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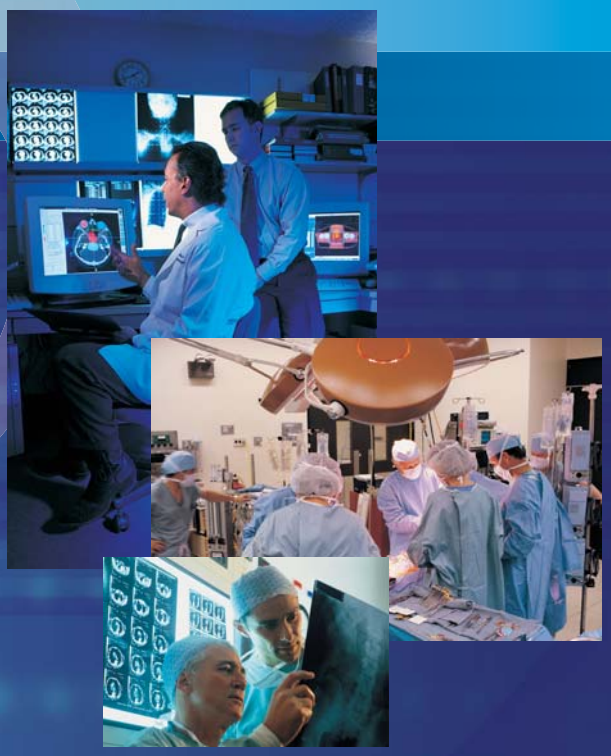
Long-Acting Beta$_2$-Agonist and Inhaled Corticosteroid Combination Therapy for Adult Persistent Asthma: Systematic Review of Clinical Outcomes and Economic Evaluation



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Canadian Agency for Drugs and Technologies in Health

Long-Acting Beta$_2$-Agonist and Inhaled Corticosteroid Combination Therapy for Adult Persistent Asthma: Systematic Review of Clinical Outcomes and Economic Evaluation

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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.

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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.

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All other authors declare no conflicts of interest.

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$_2$-agonist (SABA) agents in first-line medical management of chronic persistent asthma. The guidelines recommend add-on combination therapy of a long-acting beta$_2$-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 similar-dose 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 higher-dose 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 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 $beta_2$-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 $beta_2$-agonist
SFDs	symptom-free days

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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.[1] Patients with asthma reported symptoms or attacks daily (14%) or several times per month (37%).[2] From 1998 to 2001 approximately 80,000 people were admitted to hospital because of asthma.[2]

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.[3] 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,[4] 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.[5]

Long-acting beta$_2$-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.[6] 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.[7]

Patients with asthma who have persistent symptoms need maintenance therapy with ICS.[4,8] 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[4,8,9] 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$_2$-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.[10,11] 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.[12]

1.2 Current Clinical Practice

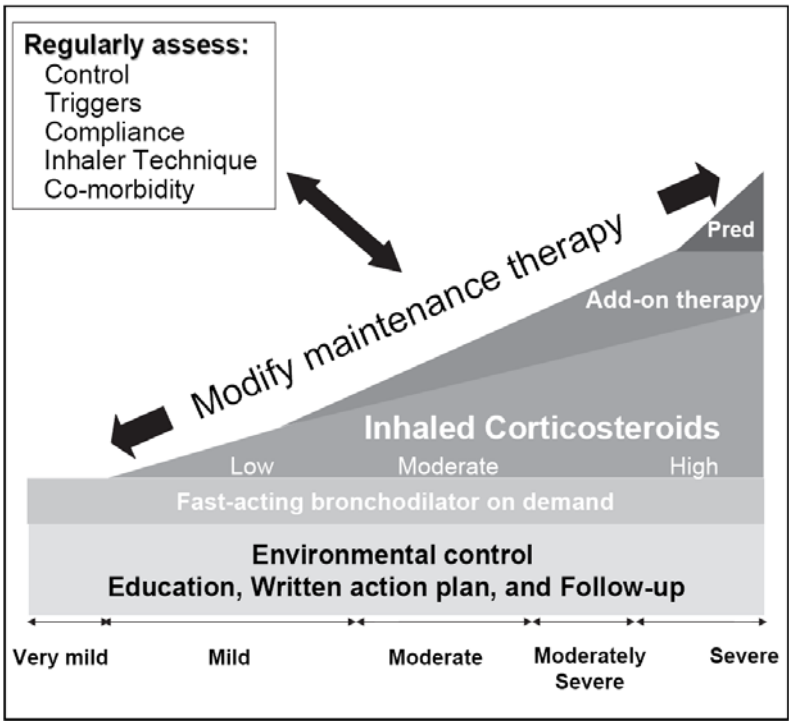
The goal of asthma management includes the alleviation of breathlessness, the improvement of airway functioning (and thus health status), the prevention and treatment of exacerbations, and the reduction of mortality. These aims can be achieved by some patients using ICS monotherapy. Guidelines on treatment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

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 beta-agonist 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*



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

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,[4] which were developed by the Canadian Thoracic Society (CTS); the National Asthma Education and Prevention Program (NAEPP) guidelines,[9] 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[8] (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 recommend starting LABA and ICS therapy only after using ICS monotherapy. No guidelines provide a 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 Beta$_2$-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 corticosteroids			
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*	100 mcg	Azmacort	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.[13] 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.[14] 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).[15]

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,[5,13,14,16-27] 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[28] and GOAL[29]).

In addition to scanning the bibliographies of previous reviews, the literature search was supplemented by scanning the reference lists of asthma guidelines.[4,8,9] 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 anti-inflammatory 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_1], 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, but a minimum duration or per cent-predicted FEV_1 was reported and ICS dose were used as inclusion criteria, 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.[8] 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.[30]

The methodological quality of all trials was assessed using the Jadad scale[31] and the Schulz criteria for allocation concealment.[30] The former is a validated five-point scale[31] 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.[32] 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-sponsored if the funding or at least one author was from a pharmaceutical company.[33]

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 (κ 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[34] 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.[35] 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 ($I^2 > 70\%$),[36] 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 χ^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.[37,38] The following MCIDs were selected a priori: PEF 18.79 L/min, FEV_1 0.23 L, per cent-predicted FEV_1 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[11,39-43] were considered to be multiple publications of other published studies,[29,44-47] and one report[48] was a subanalysis of an unpublished industry trial,[49] 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,[5,13,14,21,23] one NHS HTA,[25] and nine literature reviews[16-20,22,24,26,27]) 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

