, although
			uncommon, associated
			with the daily use of
			LABAs. (231)
			• (NR) Daily use of
			LABA generally should
			not exceed 100 mcg
			salmeterol or 24 mcg
			formoterol. (231)
			• (NR) Examples of
			trials where addition of
			salmeterol or placebo to
			ICS resulted in increased
			asthma-related deaths in
			the salmeterol group.
			Thus the FDA
			determined that a Black
			Box warning was
			warranted on all
			preparations containing
			a LABA. (231)
	IARA: long acting beta agoni		

LoE: level of evidence; LABA: long-acting beta<sub>2</sub>-agonist; ICS: inhaled corticosteroid; NA: not applicable; NR: not reported

## APPENDIX 9: QUALITY CHECKLIST FOR EVALUATION OF ECONOMIC EVALUATIONS

The following 10-point checklist is based on that of Drummond et al.<sup>148</sup> Questions were phrased for a yes/no answer and for each study the number of questions with a positive response was recorded. This number should not be interpreted as a quality score as the importance of each question is not equal.

#### Q1. Was a well-defined question posed in answerable form?

For a study to be useful in assisting in decision making it is necessary that the purpose/objective of the study be explicit. Therefore, the study should contain a specific objective which relates to what was actually done and this objective should relate to determining the economic impact of the specific treatment.

#### Q2. Was a comprehensive description of the competing alternatives given?

In economic evaluations, new treatment interventions need to be compared to current practice to assess the incremental costs and effects of their introduction. To assess the cost effectiveness of LABAs it is necessary that a study assesses the incremental costs and effects of the combination of a LABA and ICS with the current care. Currently new asthmatics are generally started on ICSs and, if not controlled, their ICS dose is either increased or a LABA is added. Thus, the study should consider the comparative efficacy of initiating therapy with the combination of a LABA and ICS rather than an ICS alone or the comparative efficacy of increasing the ICS versus adding a LABA in patients who are not controlled on ICSs.

#### Q3. Was the effectiveness of the treatment established?

For an economic evaluation to be appropriate for aiding decision making the estimates of incremental costs and effects must come from a valid and reliable source. Estimates of the incremental costs and effects for asthma treatments must come from a suitable research design which minimizes potential bias. The ideal study design would be a randomized controlled trial. Large, randomized open trials may also be appropriate as it may be argued that they more closely reflect the "real world" situation than a blinded trial. Observational studies such as a before and after or case control studies would be appropriate if it can be demonstrated that the study populations for all comparators are similar.

## Q4. Were all the important and relevant costs and consequences for each alternative identified?

An economic evaluation can be conducted from a number of perspectives. Asthma exacerbations and poor asthma control can have a financial impact on both patients and their families and caregivers. Poor asthma control may also lead to an increased burden on the healthcare system due to both additional doctors' visits and hospitalizations. Given these concerns, a study should either be from a societal perspective (incorporating costs to patients,

their families and caregivers) or from a healthcare system perspective or a justification for the omission of certain costs should be provided. A suitable justification would be that such costs would be similar in both treatment groups.

## Q5. Were costs and consequences measured accurately in appropriate physical units (e.g. number of physician visits, lost work-days, life years gained)?

Within economic evaluations, it is necessary to recognize and include all major resource items. All resources must be identified, measured and a unit cost obtained. For asthma treatment this will require recognition of all costs falling on the health and social care systems as well as costs falling on patients and their caregivers.

### Q6. Were the cost and consequences valued credibly?

An economic evaluation must involve a formal comparison of costs and outcomes. Ideally quality of life would be measured in order to allow an estimation of the effect of treatment on QALYs. This would allow for a cost utility analysis. Alternative endpoints may be used; however, justification for the clinical relevance of these endpoints should be provided.

### Q7. Were costs and consequences adjusted for differential timing?

It is necessary within an economic evaluation to discount costs and effects occurring in the future to reflect societal time preference. Most asthma studies are done over a short time horizon which would normally preclude the need for discounting. However, in the case where models are used to estimate longer term costs and outcomes it is important that future costs are discounted appropriately.

#### Q8. Was an incremental analysis of costs and consequences of alternatives performed?

Economic evaluation involves the formal synthesis of costs and outcomes. Thus studies of asthma treatment require an estimate of the incremental costs of a treatment approach as well as the incremental effects on outcomes such as clinical endpoints (e.g. symptom free days, exacerbations) or quality of life. Ideally studies would be cost effectiveness or cost utility analyses. A cost minimization analysis would be acceptable but this requires an explicit statement that outcomes are either identical or better for the least costly outcome. Otherwise studies would only be partial economic evaluations.

### Q9. Was allowance made for uncertainty in the estimates of costs and consequences?

The results of an economic evaluation are highly dependent on the assumptions taken within the analysis. It is necessary to assess the robustness of the study's results to changes in assumptions through formal sensitivity analysis.

## Q10. Did the presentation and discussion of study results include all issues of concern to users?

To aid decision makers the conclusions of the analysis should be based on an overall index or ratio of costs to consequences such as a cost-effectiveness ratio. The results should also be put into perspective through a comparison with other published literature which examined the same research question and the limitations on the generalizability of the results should be discussed.

# APPENDIX 10: CHARACTERISTICS OF ECONOMIC STUDIES NOT REVIEWED IN THE MAIN REPORT

## Table 1: Studies comparing a fixed dose combination of formoterol and ICS versus variable

		of formoterol and ICS	
Study	Price (2007)	Price (2004)	Bruggenjurgen (2005)
Country	Australia, UK	UK	Germany
Patient	Patients $> 12$ years of age with	Patients >18 years of age with	Mild to moderate perennial asthma
Population	as thma for $> 6$ months on ICS for $>$	persistent asthma receiving 400-	symptomatic on ICS.
	3 months with $>$ 1month of	2000 mcg/day ICS.	
0	1000mcg/day		
Comparators	BUD/FORM 160/4.5 mcg 1	Four week run-in on either	Fixed dose BUD/FORM 160/4.5 mcg
	inhalation BID plus additional doses	BUD/FORM 80/4.5 mcg or 160/4.5	2 inhalations BID via single Turbuhaler
	as needed (variable dose) (n=1107) BUD/FORM 160/4.5 mcg 1	mcg, two inhalations BID. Then randomized to:	Adjustable maintenance dosing
	inhalation BID plus rescue	Same fixed dose of BUD/FORM	BUD/FORM 160/4.5 mcg 1
	terbutaline (fixed dose) (n=1105)	(n=771)	inhalation BID (can increase to 2 or 4
	SALM/FP 25/125 mcg 2 inhalations	Self-adjustable maintenance dosing	inhalation BID (can increase to 2 of 4
	BID plus rescue terbutaline (n=1123)	plan (n=782)	
Form of	Cost effectiveness analysis	Cost minimization analysis	Cost minimization analysis
analysis	5	,	5
Resources	Asthma medications and healthcare	Asthma medications and healthcare	Asthma medications, healthcare
included	resources and productivity losses due	resources.	resources and productivity losses due
	to days off work.		to days off work
Perspective	Healthcare system and societal	Healthcare system	Health insurance and societal
Study design	Randomised, double-blind,	Pragmatic, randomized, open label,	Randomised, open-label, parallel
Time having	multicentre, parallel group study.	parallel-group, multicentre study	group study
Time horizon	6 months Variable dose BUD/FORM resulted	12 weeks	12 weeks
Study results	in a statistically significant reduction	There was no statistically significant difference between the	There was no statistically significant difference between the two
	in severe exacerbations relative to	two treatments with respect to	treatments with respect to
	both the fixed dose BUD/FORM and	improvement in QOL as measured	improvement in QOL as measured by
	the SALM/FP groups. Direct and	by the AQLQ, although	the AQLQ, although improvement
	total costs were also lower in the	improvement was greater in the	was greater in the fixed dose group.
	variable dose BUD/FORM group	fixed dose group. The total per	Costs were lower in the adjustable
	compared with the fixed dose	patient daily cost was £1.13 (95%	dosing group with a mean cost per
	BUD/FORM group and the	CI £1.08-£1.18) in the adjusted	patient over 12 weeks of Euro 277 as
	SALM/FP groups over the 6 month	dose group and £1.31 (95%CI	compared with Euro 340 in the fixed
	period from both the Australian and	$\pounds 1.27 - \pounds 1.34$ ) in the fixed dose	dose group.
0	UK perspective.	group.	T / 1 / 1/ 11
Comments	Lost productivity was measured by	Although the adjustable dosing	Lost productivity was measured by
	human capital approach which overestimates impact to society.	group appeared more cost effective, the teaching costs associated with	human capital approach which overestimates impact to society.
	Economic analysis using outcomes	this self management approach	The choice of cost minimization
	such as severe exacerbations rather	were not included in the analysis.	analysis is inappropriate as results
	than QALYs prevents comparisons	The choice of cost minimization	suggest that the fixed dose may be
	with other therapeutic areas and does	analysis is inappropriate as results	more beneficial in terms of quality of
	not facilitate decisions.	suggest that the fixed dose may be	life.
	Although the variable dose	more beneficial in terms of quality	
	BUD/FORM arm had statistically	of life.	
	fewer exacerbations than the other		
	two groups the three treatments did		
	not differ significantly with regards		
Study Quality	to other endpoints.	7 out of 10 items	6 out of 10 itoms
Study Quality	8 out of 10 items Astra Zeneca	7 out of 10 items Astra Zeneca	6 out of 10 items Astra Zeneca
Study Sponsorship	Asua Zelleca	Asua Lelleca	Adua Zelleca
Sponsorsnip			

		salmeterol and ICS versus formote	
Study	Rutten-van Molken (1998)	Johansson (2006)	Miller (2007)
Country	Italy, Spain, France, Switzerland, Sweden and UK	Italy, France, UK and Germany	Canada
Patient	Patients $\geq 18$ years of age with	Patients $\geq$ 12 years of age with persistent	Patients $\geq$ 12 years of age
Population	persistent asthma receiving ICS	asthma receiving at least 1000 mcg/day	with moderate to severe
	≥400 mcg/day BDP or equivalent	BDP or equivalent.	asthma receiving 40 to
			3000 mcg/day ICS.
Comparators	Formoterol 12 mcg dry powder	BUD/FORM 160/4.5 mcg 2 inhalations	BUD/FORM 160/4.5 mcg 2
-	capsules (Novartis) bid (n=241)	BID + prn (n=1067)	inhalations BID + additiona
	Vs	SALM/FP 50/250 mcg 1 inhalation BID	inhalations prn (n=1067)
	Salmeterol 50 mcg Diskhaler bid	+ rescue salbutamol prn (n=1076)	SALM/FP 50/250 1
	(n=241)	-titrated up or down based on response	inhalation BID + rescue
		1 1	salbutamol prn (n=1076)
			- titrated up or down based
			on response
Form of	Cost effectiveness analysis - cost	Cost effectiveness analysis – cost per	Cost effectiveness analysis
analysis	per episode free day and clinically	severe exacerbation avoided	cost per severe exacerbation
anaryono	relevant improvement in QOL.	severe endersation avoided	avoided
Resources	Asthma medications, healthcare	Asthma medications, healthcare resources	Asthma medications,
included	resources, travel expenses and	and productivity losses.	healthcare resources and
merudeu	productivity losses.	and productivity iosses.	productivity losses.
Perspective	Societal perspective	Healthcare system and societal	Healthcare system and
reispective	Societal perspective	perspective	societal perspective
Study design	Open label, multicentre,	Randomised, open, clinical trial	Randomised, open, clinical
Study design	randomized parallel clinical trial	Kandonnised, open, ennical tital	trial – same as Johansson
Time herizon	6 months	12 months	12 months
Time horizon			
Study results	The average cost effectiveness	The mean number of severe	The mean number of severe
	ratio was US\$11 per episode free	exacerbations per patient per year was	exacerbations per patient p
	day with formoterol and US\$12	0.31 with SALM/FP and 0.24 with	year was 0.31 with
	per episode free day with	BUD/FORM. BUD/FORM was	SALM/FP and 0.24 with
	salmeterol. With respect to the	dominant in all countries from the	BUD/FORM. BUD/FORM
	cost per clinically relevant	societal perspective and in the UK and	was dominant from both a
	improvement in QOL it was	Germany from the healthcare system	societal and healthcare
	US\$1600 with formoterol and	perspective. The ICER was €100 in Italy	perspective.
	US\$1825 with salmeterol.	and €267 in France from the healthcare	
		perspective.	
Comments	Country specific unit costs were	Lost productivity was measured by	Lost productivity was
	applied to resource use but results	human capital approach which	measured by human capital
	are a synthesis presented in US	overestimates impact to society.	approach which
	dollars, therefore making it	Economic analysis using outcomes such	overestimates impact to
	difficult to make overall	as severe exacerbations rather than	society.
	conclusions.	QALYs prevents comparisons with other	Economic analysis using
	Formoterol inhaler used in this	therapeutic areas and does not facilitate	outcomes such as severe
	study was a dry powder capsule	decisions.	exacerbations rather than
	which is not comparable to the	The definition of severe exacerbations is	QALYs prevents
	most commonly used delivery	a composite outcome including	comparisons with other
	device.	unscheduled visits required for dose	therapeutic areas and does
	Results reported average cost	changes. As all dose changes with	not facilitate decisions.
	effectiveness ratios which are	salmeterol require physician visits, this	
	meaningless for decision making.	may be biased.	
	Analysis suggests that formoterol		
	is dominant over salmeterol.		
	Economic analysis using outcomes		
	such as episode free days rather		
	than QALYs prevents comparisons		
	with other therapeutic areas and		
	does not facilitate decisions		
Study Ouality	does not facilitate decisions. 6 out of 10 items	8 out of 10 items	9 out of 10 items
Study Quality Study	does not facilitate decisions. 6 out of 10 items Novartis	8 out of 10 items Astra Zeneca	9 out of 10 items Astra Zeneca