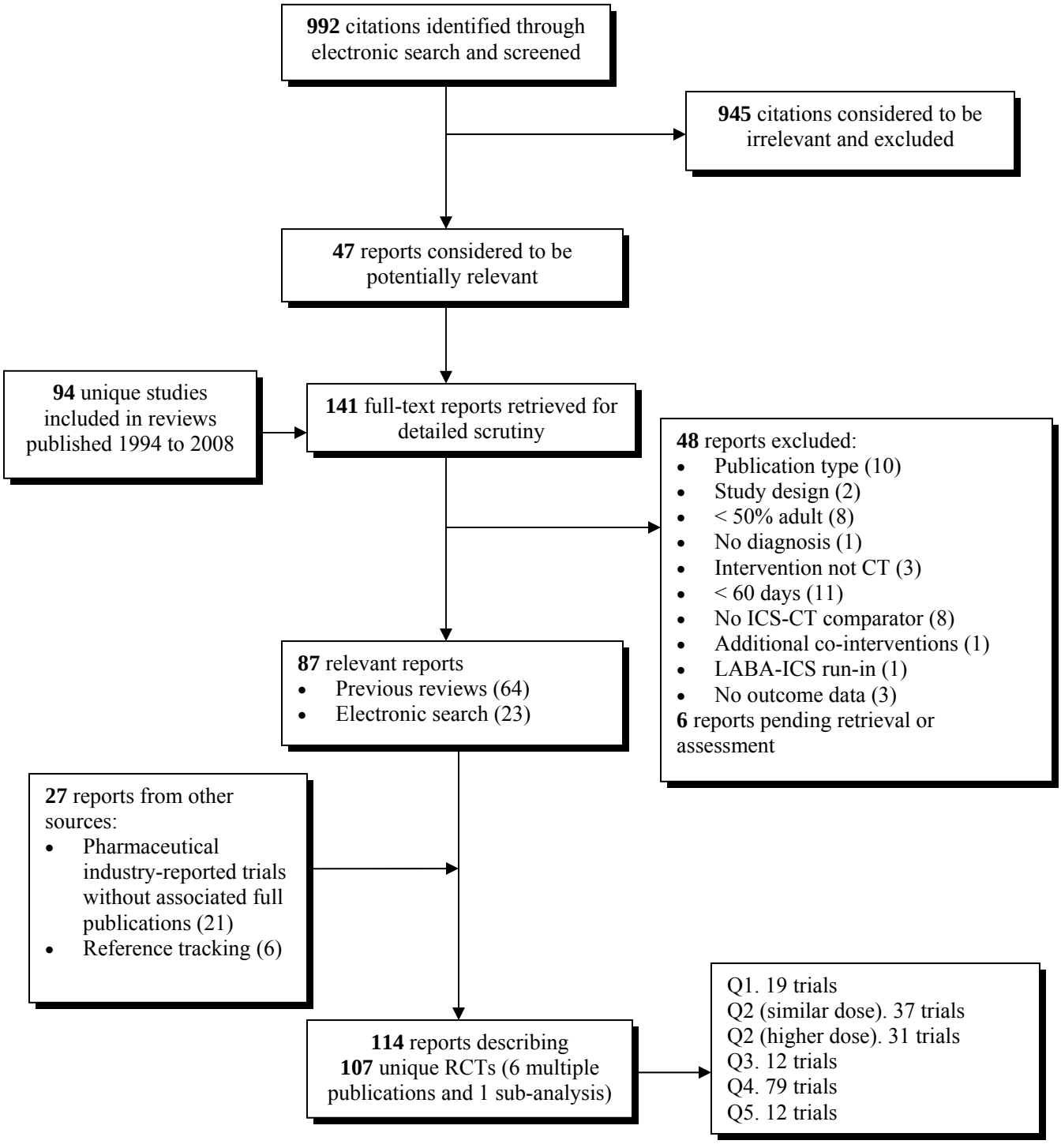
Searches of seven electronic bibliographic databases resulted in the identification of 992 records. Of these, 945 were excluded. The inter-rater agreement for the screening phase before consensus was strong ($\kappa = 0.57$, prevalence-and-bias–adjusted $\kappa = 0.90$, prevalence index = 0.87, bias index = 0.008).[50,51] 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 (www.clinicalstudyresults.org) and reference tracking of included studies resulted in the inclusion of an additional 21 and six reported trials respectively.

Figure 2: Search Results of Clinical Literature



CT = combination therapy; ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-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[52] 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[53] 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[29,46,54-70] 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[29,46,54-61,63,64,67,69,70] examined similar ICS doses, and four[62,65,66,68] examined a double or greater ICS dose. The age of included participants was 18 years or older in five (26.3%) studies.[46,59,63,66,70] Three trials[54,62,69] included only participants with mild asthma, and two[60,67] 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_1 indicated statistically significant differences favouring LABA-ICS. The difference between treatments for evening PEF was potentially clinically important. The difference in FEV_1 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$_2$-Agonists Used with Inhaled Corticosteroids Compared with Inhaled Corticosteroids in Steroid-Naive Adults (19 studies)				
Outcome	**No. of Studies (No. of patients)**	**Pooled Estimate (95% CI)**	**I^2 (%)**	**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_1 (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_1 (% 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

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

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.[68]

This systematic review identified seven more RCTs with steroid-naive adults than the previous systematic review and meta-analysis,[5] 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_1, 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[5] 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[58] 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.[37,38] 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.[71] 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[29,45,47,58,72-104] 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[45,47,58,72,74,77,79,81,86,91,98,100,102,103] compared LABA-ICS with low-dose ICS, 15 trials[29,78,82-85,87-90,92,94-96,99] with medium-dose ICS, and eight trials[73,75,76,80,93,97,101,104] with high-dose ICS. The age of included participants was 18 years or older in nine (24.3%) studies.[45,73,78,84-86,88-90] Participants had mild asthma only (three trials),[72,79,91] moderate asthma only (five trials),[83,85,87,93,95] severe asthma only (one trial),[73] intermittent to mild asthma (two trials),[58,74] intermittent to moderate asthma (two trials),[81,103] intermittent to severe asthma (six trials),[29,75,76,82,94,97] mild to moderate asthma (nine trials),[45,47,77,78,84,86,88,90,98] mild to severe asthma (five trials),[89,99,100,102,104] and moderate to severe asthma (four trials).[80,92,96,101] 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.

Table 5: Methodological Quality of 37 Long-Acting Beta$_2$-Agonist Used with Inhaled 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)

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[74,79,84,99,101] 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_1. 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 $Beta_2$-Agonists Used with Inhaled Corticosteroids versus Similar-Dose Inhaled Corticosteroids (37 studies)

Outcome	No. of Studies (No. of patients)	Pooled Estimate (95% CI)	I^2 (%)	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_1 (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$_2$-Agonists Used with Inhaled Corticosteroids versus Similar-Dose Inhaled Corticosteroids (37 studies)				
Outcome	**No. of Studies (No. of patients)**	**Pooled Estimate (95% CI)**	**I^2 (%)**	**A priori MCID**
Medium-dose ICS	11 (5,376)	WMD 0.18 L (0.13 to 0.22)	46	
Medium-dose ICS (mixed)	2 (600)	WMD 0.08 L (0.00 to 0.15)	0	
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_1 (% 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 control				
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
Mixed overall	2 (763)	RR 0.42 (0.20 to 0.92)	54	
Low-dose ICS	3 (1,036)	RR 0.80 (0.63 to 1.01)	53	
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 control				
Number of participants with one or more severe exacerbations	6 (1,820)	RR 0.96 (0.76 to 1.21)	0	Not available
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	

Table 6: Comparative Efficacy of Long-Acting Beta$_2$-Agonists Used with Inhaled Corticosteroids versus Similar-Dose Inhaled Corticosteroids (37 studies)				
Outcome	**No. of Studies (No. of patients)**	**Pooled Estimate (95% CI)**	**I^2 (%)**	**A priori MCID**
Number of severe exacerbations	2 (612)	Rate ratio 0.82 (0.54 to 1.25)	84	Not available
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	
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 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	
High-dose ICS	3 (2,334)	WMD 0.32 (0.17 to 0.46)	61	

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.[23] The previous review reported statistically significant results favouring LABA-ICS for morning PEF, absolute FEV_1, and per cent predicted FEV_1. 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 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.[53,66,106,108,111,113-115,117,118,120,121] The studies covered mild asthma only (three trials),[79,121,123]

moderate asthma only (four trials),[106,108,114,124] intermittent to mild asthma (one trial),[58] intermittent to moderate asthma (two trials),[103,113] intermittent to severe asthma (five trials),[76,105,111,115,125] mild to moderate asthma (five trials),[65,112,120,122,126] mild to severe asthma (four trials),[53,66,104,107] and moderate to severe asthma (seven trials).[101,109,110,116-119] 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.

Table 7: 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 [79,101,124] 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_1. 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_1 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 Beta$_2$-Agonists Used with Inhaled Corticosteroids versus Higher-Dose Inhaled Corticosteroids (31 studies)

Outcome	No. of Studies (No. of patients)	Pooled Estimate (95% CI)	I^2 (%)	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_1 (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	

Table 8: Comparative Efficacy of Long-Acting Beta$_2$-Agonists Used with Inhaled Corticosteroids versus Higher-Dose Inhaled Corticosteroids (31 studies)				
Outcome	**No. of Studies (No. of patients)**	**Pooled Estimate (95% CI)**	**I^2 (%)**	**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_1 (% 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 control				
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	
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	
High-dose ICS	2 (697)	RR 0.80 (0.51 to 1.25)	48	
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	

Table 8: Comparative Efficacy of Long-Acting Beta$_2$-Agonists Used with Inhaled Corticosteroids versus Higher-Dose Inhaled Corticosteroids (31 studies)				
Outcome	**No. of Studies (No. of patients)**	**Pooled Estimate (95% CI)**	**I^2 (%)**	**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 puffs/day
Mixed dose (overall)	3 (708)	WMD −0.27 (−0.72 to 0.19)	NA	
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 life				
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 meta-analysis,[14] which included 30 RCTs. The review reported statistically significant results favouring LABA-ICS for morning and evening PEF, absolute FEV_1, and per cent-predicted FEV_1. The differences between treatments for morning and evening PEF were clinically important. The estimated benefits for absolute FEV_1 and per cent-predicted FEV_1 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[10,11,127-136] assessed the efficacy of LABA-ICS combination therapies for adult persistent asthma against one another. Nine trials[10,11,127-131,133,136] compared formoterol-budesonide with salmeterol-fluticasone, two compared formoterol-beclomethasone with salmeterol-fluticasone,[134,135] and one compared formoterol-budesonide with formoterol-

beclomethasone.[133] Eight trials[10,11,127-136,128-132,134-136] compared different fixed-dose regimens. Three trials[10,11,127,129,130,132,133] compared variable dose with fixed dose. One trial[130] compared variable dose with variable dose. The comparison of LABA-ICS with a similar dose of LABA-ICS was examined in eight trials.[11,127-129,131,133,134,136] The remaining four trials[10,130,132,135] 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.[11,128,132,135] The median treatment duration was 18 weeks (IQR 12 to 26).