Table 2: He	ad-to-head comparisons of salmeterol ar continuec(	nd ICS versus formoterol and ICS in asthma
Study	Miller (2008)	Ringdal (2002)
Country	Canada	Norway
Patient Population	Patients $\geq$ 12 years of age with asthma receiving $\geq$ 500 mcg/day ICS.	Moderate to severe asthmatics, 16 to 75 years old symptomatic on 1000 to 1600 mcg/day of BDP or equivalent
Comparators	BUD/FORM 160/4.5 mcg 1 inhalation BID plus additional inhalations PRN (n=1107) (variable dose) BUD/FORM 320/9 mcg 1 inhalation BID plus terbutaline prn (1105) (fixed dose) SALM/FP 25/125 mcg 2 inhalations BID plus terbutaline prn (1123)	SALM/FP 50/250 mcg BID via Diskus (n=212) FORM 12 mcg BID + BUD 800 mcg BID via Turbuhalers (n=216)
Form of analysis	Cost effectiveness analysis – cost per severe exacerbation avoided	Cost effectiveness analysis – various outcomes
Resources included	Asthma medications, healthcare resources and productivity losses.	Asthma medications and healthcare resources.
Perspective	Healthcare system and societal perspective	Healthcare system
Study design	Randomised, controlled clinical trial	Randomised controlled trial
Time horizon	6 months	12 weeks
Study results	The mean number of severe exacerbations per patient per 6 months was 0.12 with variable dose BUD/FORM, 0.16 with fixed dose BUD/FORM and 0.19 with SALM/FP. Fixed dose BUD/FORM was dominant from both a societal and healthcare perspective.	SALM/FP led to significantly fewer exacerbations and night time symptoms but there were no significant differences in the primary efficacy measure and other secondary measures. The mean cost per patient per day was US \$2.00 with SALM/FP versus US\$3.02 US for FORM/BUD.
Comments	Canada did not participate in the clinical trial from which the efficacy and healthcare resource utilization data were drawn. Economic analysis using outcomes such as severe exacerbations rather than QALYs prevents comparisons with other therapeutic areas and does not facilitate decisions. Treatments did not differ significantly on any other efficacy measure (e.g. lung function or symptoms) apart from severe exacerbations. Lost productivity was measured by human capital approach which overestimates impact to society.	Analysis focused solely on those secondary outcomes measures where differences were detected. Analysis based on outcomes such as exacerbations and night time symptoms rather than QALYs prevents comparisons with other therapeutic areas and does not facilitate decisions. In this study BUD and FORM were delivered via separate inhalers which would lead to a larger cost difference than if they were given combination.
Study Quality	9 out of 10 items	6 out of 10 items
Study Sponsorship	Astra Zeneca	Glaxo Smith Kline

## APPENDIX 11: REVIEW OF ECONOMIC STUDIES NOT REVIEWED IN THE MAIN REPORT

#### Review of studies comparing a fixed versus variable dose of formoterol with ICS

There were three studies which compared a fixed dose of formoterol with ICS with a variable dose of formoterol with ICS<sup>158,159,165</sup> which are reviewed in detail in Appendix 5.1. In two of the studies<sup>158,159</sup> patients were randomized to either a fixed dose of formoterol with ICS or a self-adjustable maintenance dosing arm in which patients could increase or decrease the dose of formoterol and ICS based on their asthma symptoms. These two studies were conducted for the UK and for Germany. In the third study from both a UK and Australian perspective patients were randomized to either a variable dose of formoterol and ICS or a fixed dose of formoterol and ICS.

Two of the studies<sup>158,159</sup> were cost minimization analyses with effectiveness data derived from pragmatic, randomized, 12 week open trials. The third study was a cost effectiveness analysis which compared the cost per severe exacerbation avoided with effectiveness data derived from a randomized, double-blind 6 month multicentre trial. A healthcare system perspective was taken for all analyses. Two studies also adopted a secondary societal perspective<sup>159</sup>.

All studies concluded that variable dosing of formoterol and ICS was more cost effective than fixed dosing. In the two cost minimization analyses there was no statistically significant difference between the two treatments with respect to quality of life as measured by the Asthma Quality of Life Questionnaire and the costs within the fixed dosing arm were higher than in the variable dosing arm. In the cost-effectiveness analysis the variable dose arm experienced fewer severe exacerbations at a lower cost than either the fixed dosing arm or the SALM/FP arm thereby making it the dominant treatment.

For the two cost minimization analyses consideration should be given to the fact that although there was no statistical difference between the two treatment arms the improvement in QOL was greater in the fixed dose group. It would therefore have been more appropriate to conduct a cost effectiveness/utility analysis rather than a cost minimization analysis.

## Review of studies of a head to head comparison of salmeterol versus formoterol in addition to ICS

There were five studies that compared salmeterol versus formoterol in combination with ICS<sup>130,160-163</sup> which are reviewed in detail in Appendix 5.1. One study examined the cost effectiveness of formoterol via a dry powder capsule which is no longer marketed within Canada<sup>160</sup>. For the remaining four studies, three compared a variable or adjustable dosing schedule for formoterol and budesonide with a fixed dosing schedule of salmeterol and fluticasone<sup>161-163</sup>. The fourth study compared a fixed dosing schedule for both combinations<sup>130</sup>. Two studies derived efficacy data from randomized open trials<sup>161,162</sup> and two studies derived data from randomized controlled trials<sup>130,163</sup>. The studies ranged in duration from 12 weeks<sup>130</sup> to 6 months<sup>162</sup> to 12 months<sup>161,163</sup>. Studies were conducted from the perspective of Canada<sup>162,163</sup>, Norway<sup>130</sup>, and from multiple European countries<sup>160,161</sup>. All analyses were cost effectiveness analyses and all were from the healthcare system perspective with all but one<sup>130</sup> also including analysis from the societal perspective.

Two studies used efficacy data from the same clinical trial<sup>161,162</sup> and both studies found that in most countries from both the healthcare system and societal perspectives the combination of BUD/FORM was more cost effective than SALM/FP. One study found that fixed dose BUD/FORM was dominant over both variable dose BUD/FORM and fixed dose SALM/FP from both a societal and healthcare system perspective (3869). Conversely, one study found that SALM/FP was dominant over fixed dosing BUD/FORM <sup>130</sup>. In all studies the analysis focused on a single endpoint which favoured one of the two treatments whereas many of the additional endpoints within the trials were not different between the two treatments. Also, similar to many of the other studies in this area, the reporting of results as cost per exacerbation avoided rather than per QALY makes the comparison with other treatment areas difficult.

## APPENDIX 12: CHARACTERISTICS OF ECONOMIC STUDIES REVIEWED IN MAIN REPORT

Table 1	Table 1: Characteristics of the included studies in mild to moderate asthmatics		
3 STUDY	4 COMPARATORS	5 TIME HORIZON	6 PERSPECTIVE
Jonsson 2004 (Sweden)	BUD 100 mcg BID (n=322) BUD 200 mcg BID (n=312) BUD 100 mcg BID + FORM 4.5 mcg BID (n=323) BUD 200 mcg BID + FORM 4.5 mcg BID (n=315)	1 year	Healthcare system and societal
Andersson 2001 (Sweden, UK, Spain)	BUD 100 mcg BID BUD 100 mcg BID + FORM 12 mcg BID BUD 400 mcg BID BUD 400 mcg BID + FORM 12 mcg BID	l year	Healthcare system and societal
Briggs 2006 (UK)	Stratum 1: FP/SALM 50 /100 mcg BID or FP 100 mcg BID Stratum 2: FP/SALM 50/250 mcg BID or FP 250 mcg BID Stratum 3: FP/SALM 50/500 mcg BID or FP 500 mcg BID	1 year	Healthcare system
Johansson 1999 (Sweden)	SALM/FP 50/100 mcg BID (n=87) FP 100 mcg BID (n=85)	12 weeks	Healthcare system
Price 2002 (UK)	SALM/FP 50/100 mcg BID FP 100 mcg BID	12 weeks	Healthcare system
Shih 2007 (US)	SALM/FP 50/100 mcg BID FP other ICS leukotriene modifiers	l year	Healthcare system

Table 2: 0	Comparison of addition of LAB	A to ICS versus ICS in patier asthma	nts with mild to moderate
Study	Jonsson (2004)	Andersson (2001)	Briggs (2006)
Country	Sweden	Sweden, UK, Spain	UK
Patient Population	Patients 12 years of age or older with mild to moderate asthma receiving up to 400 mcg/day BUD or equivalent who were not optimally controlled when switched to 200 mcg/day BUD.	Patients 18 to 75 years of age with moderate persistent asthma receiving less than 1600 mcg BCL or equivalent.	Patients with mild, moderate and severe asthma whose ICS dose was stepped up during an 8 week run-in to achieve control and then stratified based on ICS dose and randomized. Age not reported.
Comparators	BUD 100 mcg BID (n=322) BUD 200 mcg BID (n=312) BUD 100 mcg BID + FORM 4.5 mcg BID (n=323) BUD 200 mcg BID + FORM 4.5 mcg BID (n=315)	BUD 100 mcg BID BUD 100 mcg BID + FORM 12 mcg BID BUD 400 mcg BID BUD 400 mcg BID + FORM 12 mcg BID	Stratum 1: no ICS at baseline randomized to FP/SALM 50/100 or FP 100 Stratum 2: $\leq$ 500 mcg BDP at baseline randomized to FP/SALM 50/250 or FP 250 Stratum 3: 500-1000 BDP at baseline randomized to FP/SALM 50/500 or FP 500
Form of	Cost effectiveness analysis – cost	Cost effectiveness analysis - cost	Cost utility analysis
analysis Resources included	per symptom free day Asthma medications and healthcare resources and productivity losses due to days off work	per symptom free day Asthma medications and healthcare resources. Sensitivity analysis included costs of work absences.	Asthma medications and healthcare resources.
Perspective	Healthcare system and societal perspectives	Healthcare system and societal perspective	Healthcare system
Study design	Randomised controlled trial	Randomised controlled trial	Randomised controlled trial
Time horizon Study results	1 year BUD 400 mcg/day and BUD 400 mcg/day + FORM dominated BUD 200 mcg/day + FORM. BUD 400 mcg/day + FORM provided more SFDs than BUD 400 mcg/day, but was also more expensive. The ICER for the combination was 2.32 Euro per SFD.	1 year When comparing BUD 200mcg/day with BUD 200mcg/day + FORM, the combination was dominant in both Sweden and Spain and resulted in an incremental cost per SFD of Euro 4.67 in the UK. When comparing BUD 800 mcg/day with BUD 800 mcg/day + FORM, the combination was dominant in Sweden and resulted in an incremental cost per SFD of Euro 6.60 in the UK and Euro 2.51 in Spain.	1 year The cost per QALY for SALM/FP versus FP was £13700 for stratum 1 (£11000 – £18300, 95% CI), £11000 for stratum 2 (£8600 – £14600, 95% CI), and £7600 for stratum 3 (£4800 – £10700, 95% CI).
Comments	Methods for valuing lost productivity not provided. The ICER for BUD 200 mcg bid + FORM compared to BUD 100 mcg BID (7.29) is not reported and is higher than for comparisons reported in the study, implying that BUD 100 mcg BID could be the most cost effective option. The reporting of the ICER using SFDs rather than QALYs prevents comparisons with other therapeutic areas and does not facilitate decisions.	Numbers in each arm were not reported. Resource usage was collected through a survey or interview of physicians. The reporting of the ICER using SFDs rather than QALYs prevents comparisons with other therapeutic areas and does not facilitate decisions.	Utility scores were based on a mapping of AQLQ scores. The mapping algorithm is unpublished and not provided. Data is based on regression modeling rather than the raw data from the clinical trials due to differences in baseline characteristics.
Study Quality	8 out of 10 items	9 out of 10 items	9 out of 10 items
Sponsorship	Astra Zeneca	Astra Zeneca	Glaxo Smith Kline