Three[10,129,131] 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-Acting Beta$_2$-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 salmeterol-fluticasone compared with formoterol-budesonide for an increase in SFDs. There was a statistically significant difference favouring formoterol-budesonide compared with salmeterol-fluticasone 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)**	**Pooled Estimate (95% CI)**	**I^2 (%)**	**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_1 (absolute)	8 (11,119)	WMD 0.01 L (−0.01 to 0.02)	22	0.23 L
FEV_1 (% 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				
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 $beta_2$-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)**	**I^2 (%)**	**A Priori MCID**
Pulmonary function				
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_1 (% predicted)	1 (241)	WMD −3.10 (−6.89 to 0.69)	NA	10% to 12%
FEV_1 (absolute)	2 (469)	WMD 0.01 L (−0.18 to 0.15)	75	0.23 L
Asthma symptom control				
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 $beta_2$-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 meta-analysis,[21] 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)**	**I^2 (%)**	**A Priori MCID**
Pulmonary function				
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_1 (absolute)	1 (216)	WMD 0.05 L (−0.07 to 0.17)	NA	0.23 L
Asthma symptom control				
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_1 = forced expiratory volume in one second; MCID = minimal clinically important difference; min = minute; NA = not available; PEF = peak expiratory flow; SABA = short-acting $beta_2$-agonist; WMD = weighted mean difference.

SMART therapy

Three studies[10,129,131] 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[131] compared formoterol-budesonide to a similar dose of salmeterol-fluticasone. Two studies[10,129] compared formoterol-budesonide to double-dose salmeterol-fluticasone. Two studies[129,131] 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.[10,129] 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.[10,129] 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[49,137-147] compared the potential steroid-sparing effects of LABA-ICS combination therapy with ICS monotherapy. Seven trials[49,137,138,140,141,144,147] 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[142] used the abrupt dose-reduction design with patients symptomatic on ICS monotherapy. Four trials[139,143,145,147] 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[49,137,142,144-146] compared salmeterol-fluticasone with fluticasone alone, three[138,140,141] compared formoterol-budesonide with budesonide alone, one[147] compared salmeterol-beclomethasone with beclomethasone alone, one[139] compared salmeterol-budesonide with budesonide alone, and one[143] 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.[138-141,143,145-147] Three trials[49,137,146] included only participants with moderate asthma, and one[145] included only participants with severe asthma. The remaining trials examined participants with asthma that was intermittent to mild (one trial),[147] intermittent to severe (three trials),[138,140,141] mild to moderate (one trial),[139] mild to severe (one trial),[144] and moderate to severe (one trial).[143] One trial[142] 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.

Table 15: Steroid-Sparing Effect of Long-Acting Beta$_2$-Agonist and Inhaled Corticosteroid Combination Therapy (12 studies)				
Outcome	**No. of Studies (No. of patients)**	**Pooled Estimate (95% CI)**	**I^2 (%)**	**A Priori MCID**
Pulmonary function				
PEF a.m.	10 (2,660)	WMD 18.20 (14.24 to 22.16)	0	18.79 L/min
Design 1	7 (2,408)	WMD 17.58 (13.25 to 21.90)	0	
Design 2	3 (252)	WMD 21.44 (11.60 to 31.28)	0	
PEF p.m.	7 (1,323)	WMD 16.12 (11.71 to 20.53)	0	18.79 L/min
Design 1	4 (1,071)	WMD 15.70 (10.80 to 20.59)	0	
Design 2	3 (252)	WMD 17.94 (7.78 to 28.09)	0	
FEV_1 (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_1 (% 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 Beta$_2$-Agonist and Inhaled Corticosteroid Combination Therapy (12 studies)				
Outcome	**No. of Studies (No. of patients)**	**Pooled Estimate (95% CI)**	**I^2 (%)**	**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,[13] 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,[45-47,56,57,59,61-65,68,69,72,74,81,91,98,100,102,103,113,122,123] 37 medium-dose trials,[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 trials[73,75,76,80,93,97,101,104,108,115,116,118,120,141-143,145,146] 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.[20] 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.[16] 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 Beta$_2$-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)**	**I^2 %**
Number of participants experiencing 1 or more AEs		61 (16,647/29,506)	59 (16,647/29,311)	RR 0.99 (0.97 to 1.01)	5
Total SAEs		53 (843/28,781)	All studies	RR 1.03 (0.90 to 1.19)	0
Headache		51 (2,167/26,323)	All studies	RR 0.95 (0.88 to 1.03)	0
Withdrawal due to AE		49 (643/24,800)	48 (643/24,638)	RR 0.98 (0.83 to 1.15)	0
Upper respiratory tract infection		39 (2,468/20,553)	All studies	RR 1.01 (0.94 to 1.09)	0
Candidiasis		29 (339/16,196)	All studies	RR 0.85 (0.64 to 1.14)	18
Treatment-related AEs		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
Worsening 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
Hoarseness		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.[148] 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.[130,149-164] 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,[158,159,165] and four were head-to-head comparisons of two LABAs.[160-163] 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,[5,149-153] and five studies examined LABA-ICS therapy in patients with moderate to severe asthma that was not controlled on ICS monotherapy.[130,154-157]

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,[151-153,164] and two examined formoterol-budesonide.[149,150] 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.[149] Two studies were conducted from a Swedish context;[149,161] two from a UK context;[151,158] one from a Swedish, UK, and Spanish context;[150] and one from a US context.[164]

Five studies were cost-effectiveness analyses.[149,150,158,161,164] Four studies measured effectiveness by SFDs,[149,150,152,164] two by successfully controlled weeks,[152,153] and one by rescue-free days.[164] 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).[151] For all studies the effectiveness data were derived from an RCT of one year's[149-151,164] or 12 weeks' duration.[152,153] All studies included analysis from a health care perspective. Two studies also conducted analysis from a societal perspective.[149,150]

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.[150]

In all but one study,[151] 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,[151] 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[155,156] compared salmeterol-fluticasone with a similar dose of fluticasone alone, and two studies compared formoterol-budesonide with a higher dose of fluticasone[157] and salmeterol-fluticasone with a higher dose of budesonide.[154] Three studies were conducted from a Swedish context,[154-156] and one was conducted from the context of Germany and the Netherlands.[157]

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.[154-156] In all cases, the effectiveness data were derived from RCTs that lasted 12 weeks, except in one study, which lasted 24 weeks.[154] The health care system perspective was used in all studies. One study included a secondary analysis from a societal perspective.[157]