Table 2: Comparison of addition of LABA to ICS versus ICS in patients with mild to moderate asthma (continued)			
Study	Johansson (1999)	Price (2002)	Shih (2007)
Country	Sweden	UK	US
Patient Population	Adult and adolescent asthmatics (12 and older) receiving 252 to 420 mcg/day BDP or equivalent or salmeterol 42 mcg/day	Adult and adolescent asthmatics (12 to 70 years) receiving BDP 252 to 420 mcg/day or equivalent or salmeterol 42 mcg/day	Adult and adolescent asthmatics (12 and older) with mild to moderate asthma
Comparators	SALM/FP 50/100 mcg BID via Diskus (n=87) FP 100 mcg BID via Diskus (n=85)	SALM/FP 50/100 mcg BID via Diskus FP 100 mcg BID via Diskus	SALM/FP 50/100 mcg BID vs FP vs other ICSs vs leukotriene modifiers (LTM)
Form of analysis	Cost effectiveness analysis – cost per successfully treated week and per symptom free day	Cost effectiveness analysis – cost per successfully controlled week	Cost effectiveness analysis – cost per symptom free day and rescue medication free days based on a decision analysis model
Resources included	Asthma medications and healthcare resources.	Asthma medications and healthcare resources.	Asthma medication and healthcare resources, excluding costs of adverse events
Perspective	Healthcare system	Healthcare system	Healthcare system
Study design	Randomised controlled trial	Randomised controlled trial	Randomised controlled trials
Time horizon	12 weeks	12 weeks	1 year
Study results	The combination was both more costly and more effective. The ICER was US\$16.18 per successfully treated week and US\$5.40 per symptom free day.	The combination was both more costly and more effective. The ICER was £20.83 per successfully controlled week.	The combination was more effective and more costly than all competitors. The ICER was US\$9.55 per symptom free day vs FP and US\$8.93 per rescue free day vs FP. FP dominated other ICS.
Comments	Healthcare resource use was assessed retrospectively. ER visits and primary care visits were extrapolated from medication usage. The sensitivity of the results to the efficacy endpoints was assessed, but not to costs. The reporting of the ICER using SFDs and successfully treated weeks rather than QALYs prevents comparisons with other therapeutic areas and does not facilitate decisions.	Numbers in each arm were not reported. Analysis was conducted through a Markov Model with health states relating to control, exacerbations and treatment failure. The reporting of the ICER using successfully controlled weeks rather than QALYs prevents comparisons with other therapeutic areas and does not facilitate decisions. The incremental cost per QALY was estimated, but was based on retrospective modeling without direct utility measurements. The estimated incremental cost for QALY was £1357.	The reporting of the ICER using SFDs and rescue medication free days rather than QALYs prevents comparisons with other therapeutic areas and does not facilitate decisions. The utility decrement associated with days of asthma symptoms was used to suggest benchmark acceptable amounts to pay per SFD and rescue medication free days however this was based on retrospective modeling. Dose ranges for medications other than SALM/FP were not provided.
Study Quality	8 out of 10 items	8 out of 10 items	8 out of 10 items
Study Sponsorship	GSK	GSK	GSK

Table 3:	Characteristics of the included studies	in moderate to severe	e asthmatics
7 STUDY	8 COMPARATORS	9 TIME HORIZON	10PERSPECTIVE
Lundbäck 2000 (Sweden)	SALM/FP 50/250 BID via Diskus or Accuhaler (n=180) BUD 800 mcg BID via Turbuhaler (n=173)	24 weeks	Healthcare system
Palmqvist 1999 (Sweden)	SALM/FP 50/250 mcg BID via Diskus (n=81) FP 250 mcg BID via Diskus (n=81)	12 weeks	Healthcare system
Pieters 1999 (Sweden)	SALM/FP 50/500 mcg BID via Diskus (n=167) FP 500 mcg BID via Diskus (n=165)	12 weeks	Healthcare system
Ericsson 2006 (Germany, The Netherlands)	BUD/FORM 160/4.5 mcg BID via Turbuhaler (n=168) FP 250 mcg BID via Diskus (n=176)	12 weeks	Healthcare system and societal

Table 4: Comparison of addition of LABA to ICS versus ICS in patients with moderate to severe			
		asthma	
Study	Lundback (2000)	Pieters (1999)	Palmqvist (1999)
Country	Sweden	Sweden	Sweden
Patient	Moderate to severe	Adult and adolescent asthmatics	Adult and adolescent asthmatics
Population	asthmatics, >12 years of age symptomatic on 800-1200	receiving 2000 mcg/day BDP or equivalent	receiving 462 to 672 mcg/day BDP or equivalent
	mcg/day BDP or 400-800	equivalent	or equivalent
	mcg/day FP.		
Comparators	SALM/FP 50/250 BID via	SALM/FP 50/500 mcg BID via	SALM/FP 50/250 mcg BID via
P	Diskus or Accuhaler (n=180)	Diskus (n=167)	Diskus (n=81)
	BUD 800 mcg BID via	FP 500 mcg BID via Diskus (n=165)	FP 250 mcg BID via Diskus (n=81)
	Turbuhaler (n=173)		
Form of	Cost effectiveness analysis -	Cost effectiveness analysis - cost per	Cost effectiveness analysis – cost per
analysis	cost per successfully treated	successfully treated week, episode	successfully treated week, episode
	week, episode free day and	free day and symptom free day	free day and symptom free day
	symptom free day		
Resources	Asthma medications and	Asthma medication and healthcare	Asthma medications and healthcare
included	healthcare resources.	resources	resources
Perspective	Healthcare system	Healthcare system	Healthcare system
Study design	Randomised controlled trial	Randomised controlled trial	Randomised controlled trial
Time horizon	24 weeks	12 weeks	12 weeks
Study results	SALM/FP was significantly more effective and more	SALM/FP was significantly more effective and more costly. The ICER	SALM/FP was significantly more effective and more costly. The ICER
	costly.	for successfully treated week was	for SALM/FP vs FP was US\$1.52
	The ICER was US\$3.9 for an	US\$23.31 for the combination vs FP	per successfully treated week,
	additional successfully	and US\$8.10 per symptom-free day	US\$0.47 per episode-free day and
	treated week, US\$0.93 for an	and US\$14.56 per episode-free day.	US\$0.47 per symptom-free day.
	additional episode free day	and obstition per episode nee day.	obto. If per symptom nee duy.
	and US\$1.12/day for an		
	additional symptom free day.		
Comments	The reporting of the ICER	Healthcare resource use was assessed	Healthcare resource use was assessed
	using outcomes such as SFDs	retrospectively. ER visits and	retrospectively. ER visits and
	rather than QALYs prevents	primary care visits were extrapolated	primary care visits were extrapolated
	comparisons with other	from medication usage. The	from medication usage. The
	therapeutic areas and does	sensitivity of the results to the	sensitivity of the results to the
	not facilitate decisions.	efficacy endpoints was assessed, but	efficacy endpoints was assessed, but
		not to costs.	not to costs.
		The reporting of the ICER using	The reporting of the ICER using
		outcomes such as SFDs rather than	outcomes such as SFDs rather than
		QALYs prevents comparisons with other therapeutic areas and does not	QALYs prevents comparisons with other therapeutic areas and does not
		facilitate decisions.	facilitate decisions.
Study Quality	9 out of 10 items	8 out of 10 items	8 out of 10 items
Study	Glaxo Smith Kline	Glaxo Smith Kline	Glaxo Smith Kline
Sponsorship			

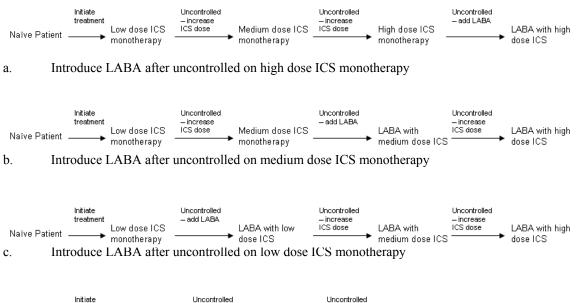
Table 4: Co	mparison of addition of LABA to ICS versus ICS in patients with moderate to severe asthma (continued)
Study	Ericsson (2006)
Country	Germany and the Netherlands
Patient Population	Adults (18 years of age or older) with moderate asthma receiving 200 to 1000 mcg/day ICS
Comparators	BUD/FORM 160/4.5 mcg BID via Turbuhaler (n=168) FP 250 mcg BID via Diskus (n=176)
Form of analysis	Cost effectiveness analysis – cost per episode free day
Resources included	Asthma medication and healthcare resources. Productivity costs were included in the societal perspective.
Perspective	Healthcare system and secondarily societal
Study design	Randomised controlled trial
Time horizon	12 weeks
Study results	The mean number of episode free days was significantly higher in the BUD/FORM group as compared with the FP group. From both the healthcare and societal perspectives costs were lower in the combination group for both Germany and Netherlands.
Comments	The reporting of the ICER using outcomes such as episode free days rather than QALYs prevents comparisons with other therapeutic areas and does not facilitate decisions.
Study Quality	9 out of 10 items
Study Sponsorship	Astra Zeneca

### APPENDIX 13: METHODOLOGICAL QUALITY OF ECONOMIC STUDIES REVIEWED IN MAIN REPORT

				Tab	le 1: (	Qualit	y Ass	sessn	nent c	of Eco	nomi	c Eva	luatio	ons				
	L Jonsson 2004	Andersson 2001	Briggs 2006	≺ Johansson 1999	Z Price 2002		A Lundbäck 2000	≺ Pieters 1999	≺ Palmqvist 1999	LEricsson 2006	A Price 2007	<b>A</b> Price 2004	A Bruggenjurgen 2005	≺ Rutten-van Molken 1998	A Johansson 2006	A Miller 2007	A Miller 2008	Z Ringdal 2002
Q1	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Q2	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q4	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y
Q5	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q6	N	N	N	N	N	N	N	N	N	N	N	Y	Y	N	N	N	N	N
Q7	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q8	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	N
Q9	N	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	N
Q10	Y	Y	Y	Y	N	Y	Y	N	N	Y	Y	Y	N	N	N	Y	Y	N
Total	8	9	9	8	8	8	9	8	8	9	8	7	6	6	8	9	9	6

## **APPENDIX 14: VALUES FOR ECONOMIC ANALYSIS**

#### Figure 1: Treatment strategies



Initiate	Uncontrolled	Uncontrolled
treatment	- increase	-increase
Naïve Patient LABA with low dose ICS	ICS dose LABA with medium dose	ICS dose LABA with high

d. Introduce LABA to ICS naïve patients

Table 1: Definition of low, moderate, and high dose ICS						
ICS Therapy	Low	Medium	High			
BUD Turbuhaler	$\leq$ 400 mcg/day	400-800 mcg/day	> 800 mcg/day			
FP MDI	$\leq$ 250 mcg/day	251-500 mcg/day	> 500 mcg/day			
FP Diskus	$\leq$ 250 mcg/day	251-500 mcg/day	> 500 mcg/day			
BDP	$\leq$ 500 mcg/day	501-1000 mcg/day	> 1000 mcg/day			

Source: Lemiere et al. 2004<sup>4</sup>

Table 2: Parameter values for baseline clinical						
	Base value	SE	Distribution			
Weekly Probability of Step Up						
Naïve Patients (low dose ICS)	0.005	0.000001	Beta			
On medium dose ICS	0.006	0.000001	Beta			
On high dose ICS	0.006	0.000006	Beta			
Uncontrolled on high dose ICS	0.008	0.000008	Beta			
Weekly Rate of Exacerbation						
Naïve Patients (low dose ICS)	0.003	0.000001	Beta			
On medium dose ICS	0.011	0.000004	Beta			
On high dose ICS	0.014	0.000031	Beta			
Uncontrolled on high dose ICS	0.014	0.000045	Beta			
Weekly Probability of Step down	0.002	0.001	Beta			
Percentage of exacerbations self managed	0.000	-	Fixed			
Percentage of medically managed exacerbations managed by GP	0.937	0.0005	Beta			
Percentage of hospital managed exacerbations discharged without admission	0.928	0.0006	Beta			

Table 3: Paramete	r values for rela	ative risk	
	Base Value	SE	Distribution
Weekly Probability of Step Up			
Naïve Patients			
Low dose ICS vs LABA+low dose ICS	1.027	0.386	Lognormal
Uncontrolled on low dose ICS			
Medium dose ICS vs LABA+low dose ICS	0.936	0.310	Lognormal
Uncontrolled on medium dose ICS			
High dose ICS vs LABA+medium dose ICS	0.872	0.623	Lognormal
Uncontrolled on high dose ICS			
High dose ICS vs LABA+high dose ICS	0.841	0.445	Lognormal
Washly Data of Franceschation			
Weekly Rate of Exacerbation			
Naïve Patients	0.900	0.577	I a an a mu al
Low dose ICS vs LABA+low dose ICS	0.800	0.577	Lognormal
Uncontrolled on low dose ICS	0.925	0.245	T 1
Medium dose ICS vs LABA+low dose ICS	0.825	0.245	Lognormal
Uncontrolled on medium dose ICS	0.705	0.949	Loomonuol
High dose ICS vs LABA+medium dose ICS	0.705	0.848	Lognormal
Uncontrolled on high dose ICS	0.05(	0.947	T 1
High dose ICS vs LABA+high dose ICS	0.956	0.847	Lognormal