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).[157] In the other three studies, LABA-ICS was more costly and more effective.[154-156] 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.[166]

b) Target population

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

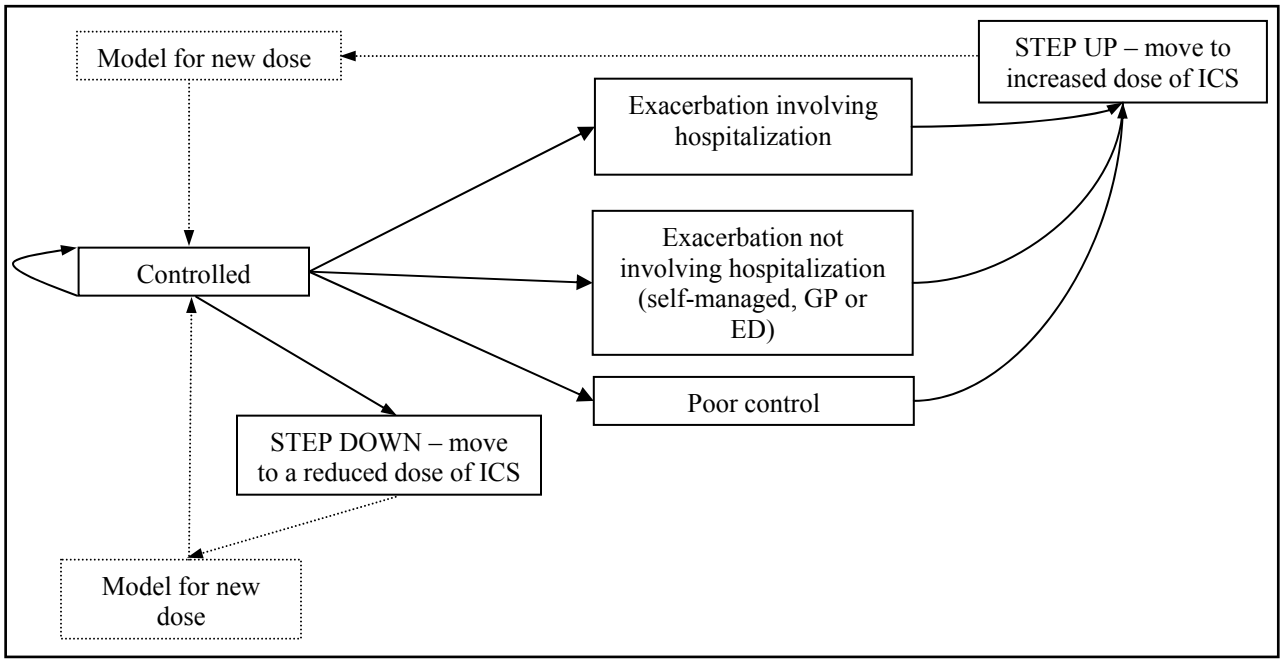
- patients with asthma who are aged 12 years or older and who are steroid-naive
- patients who are aged 12 years or older with asthma that is uncontrolled on a low dose of ICS monotherapy
- patients who are aged 12 years or older with asthma that is uncontrolled on a medium dose of ICS monotherapy.

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).

Figure 3: Markov Model



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

The dose of ICS was based on Canadian guidelines for the management of asthma[4] (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.[167] 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.[25] 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[25] 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.[168,169] 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.[169] 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.[168]

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.[170] 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.[171] 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.[169,172] The costs of hospitalizations were derived from the Ontario Case Costing Initiative data.[173]

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.[25] 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.[151,153]

l) 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.[174] 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[151,153]
- 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.[175] 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.[176]

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 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[1]
Strategy C: Introduce LABA after asthma is uncontrolled on low-dose ICS monotherapy	78.78	0.1798256	1,627,739.53[2]
Strategy D: Introduce LABA to ICS-naive patients	183.19	0.1798572	3,297,180.25[3]
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†
Strategy D	842.75	0.7792474	3,915,346.07‡

ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-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†	476.29†
Strategy D	183.19	0.03516	10.9238	13,384.66‡	1374.56‡
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†	114.31†
Strategy D	842.75	0.18538	29.6783	15,894.06‡	380.51‡

*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 $4,300 and a hospital-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.

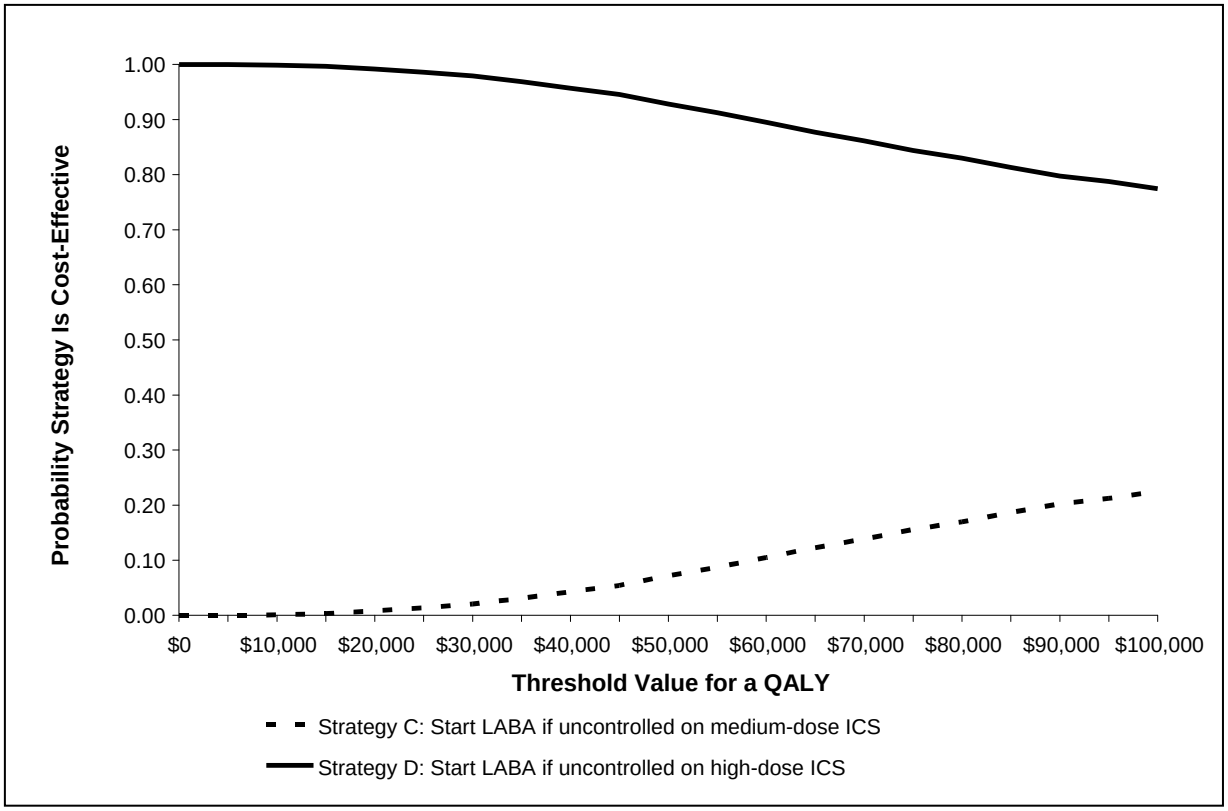
The probabilities that each of the four treatment strategies is the optimum based on alternative threshold values of a QALY appear in Figure 4. For all threshold values, the probability that Strategy A or Strategy B is the optimum is 0%. The probability that strategy C is the optimum increases the higher 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 cost-effective 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.[177] 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,[178] 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.[178] 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.[179-181] 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.[33] 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, 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.

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[182] 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[37,38] 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.[183]

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.[33,184]

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.[185] 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.

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APPENDIX 1: LITERATURE SEARCH STRATEGIES

APPENDIX 1.1: LITERATURE SEARCH STRATEGY FOR CLINICAL EFFECTIVENESS STUDIES

OVERVIEW	
Interface:	Ovid
Databases:	EBM Reviews – Cochrane Central Register of Controlled Trials <3rd Quarter 2008>
	EMBASE <1988 to 2008>
	Medline® <1950 to 2008>
Date of Search:	31Jul08
Study Types:	Left open
Limits:	2006-2008

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
Fs	Floating subheading
Exp	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
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.mp	Title, Abstract, Subject Heading, CAS Registry/EC Number Word
.rn	CAS registry number

MULTI-FILE STRATEGY		
Line #	**Search Strings**	**Results**
	MEDLINE/CENTRAL 1. 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. 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 11. (exp Adrenergic beta-agonists/ or "Receptors, Adrenergic, beta-2"/) and (long adj acting).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.rn. 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"	345 / 140
	EMBASE 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. *beclometasone/ or *beclometasone dipropionate/ or 4419-39-0.rn. 5. *fluticasone/ or *fluticasone furoate/ or *fluticasone propionate/ or 90566-53-3.rn. 6. exp *Budesonide/ or 51333-22-3.rn. 7. exp *CICLESONIDE/ or 126544-47-6.rn. 8. 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.	792

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:	Wiley
Databases:	**The Cochrane Library (Issue 3 2008)** o Cochrane Database of Systematic Reviews (CDSR) o Database of Abstracts of Reviews of Effects (DARE) o Health Technology Assessment Database (HTA)
Date of Search:	05Sep08
Study Types:	Controlled Trials, Systematic Reviews, Health Technology Assessments
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
NEAR/#	Required words are adjacent to each other within # of words
ti	Title
ab	Abstract
kw	Heading Word; usually includes subject headings and controlled vocabulary

MULTI-FILE STRATEGY

Line #	Search Strings	Results
1	(ASTHMA*):ti,ab,kw	18 CDSR 4 DARE 5 HTA
2	(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):ti,ab,kw	
3	(inhale*) AND (glucocorticoid* or corticosteroid* or steroid*):ti,ab,kw or (ICS):ti,ab,kw	

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)

OVERVIEW

Interface:	National Library of Medicine (NLM)
Databases:	PubMed®
Date of Search:	29Aug08
Study Types:	Left Open
Limits:	Last 180 days

SYNTAX GUIDE

MeSH	Medical Subject Heading terms
RN	EC/RN Number
TIAB	Title/Abstract
*	Truncation symbol, or wildcard: retrieves plural or variations of a word

STRATEGY

Line #	Search Strings	Results
55	Search #51 AND #52 Limits: **added to PubMed in the last 180 days**	81
53	Search #51 AND #52	1513
52	Search Asthma*	107649
51	Search #49 OR #50	2217
50	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]	571
49	Search #37 AND #48	1951
48	Search #39 OR #44 OR #45	104827
45	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 perforomist OR 73573-87-2[RN]	67626
44	Search long[tiab] AND (beta*[TIAB] OR agonist*[TIAB] OR bronchodilator*[TIAB])	38894
39	Search ("Adrenergic beta-agonists" [MESH] OR "Receptors, Adrenergic, beta-2"[MESH]) AND "long acting"[TIAB]	907
37	Search #33 OR #34 OR #35	15523
35	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	10622

	pulmicort OR flovent OR Flixotide OR QVAR OR alvesco OR asthmanex OR asmanex	
34	Search ((inhale* OR "Administration, Inhalation"[Mesh:noexp]) AND (glucocorticoid* OR corticosteroid* OR steroid*))	9022
33	Search "Administration, Inhalation"[Mesh] AND Glucocorticoids[Mesh]	1121

OVERVIEW

Interface:	ISI Thomson Research
Databases:	BIOSIS Previews® (1969-2008) Web of Science® (1900-2008)
Date of Search:	28Aug08
Study Types:	Randomized Controlled Trials
Limits:	2006-2008

SYNTAX GUIDE

TS=	Topic
*	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 same keyword phrase.
TI=	Title of Article
SO=	Source

MULTI-FILE STRATEGY

Line #	Search Strings	Results
14	#13 AND #12	98 BIOSIS 254 WOS
13	TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation 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	
9	TS=(symbicort or seretide or advair or viani or adoair or seroflo or fostair or innovair) OR 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)	
5	TS=(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 TS=(salmeterol or serevent or serobid or salmetadur or arial or beglan or betanican or inaspir)	
4	#3 OR #2 OR #1	
3	TI=(iCS)	
2	TS=(inhale*) AND TS=(glucocorticoid* or corticosteroid* or steroid*)	
1	TS=(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)	

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

OVERVIEW	
Interface:	Wiley
Databases:	The Cochrane Library (Issue 3 2008) o NHS Economic Evaluation Database (NHS EED)
Date of Search:	September 5, 2008
Study Types:	Not required
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
NEAR/#	Required words are adjacent to each other within # of words
ti	Title
ab	Abstract
kw	Heading Word; usually includes subject headings and controlled vocabulary

MULTI-FILE STRATEGY

Line #	Search Strings	Results
1	(ASTHMA*):ti,ab,kw	27
2	(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):ti,ab,kw	
3	(inhale*) AND (glucocorticoid* or corticosteroid* or steroid*):ti,ab,kw or (ICS):ti,ab,kw	
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)	

OVERVIEW	
Interface:	Wiley
Databases:	HEED: Health Economic Evaluations Database
Date of Search:	September 5, 2008
Study Types:	Not required
Limits:	None applied

SYNTAX GUIDE	
*	Truncation symbol, or wildcard: retrieves plural or variations of a word
AX	All Data
CS	Combined search lines

MULTI-FILE STRATEGY

ID	Search Strings	Results
1.	AX=asthma*	92
2.	AX=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	
3.	(AX=inhale* AND AX=glucocorticoid* or corticosteroid* or steroid*) OR AX=ICS	
4.	CS=2 or 3	
5.	AX=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	
6.	(AX=long AND AX=beta* or agonist* or bronchodilator*) OR AX=LABA	
7.	CS= 5 or 6	
8.	CS= 4 and 7	
9.	(AX=symbicort or seretide or advair or viani or adoair or seroflo or fostair or innovair) OR (AX=budesonide AND formoterol) OR (AX=fluticasone AND salmeterol) OR (AX=ICS AND LABA)	
10.	CS= 8 or 9	
11.	CS=1 and 10	

ORGANIZATIONS AND SOCIETIES

Centre for Health Economics and Policy Analysis (CHEPA), McMaster University
http://www.chepa.org/

ISPOR (International Society for Pharmacoeconomics and Outcomes Research), 2003-2008
http://www.ispor.org/

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 (≥ 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: http://clinicaltrials.gov/ct2/show/NCT00290264 (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 (≥ 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:** / /2008 **Record 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.	☐	☐	☐
c. 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 ≥ 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. [*Check "Yes" if no cointervention*]	☐	☐	☐
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.

RELEVANT TO QUESTION(S):

☐ I. What is the clinical effectiveness of LABA plus ICS maintenance therapy (either as fixed dose or single ingredient products) compared to ICS monotherapy in newly diagnosed patients with persistent asthma (ICS treatment

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 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
16. 5. Method of double-blinding described and appropriate (identical placebo, active placebo, dummy)	17. 1	18. 0
19. 6. Method of randomization described and it was **in**appropriate (allocated alternately, according to date of birth, hospital number, etc.)	20. -1	21. 0
22. 7. Method of double-blinding described but it was **in**appropriate (comparison of tablet vs. injection with no double dummy)	23. -1	24. 0
25. **OVERALL SCORE (Maximum 5)**	26.	

Concealment of treatment allocation – Schulz

27. Concealment of treatment allocation	☐ Adequate ☐ Inadequate ☐ Unclear
28.	30.
29. Adequate:	31. e.g. central randomization; numbered/coded containers; drugs prepared by pharmacy; serially numbered, opaque, sealed envelopes
32. Inadequate:	33. e.g. alternation, use of case record numbers, dates of birth or day of week; open lists
34. Unclear:	35. Allocation concealment approach 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): 99–NR			7. Publication Type:	1– journal article 2–industry reported trial 3–abstract
8. Funding:	1–government 2–institution	3–Industry A–AZ B–GSK C– Graceway	D–Nycomed E–Novartis F-other	4–No funding 5–other (describe) 99–NR

III. STUDY CHARACTERISTICS

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

		99–NR	

12. Duration of treatment (mo. or wks):	13. Recruitment dates (mm/yy–mm/yy):	99/99–NR
14. Run-in phase duration (mo. or wks)		
15. Run-in treatment (describe):		

IV. TREATMENT GROUPS

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

times/day: 1 – once AM 2 – once PM	3 – twice/day 4 – other					
25. Total dose (mcg) /day						
26. Drug 2: name						
27. Delivery device: 1 – diskhaler 2 – pMDI * Do not record spacer use.	3 – MDI 4 – Turbuhaler 5–other					
28. Dosing: 1–fixed 2– variable 3–NR						
29. No. times/day: 1 – once AM 2 – once PM	3 – twice/day 4 – other					
30. Total dose (mcg) /day						
31. Additional treatment allowed (describe)						
32. Compliance measured 1–yes ND 2–diary card 3–weight 4–internal counter 4–no						

V. BASELINE CHARACTERISTICS (when possible report data post run-in/pre-treatment)

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

43. AM PEF L/min					
44. AM % pred PEF					
45. PM PEF L/min					
46. PM % pred					
47. % predicted PEF					
48. Reversibility					
49. FEV_1 (mL/L)					
50. % predicted FEV_1					
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					
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:			