Table 4: Parameter values for costs and utilities						
	Base Value	SE	Distribution			
Weekly Cost of Drug Therapy						
ICS low	5.80	-	Fixed			
ICS medium	10.63	-	Fixed			
ICS high	19.75	-	Fixed			
LABA/ICS low	14.78	-	Fixed			
LABA/ICS medium	23.28	-	Fixed			
LABA/ICS high	38.88	-	Fixed			
Cost of Exacerbation						
GP managed	56.10	-	Fixed			
ER visit	261.21	-	Fixed			
Inpatient admission	3541.00	248.39	Gamma			
Utility Values						
No exacerbation	0.78	0.009	Lognormal <sup>#</sup>			
Non medical	0.57	0.078	Lognormal <sup>#</sup>			
GP	0.57	0.078	Lognormal #			
ER	0.57	0.078	Lognormal #			
Inpatient	0.33	0.014	Lognormal #			

<sup>#</sup>Distribution represents uncertainty around the disutility associated with health states

		Table	5: Calculatio	n of weekly drug costs			
	Weekly	Prescription	Daily dose	Doses per prescription	Duration	inc 8% mark up plus \$7	Weight
Low dose LABA/ICS	14.78						
symbicort 100/6 1 puff bid	8.38	60.00	2	120	60	71.80	0.25
symbicort 100/6 2 puff bid	16.75	60.00	4	120	30	71.80	0.25
advair diskus 50/100 1 puff bid	21.37	78.34	2	60	30	91.61	0.25
advair mdi 25/125 1 puff bid	12.63	93.78	2	120	60	108.28	0.25
Medium dose LABA/ICS	23.28						
symbicort 200/6 2 puff bid	21.29	78.00	4	120	30	91.24	0.5
advair diskus 50/250 1 puff bid	25.27	93.78	2	60	30	108.28	0.25
advair mdi 25/125 2 puff bid	25.27	93.78	4	120	30	108.28	0.25
High dose LABA/ICS	38.88						
symbicort 200/6 4 puff bid	42.58	78.00	8	120	15	91.24	0.5
advair diskus 50/500 1 puff bid	35.18	133.12	2	60	30	150.77	0.25
advair mdi 25/250 2 puff bid	35.18	133.12	4	120	30	150.77	0.25
Low dose ICS	5.80						
Pulmicort 100 1 puff bid	2.79	30.40	2	200	100	39.83	0.25
Pulmicort 200 1 puff bid	5.09	60.85	2	200	100	72.72	0.25
Flovent MDI 50mcg 2 puff bid	7.66	23.93	4	120	30	32.84	0.5
Medium dose ICS	10.63						
Pulmicort 200 2 puff bid	10.18	60.85	4	200	50	72.72	0.25
Pulmicort 400 1 puff bid	8.77	109.50	2	200	100	125.26	0.25
Flovent MDI 125mcg 2 puff bid	11.80	40.32	4	120	30	50.55	0.25
Flovent diskus 250 mcg 1 puff bid	11.80	40.32	2	60	30	50.55	0.25
High dose ICS	19.75						
Pulmicort 400 2 puff bid	17.54	109.50	4	200	50	125.26	0.5
Flovent MDI 250mcg 2 puff bid	21.95	80.64	4	120	30	94.09	0.25
Flovent diskus 500 mcg 1 puff bid	21.95	80.64	2	60	30	94.09	0.25

## **APPENDIX 15: DETAILED RESULTS OF ECONOMIC ANALYSIS**

Table 1: Sensitivity analysis						
	Incremental Cost per QALY gained (12 weeks)					
	Strategy B vs	Strategy C vs	Strategy D vs			
Scenario	Strategy A	Strategy B	Strategy C			
Base Case	\$193,794	\$1,627,740	\$3,297,180			
No ICS step down	\$190,567	\$1,580,721	\$3,297,180			
Half the cost of exacerbations	\$204,128	\$1,638,074	\$3,307,515			
Double the cost of exacerbations	\$173,124	\$1,607,069	\$3,276,510			
25% of exacerbations self-managed	\$199,218	\$1,635,017	\$3,306,616			
50% of exacerbations self-managed	\$204,657	\$1,642,315	\$3,316,077			
75% of exacerbations self-managed	\$210,109	\$1,649,631	\$3,325,563			
Alternative utility values (Briggs et al)	\$239,227	\$2,009,355	\$4,070,188			
Alternative utility values (Price and	\$213,467	\$1,792,988	\$3,631,911			
Briggs)						
Lowest relative risk for withdrawals with	\$188,500	\$1,610,466	\$2,841,837			
LABA						
Highest relative risk for withdrawals	\$208,834	\$1,704,341	\$7,892,327			
with LABA						
Lowest relative risk for exacerbations	\$159,095	\$811,005	\$981,913			
with LABA						
Highest relative risk for exacerbations	Strategy A	Strategy B dominant	Strategy C dominant			
with LABA	dominant					

Table 2: Results of probabilistic analysis: cost-utility analysis						
Time horizon	Costs	QALYs	Incremental Cost per QALY gained			
12 week						
Strategy A	74.91	0.179819				
	(72.67, 78.18)	(0.176, 0.184)				
Strategy B	74.93	0.179819	\$577,812.43 <sup>1</sup>			
	(72.69, 78.20)	(0.176, 0.184)				
Strategy C	78.86	0.179821	\$1,929,583.70 <sup>2</sup>			
	(75.48, 83.11)	(0.176, 0.184)				
Strategy D	183.93	0.179829	\$12,570,692.83 <sup>3</sup>			
	(180.30,190.78)	(0.176, 0.184)				
One year						
Strategy A	353.54	0.778954				
	(335.84,375.39)	(0.762,0.795)				
Strategy B	355.11	0.778956	$637,687.25^{1}$			
	(336.87,377.64)	(0.762,0.795)				
Strategy C	426.67	0.778988	$2,236,925.59^2$			
	(381.67,481.71)	(0.762,0.795)				
Strategy D	\$849.59	0.7789541	Dominated by			
	(806.02,918.33)	(0.762,0.795)	Strategy C			

Figures in parenthesis are 95% certainty intervals <sup>1</sup> versus Strategy A, <sup>2</sup> versus Strategy B, <sup>3</sup> versus Strategy

## APPENDIX 16: METHODS FOR BUDGET IMPACT ANALYSIS

#### Objective

The objective for the budget impact analysis was to forecast expenditure for LABAs and ICS for use in asthma for the years 2008/2009, 2009/10 and 2010/11 under different assumptions concerning changes in prescribing patterns. British Columbia data was used as a sample case as it included the required information relating to dose needed for the methodology outlined below.

Under the base case scenario we assumed that prescribing patterns will follow the trends of the previous years incorporating the observed proportional changes in prescribing for each class. Given the findings of the economic analysis, alternate scenarios relate to proportional declines in the volume of prescriptions for LABAs at low and medium doses within combination inhalers and in single entity inhalers and a subsequent increase in the prescribed dose of ICS monotherapy.

#### Methods

Forecasts for the expenditure under the base case were obtained using the following stepped approach.