Secondary:				
91. PEF:	102. exacerbations:		113. Change in dose of ICS:	
92. PEF:	103. Symptom score:		114. Composite:	
93. PEF:	104. Symptom score:		115. Composite:	
94. PEF:	105. Symptom score:		116. Composite:	
95. FEV:	106. Symptom score:		117. Composite:	
96. FEV:	107. Symptom score:		118. Other:	
97. FEV:	108. BHR:		119. Other:	

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[127]	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Aubier M 1999[75]	Yes	Yes	Yes	No	No	No	No	3	Unclear
Baraniuk J 1999[109]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Bateman ED 2001[98]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Bateman ED 2003[106]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Bateman ED 2004[29]	Yes	Yes	Yes	No	No	No	No	3	Unclear
Bergmann K-C 2004[108]	Yes	Yes	Yes	Yes	No	No	No	4	Adequate
Boonsawat W 2008[56]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Bouros D 1999[107]	Yes	No	Yes	No	No	No	No	2	Unclear
Bousquet J 2007[10]	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
Boyd G 1995[73]	Yes	No	Yes	No	Yes	No	No	4	Unclear
Buhl R 2003[72]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Buhl R 2004[186]	Yes	No	Yes	No	No	No	No	2	Unclear
Busse W W 2003[137]	Yes	Yes	Yes	No	No	No	No	3	Unclear
Busse WW 2008[133]	Yes	No	Yes	No	No	No	No	2	Unclear
Canonica GW 2004[187]	Yes	No	Yes	No	No	No	No	2	Unclear
Chuchalin AG 2008[62]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Chuchalin AG 2002[46]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Condemi JJ 1999[110]	Yes	Yes	Yes	No	No	No	No	2	Unclear
Corren J 2007[47]	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
Creticos PS 1999[55]	Yes	No	No	No	No	No	No	1	Unclear
Dahl R 2006[128]	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Di Franco A 1999[54]	Yes	No	Yes	No	No	No	No	2	Unclear
FitzGerald JM 1999[90]	Yes	Yes	Yes	No	Yes	No	No	4	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
FitzGerald JM 2005[11]	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Fowler SJ 2002[77]	Yes	Yes	Yes	No	No	No	No	3	Unclear
Greening AP 1994[111]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Grutters JC 1999[59]	Yes	Yes	No	No	No	No	No	2	Unclear
Langton Hewer S 1995[83]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Ind PW 2003[76]	Yes	Yes	Yes	No	No	No	No	3	Unclear
Ind PW 2004[188]	Yes	No	Yes	No	No	No	No	2	Unclear
Jenkins C 2000[80]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Jenkins C 2006[93]	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Johansson G 2001[112]	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Kavuru M 2000[81]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Kelsen SG 1999[114]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Kemp JP 1998[82]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Kerwin EM 2008[61]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Kips JC 2000[138]	Yes	Yes	No	No	No	No	No	2	Unclear
Koenig SM 2008[95]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Koopmans JG 2006[78]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Kuna P 2006[45]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Kuna P 2007[129]	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Lalloo UG 2003[113]	Yes	Yes	Yes	No	No	No	No	3	Unclear
Lemanske RF 2001[79]	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Leuppi JD 2003[189]	Yes	No	Yes	No	No	No	No	2	Unclear
Li X 1999[86]	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
Lundback B 2006[84]	Yes	Yes	Yes	No	Yes	No	No	4	Adequate
Lundborg M 2006[190]	Yes	No	Yes	Yes	No	No	No	3	Unclear
Mitchell C 2003[115]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Molimard M 2001[85]	Yes	No	Yes	Yes	No	No	No	3	Adequate
Morice AH 2007[96]	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Murray JJ 2004[64]	Yes	Yes	Yes	Yes	No	No	No	4	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
Murray JJ 1999[117]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Nathan RA 2006[94]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Nelson HS 2003[57]	Yes	Yes	Yes	No	No	No	No	3	Unclear
Nielsen LP 1999[139]	Yes	Yes	No	No	Yes	No	No	3	Unclear
Noonan M 2006[92]	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
O'Byrne PM 2005[105]	Yes	Yes	Yes	Yes	No	No	No	4	Unclear
O'Byrne PM 2001[58]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Overbeek SE 2005[70]	Yes	Yes	Yes	No	No	No	No	3	Unclear
Papi A 2007[132]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Papi A 2007[134]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Pauwels RA 1997[140]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Pearlman DS 2004[74]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Peters SP 2007[123]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Peters SP 2008[101]	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
Pohl WR 2006[141]	Yes	Yes	Yes	Yes	No	No	No	4	Unclear
Price D 2002[91]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Rabe KF 2006[122]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Ringdal N 2002[130]	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Rojas RA 2007[60]	Yes	Yes	Yes	No	No	No	No	3	Unclear
SAM30002[124]	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
SAM30007[146]	Yes	Yes	Yes	No	No	No	No	3	Unclear
SAM30013[126]	Yes	Yes	Yes	No	No	No	No	3	Unclear
SAM40008[145]	Yes	Yes	Yes	No	No	No	No	3	Unclear
SAM40010[136]	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
SAM40034[66]	Yes	Yes	Yes	Yes	No	No	No	4	Unclear
SAM40036[65]	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
SAM40048[135]	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
SAM40065[99]	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
SAM40090[144]	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[53]	Yes	Yes	Yes	No	No	No	No	3	Unclear
SAS30015[68]	Yes	Yes	Yes	No	No	No	No	3	Unclear
SAS30039[67]	Yes	Yes	Yes	Yes	No	No	No	4	Unclear
SAS40026[49]	Yes	Yes	Yes	No	No	No	No	3	Unclear
SAS40036[102]	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
SAS40068[69]	Yes	Yes	Yes	Yes	No	No	No	4	Unclear
Schermer TRJ 2007[142]	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Scicchitano R 2004[119]	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate
Self T 1998[143]	Yes	Yes	Yes	No	No	No	No	3	Unclear
SFA103153[100]	Yes	Yes	Yes	Yes	No	No	No	4	Unclear
Shapiro G 2000[87]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
SLGA5021[125]	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
SLGF75/FLIC 14[103]	Yes	Yes	Yes	Yes	No	No	No	4	Unclear
SLGQ97/SLGB4010[104]	Yes	Yes	Yes	Yes	Yes	No	No	5	Unclear
SLMF4002 (SMS40012)[147]	Yes	Yes	Yes	No	No	No	No	3	Unclear
Stallberg B 2003[191]	Yes	No	Yes	No	No	No	No	2	Unclear
Strand AM 2004[63]	Yes	Yes	Yes	No	No	No	No	3	Unclear
van der Molen T 1997[88]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
van Noord JA 1999[120]	Yes	Yes	Yes	No	No	No	No	3	Unclear
van Noord JA 2001[97]	Yes	Yes	Yes	No	Yes	No	No	4	Unclear
Vermetten FAAM 1999[121]	Yes	Yes	Yes	No	No	No	No	3	Unclear
Vogelmeier C 2005[131]	Yes	No	Yes	Yes	No	No	No	3	Unclear
Wallin A 2003[116]	Yes	Yes	Yes	No	No	No	No	3	Unclear
Woolcock A 1996[118]	Yes	Yes	Yes	No	No	No	No	3	Unclear
Zetterstrom O 2001[89]	Yes	Yes	Yes	Yes	Yes	No	No	5	Adequate

APPENDIX 6: CHARACTERISTICS OF STUDIES INCLUDED IN CLINICAL REVIEW

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Aalbers R 2004[127] **Pub status:** Journal article **No. countries:** 6 **No. centers:** 93 **Design:** randomized, parallel, open label **Funding:** Industry: AstraZeneca	**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):** 84±23.8 **PEF AM L/min (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):** 385.7±150.8 **Duration of asthma yr. (mean±SD):** 12±15.3 **Smoking status:** all <10 pack-yr	**GROUP 1** **Drug mcg/day:** FORM/BUD 12 to 36/400 to 1600 **Dosing:** variable **Treatment duration:** 30 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** FORM/BUD 18/800 **Dosing:** fixed **Treatment duration:** 30 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 3** **Drug mcg/day:** SAL/FP 100 /500 **Dosing:** fixed **Treatment duration:** 30 wk. **Device:** Diskhaler® **Withdraw LOE:** NR **Reliever Tx:** terbutaline or salbutamol as needed **Run-in Tx:** (Period 1, unblinded) Previous ICS dose, no LABA allowed; (Period 2, double-blind) fixed dose FORM/BUD 24/800 mcg or SAL/FP 100/500 mcg **Run-in duration:** Period 1 was10-14 days; Period 2 was 1 mo.	**Definition of exacerbation:** OCS for ≥ 3 days or if ED visit and/or hospitalization were needed. If OCS needed > 10 days, 11th day was considered a 2nd exacerbation. **Clinical outcomes reported:** **Primary** • well-controlled asthma wk. **Secondary** • PEF AM • PEF PM • FEV_1 • DTS (5 pt. scale) • SABA use • asthma control wk. • total exacerbations • NTA • step-up, step-down tx required • study drug inhalations/day	**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 3rd 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_1; forced expiratory volume in 1 second; FORM = formoterol fumarate; FP = fluticasone propionate; ICS = inhaled corticosteroid; ITT = intention to treat; LABA = long-acting $beta_2$-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 $beta_2$-agonist; SAL = salmeterol xinafoate; SFD = symptom-free days; SD = standard deviation; TAA = triamcinolone acetonide

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Aubier M 1999[75] **Pub status:** Journal article **No. countries:** 3 **No. centers:** 55 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 503 **Analyzed:** 403 **Withdrawals:** 100 **ITT analysis:** all available data **Asthma stage and severity:** symptomatic, intermittent to severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 136 **Age yr. (mean±SD):** 46±16.5 **Males %:** 59 **FEV_1 % predicted (mean±SD):** 73±15.5 **PEF AM L/min (mean±SD):** 359±95.6 **Duration of asthma yr. %:** 47 (<10 yr.); 53 (>10 yr.) **Smoking status (never/past/current %):** 42/38/15 **GROUP 2** **N:** 143 **Age yr. (mean±SD):** 48±15 **Males %:** 50 **FEV_1 % predicted (mean±SD):** 73±15.7 **PEF AM L/min (mean±SD):** 345±86.3 **Duration of asthma yr. %: 43** (<10yr.); 57 (>10yr.) **Smoking status (never/past/current %):** 44/40/16 **GROUP 3** **N:** 124 **Age yr. (mean±SD):** 50±16 **Males %:** 53 **FEV_1 % predicted (mean±SD):** 73±18.0 **PEF AM L/min (mean±SD):** 351±104.1 **Duration of asthma yr. %:** 46 (<10yr.); 54 (>10yr.) **Smoking status (never/past/current %):** 50/39/12	**GROUP 1** **Drug mcg/day:** SAL/FP 100/1000 + PLA **Dosing:** fixed **Treatment duration:** 28 wk. **Device:** Diskus®: one **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** SAL 100 + FP 1000 **Dosing:** fixed **Treatment duration:** 28 wk. **Device:** Diskus®: two **Withdraw LOE:** NR **GROUP 3** **Tx/dose/day:** FP 1000 + PLA **Dosing:** fixed **Treatment duration:** 28 wk. **Device:** Diskus® **Withdraw LOE:** NR **Reliever Tx:** salbutamol as needed **Run-in Tx:** continued same dose of current ICS, other asthma drugs taken continued unchanged. **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **Clinical outcomes reported:** **Primary** • PEF AM **Secondary** • PEF PM • FEV_1 • FEV_1 % predicted • asthma symptom score (5 pt. scale) • SFD • SFN • RFD • RFN	**Study objective:** To determine if SAL/FP in a combination Diskus® inhaler would be superior to FP alone or to the same doses of SAL and FP in separate inhalers in patients who were symptomatic on current ICS tx.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Baraniuk J 1999[109] **Pub status:** Journal article **No. countries:** 1 **No. centers:** 50 **Design:** randomized, parallel, double blind, triple dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 680 **Analyzed:** 630 **Withdrawals:** 50 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, moderate, severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 231 **Age yr. (mean±SD):** 41±16.8 **Males %:** 41 **FEV_1 % predicted (mean±SD):** 63.1±11.9 **PEF AM L/min (mean±SD):** 361±121.6 **Duration of asthma:** NR **Smoking status:** all non-smokers **GROUP 2** **N:** 223 **Age yr. (mean±SD):** 40±15.5 **Males %:** 39 **FEV_1 % predicted (mean±SD):** 63.1±12.3 **PEF AM L/min (mean±SD):** 344±104.5 **Duration of asthma:** NR **Smoking status:** all non-smokers **GROUP 3** **N:** 226 **Age yr. (mean±SD):** 39±14.8 **Males %:** 35 **FEV_1 % predicted (mean±SD):** 63.4±12.0 **PEF AM L/min (mean±SD):** 349±105.2 **Duration of asthma:** NR **Smoking status:** all non-smokers	**GROUP 1** **Drug mcg/day:** SAL/FP 100/200 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE n :** 2 **GROUP 2** **Drug mcg/day:** FP 500 + PLA **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE n:** 2 **GROUP 3** **Drug mcg/day:** TAA 1200 + PLA **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE n:** 9 **Reliever Tx:** albuterol as needed **Run-in Tx:** Continued usual daily dose ICS. Fixed dose theophylline allowed if already on it. **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • FEV_1 AM **Secondary** • FEV_1 % predicted • PEF AM • PEF PM • PEF % predicted • SABA use • RFD • NTA requiring SABA • asthma symptom score (5 pt. scale) • SFD • physician global assessment	**Study objective:** To compare the efficacies of medium dose FP and TAA and low-dose FP + SAL in patients uncontrolled on low dose ICS. **Additional details:** All groups used MDI with CFC propellant