- 1. The province gave estimates for the total costs and total volume for LABA inhalers, ICS inhalers and LABA and ICS combination inhalers for the past 5 years
- 2. Therapies used for the treatment of asthma are not exclusively used for the treatment of this disease. Therefore, the proportions of prescriptions for each medication in years 2003 through 2008 which were for asthma were estimated based on Ontario data provided by IMS
- 3. The proportions for type of medication were applied to the data from Step 1 to estimate the volume and cost of prescriptions for asthma by medication for each of the past five years.
- 4. The rate of increase in the number of claims for each medication was obtained by analyzing data from the most recent and least recent years provided by the province. This rate of increase was used to estimate volume by class for 2008/2009, 2009/10 and 2010/11.
- 5. The forecasted claims for the year are weighted by the average cost per claim by medication in the most recent year to provide the forecasted cost by class for 2008/2009, 2009/10 and 2010/11.

The base case forecast is compared to three alternative scenarios which include:

a) switching patients on a low dose combination LABA/ICS inhaler to an increased dose of ICS monotherapy

- b) switching patients on either a low dose or a medium dose combination LABA/ICA inhaler to an increased dose of ICS monotherapy
- c) switching patients on either a low dose or a medium dose combination LABA/ICS inhaler to an increased dose of ICS monotherapy and adding a low dose of ICS to those receiving LABA therapy in a single inhaler and removing their LABA.

The methodology adopted to determine the budget impact of the above changes is to assume different proportional reductions in total prescriptions for each low and medium dose combination therapy and for single inhaler LABA therapy - 25%, 50%, 75% and 100%.

For Scenario A these alternate estimates were obtained as follows.

- 1. The volume and cost of prescriptions for the low dose combination therapy were reduced in each of the years 2008/2009, 2009/10 and 2010/11 by the relevant percentage.
- 2. The decrease in total volume of prescriptions for the low dose combination therapy compared to the base case was estimated.
- 3. The volume of the next higher dose of ICS monotherapy prescriptions in the alternate scenarios was the volume in the base case scenario plus the volume identified in Step 2.
- 4. The forecasted claims for the year from Step 3 were weighted by the average cost per claim by medication in the most recent year to provide the forecasted cost by medication for 2008/2009, 2009/10 and 2010/11.

These steps were repeated to obtain estimates for Scenario B and Scenario C.

# APPENDIX 17: DETAILED RESULTS OF THE BUDGET IMPACT ANALYSIS

Table 1: Impact of 25% Reduction in low a	nd moderate	dose LABA use	Э
	2008-2009	2009-2010	2010-2011
Annual Budget Estimates			
Base Case	\$9,496,412	\$10,239,735	\$10,983,057
Scenario 1: Low dose combination switch to higher dose ICS	\$9,486,533	\$10,229,347	\$10,972,160
Scenario 2: Low and medium dose combination switch to higher dose ICS	\$9,394,133	\$10,126,059	\$10,857,986
Scenario 3: Low and medium dose combination switch to higher dose ICS, switch from LABA in single inhaler to low dose ICS	\$9,279,819	\$9,995,767	\$10,711,715
Cost Savings			
Scenario 1: Low dose combination switch to higher dose ICS	\$9,879	\$10,388	\$10,896
Scenario 2: Low and medium dose combination switch to higher dose ICS	\$102,279	\$113,675	\$125,071
Scenario 3: Low and medium dose combination switch to higher dose ICS, switch from LABA in single inhaler to low dose ICS	\$216,593	\$243,967	\$271,342

Table 2: Impact of 50% Reduction in lo	w and moderate	e dose LABA us	e
	2008-2009	2009-2010	2010-2011
Annual Budget Estimates			
Base Case	\$9,496,412	\$10,239,735	\$10,983,057
Scenario 1: Low dose combination switch to higher dose ICS	\$9,476,653	\$10,218,958	\$10,961,264
Scenario 2: Low and medium dose combination switch to higher dose ICS	\$9,291,854	\$10,012,384	\$10,732,914
Scenario 3: Low and medium dose combination switch to higher dose ICS, switch from LABA in single inhaler to low dose ICS	\$9,063,226	\$9,751,800	\$10,440,374
Cost Savings			
Scenario 1: Low dose combination switch to higher dose ICS	\$19,759	\$20,776	\$21,793
Scenario 2: Low and medium dose combination switch to higher dose ICS	\$204,558	\$227,350	\$250,142
Scenario 3: Low and medium dose combination switch to higher dose ICS, switch from LABA in single inhaler to low dose ICS	\$433,186	\$487,935	\$542,683

Table 3: Impact of 75% Reduction in Ic	w and moderate	e dose LABA us	e
	2008-2009	2009-2010	2010-2011
Annual Budget Estimates			
Base Case	\$9,496,412	\$10,239,735	\$10,983,057
Scenario 1: Low dose combination switch to higher dose ICS	\$9,466,773	\$10,208,570	\$10,950,368
Scenario 2: Low and medium dose combination switch to higher dose ICS	\$9,189,575	\$9,898,709	\$10,607,843
Scenario 3: Low and medium dose combination switch to higher dose ICS, switch from LABA in single inhaler to low dose ICS	\$8,846,633	\$9,507,832	\$10,169,032
Cost Savings			
Scenario 1: Low dose combination switch to higher dose ICS	\$29,639	\$31,164	\$32,689
Scenario 2: Low and medium dose combination switch to higher dose ICS	\$306,837	\$341,025	\$375,214
Scenario 3: Low and medium dose combination switch to higher dose ICS, switch from LABA in single inhaler to low dose ICS	\$649,779	\$731,902	\$814,025

Table 4: Impact of 100% Reduction in low and moderate dose LABA use			
	2008-2009	2009-2010	2010-2011
Annual Budget Estimates			
Base Case	\$9,496,412	\$10,239,735	\$10,983,057
Scenario 1: Low dose combination switch to higher dose ICS	\$9,456,893	\$10,198,182	\$10,939,471
Scenario 2: Low and medium dose combination switch to higher dose ICS	\$9,087,296	\$9,785,034	\$10,482,772
Scenario 3: Low and medium dose combination switch to higher dose ICS, switch from LABA in single inhaler to low dose ICS	\$8,630,039	\$9,263,865	\$9,897,691
Cost Savings			
Scenario 1: Low dose combination switch to higher dose ICS	\$39,519	\$41,552	\$43,585
Scenario 2: Low and medium dose combination switch to higher dose ICS	\$409,116	\$454,700	\$500,285
Scenario 3: Low and medium dose combination switch to higher dose ICS, switch from LABA in single inhaler to low dose ICS	\$866,373	\$975,870	\$1,085,366