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Bateman ED 2004[29] **Pub status:** Journal article **No. countries:** 44 **No. centers:** 326 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 3,416 **Analyzed:** 3,416 **Withdrawals:** 526 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, intermittent-severe **Baseline ICS use, stratum 1/2/3:** naïve/non-naïve/non-naïve **GROUP 1** **N, stratum 1/2/3:** 548/ 585/ 576 **Age yr. (mean±SD) stratum 1/2/3:** 36.1±15.6/40.4±16.4/44.1±15.9 **Males %, stratum 1/2/3:** 43/42/43 **FEV_1 % predicted (mean±SD), stratum 1/2/3:** 77±18.7/78±18.2/75±18.6 **PEF AM L/min (mean±SD), stratum 1/2/3:** 344±91.2/349±98.4/345±98.7 **Duration of asthma:** ≥ 6 mo. **Smoking status:** all < 10 pack-yr **GROUP 2** **N, stratum 1/2/3:** 550/ 578/ 579 **Age yr. (mean±SD) stratum 1/2/3:** 36.4±15.6/40.3±16.6/42.7±15.7 **Males %, stratum 1/2/3:** 43/40/41 **FEV_1 % predicted, mean±SD, stratum 1/2/3:** 79±18.8/77±18.4/76±17.6 **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	**GROUP 1** **Drug mcg/day, stratum 1/2/3:** SAL100 + FP 200-1000 or FP 200-1000 or 500-1000 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** diskhaler **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day, stratum 1/2/3:** FP 200-1000 or 200-1000 or 500-1000 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** diskhaler **Withdraw LOE:** NR **Reliever Tx:** NR **Run-in Tx:** Usual dose ICS (if any) **Run-in duration:** 4 wk.	**Definition of exacerbation:** Required OCS and/or hospitalization or ED visit **List of clinical outcomes reported:** **Primary** • well-controlled asthma during phase 1. **Secondary** • time to asthma control • exacerbation: rate/yr. • AQLQ score • FEV_1 AM • DTS • SABA use • PEF AM • NTA	**Study objective:** To compare the efficacy of increasing the dose of FP alone or in combination with SAL to achieve asthma control as defined by GINA guidelines. **Additional details: This was the GOAL study.** Stratum 1 participants not on ICS pre study. Stratum 2 participants on BDP ≤ 500 mcg daily or equivalent. Stratum 3 participants on BDP 500 – 1000 mcg daily or equivalent. **Phase 1:** tx stepped up every 12 wk. until total asthma control achieved or SAL/FP 100/1000 mcg or FP 1000 mcg reached. **Phase 2**: remained on phase 1 tx until end of year 1. No step down tx performed in this phase.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Bateman ED 2003[106] **Pub status:** Journal article **No. countries:** 6 **No. centers:** 37 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: AstraZeneca	**Randomized:** 344 **Analyzed:** 309 **Withdrawals:** 35 **ITT analysis:** yes **Asthma stage and severity:** moderate persistent **Baseline ICS use:** non-naïve **GROUP 1** **N:** 168 **Age yr. (mean±SD):** 42.6±14.3 **Males %:** 42 **FEV_1 % predicted (mean):** 77.2 **PEF AM L/min (mean):** 354 **Duration of asthma yr. (mean±SD):** 16.3±16.5 **Smoking status (never/past/current %):** 69.6/25/5.4 **GROUP 2** **N:** 176 **Age yr. (mean±SD):** 41.8±14.3 **Males %:** 78 (44) **FEV_1 % predicted (mean):** 79.2 **PEF AM L/min (mean):** 363 **Duration of asthma yr. (mean±SD):** 16.3±16.3 **Smoking status (never/past/current %):** 71/22.2/6.8	**GROUP 1** **Drug mcg/day:** FORM/BUD 12/400 + PLA **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Turbuhaler® **Withdraw LOE n:** 3 **GROUP 2** **Tx/dose/day:** FP 500 + PLA **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskus® **Withdraw LOE n:** 8 **Reliever Tx:** terbutaline or albuterol as needed. **Run-in Tx:** BUD 400 mcg + PLA **Run-in duration:** 2 wk.	**Definition of exacerbation:** Mild: awakened due to asthma, AM PEF at least 20% below baseline, or need to use at least 4 inhalations of rescue medication over baseline use on 2 consecutive days or nights. Severe: need for OCS, AM PEF at least 30% below baseline on 2 consecutive days, or discontinued study due to worsening asthma. **List of clinical outcomes reported:** **Primary** • PEF AM **Secondary** • PEF PM • FEV_1 (L) • FVC • SABA use • RFD • asthma control days % • SFD • NTA • mild exacerbations • severe exacerbations	**Study objective:** To compare the efficacy of FORM/BUD to high dose FP in moderate-persistent asthma. **Additional details:** Both groups received both types of inhalers.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Bateman ED 2006[192] **Pub status:** Journal article **No. countries:** 12 **No. centers:** 68 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 484 **Analyzed:** 484 **Withdrawals:** 10 **ITT analysis:** yes **Asthma stage and severity:** asymptomatic, moderate **Baseline ICS use:** pre run-in naïve; post run-in non-naïve **GROUP 1** **N:** 246 **Age yr. (mean±SD):** 40.3±15.9 **Males %:** 39 **FEV_1 % predicted (mean±SD):** 69.6±6.4 **PEF AM L/min (mean±SD):** 327±89 **Duration of asthma:** ≥ 6 mo. **Smoking status:** all ≤ 10 pack-yr **GROUP 2** **N:** 238 **Age yr. (mean±SD):** 40.7±15.1 **Males %:** 42 **FEV_1 % predicted (mean±SD):** 70.5±6.4 **PEF AM L/min (mean±SD):** 332±92 **Duration of asthma:** ≥ 6 mo. **Smoking status:** all ≤ 10 pack-yr	**GROUP 1** **Drug mcg/day:** SAL/FP 100/200 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskus®/Accuhaler™ **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** FP 500 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskus®/Accuhaler™ **Withdraw LOE:** NR **Reliever Tx:** salbutamol as needed **Run-in Tx:** SAL/FP 100/500 mcg **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • PEF AM **Secondary** • PEF PM • FEV_1 • SABA use daytime • SABA use nighttime • well controlled asthma • total asthma control • SFD • SFN • RFD • RFN	**Study objective:** To determine if SAL or FP dose can be reduced without loss of asthma control once control is obtained with SAL/FP 100/500 mcg/d. **Additional details:** Phase 1 open label tx with SAL/FP 100/500 mcg; in the randomized phase Grp 1 had FP stepped down, Grp 2 had SAL stopped. **Definition of total and well controlled asthma**: used the criteria in the GOAL study

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Bateman ED 2001[98] **Pub status:** Journal article **No. countries:** 10 **No. centers:** 69 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 497 **Analyzed:** 497 **Withdrawals:** 67 **ITT analysis: yes** **Asthma stage and severity:** symptomatic, mild-moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 165 **Age yr. (mean±SD):** 40.7±16.8 **Males %:** 44 **FEV_1 % predicted (mean):** 75 **PEF AM L/min (mean):** 353 **Duration of asthma yr. %:** 53 (<10 yr.); 47 (≥10 yr.) **Smoking status (past/current %):** 17/13 (all < 10 pack-yr.) **GROUP 2** **N:** 167 **Age yr. (mean±SD):** 38.6±17 **Males %:** 47 **FEV_1 % predicted (mean):** 76 **PEF AM L/min (mean):** 373 **Duration of asthma yr. %:** 48.5 (<10 yr.); 51.5 (≥ 10 yr.) **Smoking status (past/current %):** 25/9 (all < 10 pack-yr.) **GROUP 3** **N:** 165 **Age yr. (mean±SD):** 39.5±16 **Males %:** 41 **FEV_1 % predicted (mean):** 76 **PEF AM L/min (mean):** 354 **Duration of asthma yr. %:** 49 (<10 yr.); 51 (≥10 yr.) **Smoking status (past/current %):** 21/11 (all < 10 pack-yr.)	**GROUP 1** **Tx Drug mcg/day:** SAL/FP 100/200 + PLA **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI_{HFA} + PLA Diskus™ **Withdraw LOE n:** 1 **GROUP 2** **Drug mcg/day:** SAL/FP 100/200 + PLA **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskus™ + PLA MDI_{HFA} **Withdraw LOE n:** 2 **GROUP 3** **Drug mcg/day:** FP 200 + PLA **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI_{CFC} + PLA Diskus™ **Withdraw LOE n:** 0 **Reliever Tx:** salbutamol as needed **Run-in Tx:** Usual ICS 400-500 mcg/d BDP equivalent or FP 200-250 mcg/d **Run-in duration:** 12 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • PEF AM **Secondary** • PEF PM • diurnal variation % predicted • FEV_1 • FEV_1 % predicted • SFD • SFN • RFD	**Study objective:** To demonstrate equivalent efficacy and comparable safety of the lowest strength SAL/FP 100/200 MDI and Diskus™ and to show that SAL/FP 100/200 MDI_{HFA} was more efficacious than FP 200 via MDI_{CFC} **Additional details:** Grp 1 combination SAL/FP was delivered by an MDI using HFA propellant, Grp 3 FP was delivered in an MDI using CFC propellant

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Bergmann KC 2004[108] **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_1 % 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_1 % 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® **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** FP 1000 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskus® **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 **Secondary** • PEF PM • PEF PM % predicted • FEV_1 • FEV_1 % 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.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Boonsawat W 2008[56] **Pub status:** Journal article **No. countries:** 9 **No. centers:** 69 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**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 **FEV_1 % predicted (mean±SD):** 94.3±14.5 **PEF AM L/min (mean±SD):** 441.1**±**114.9 **Duration of asthma:** ≥ 6 mo. **Smoking status:** all <10 pack-yr **GROUP 2** **N:** 154 **Age yr. (mean±SD):** 34.0±14 **Males %:** 44 **FEV_1 % predicted (mean±SD):** 96.1±15.3 **PEF AM L/min (mean±SD):** 448.6±108.3 **Duration of asthma:** ≥ 6 mo. **Smoking status:** all <10 pack-yr **GROUP 3** **N:** 155 **Age yr. (mean±SD):** 33.4±15.3 **Males %:** 54 **FEV_1 % predicted (mean±SD):** 95.6±14.6 **PEF AM, L/min, (mean±SD):** 458.7**±**109.4 **Duration of asthma:** ≥ 6 mo. **Smoking status:** all <10 pack-yr.	**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 **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.	**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 hospitalization. **List of clinical outcomes reported:** **Primary** • PEF AM **Secondary** • PEF PM • FEV_1 • SFD • RFD • symptom control • well controlled asthma • FEF_{25-75} • exacerbations	**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 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[107] **Pub status:** Journal article **No. countries:** 1 **No. centers:** 11 **Design:** randomized, parallel, open label **Funding:** Industry: Novartis	**Randomized:** 134 **Analyzed:** 132 **Withdrawals:** 10 **ITT analysis:** no **Asthma stage and severity:** symptomatic, mild-severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 69 **PEF AM L/min (mean±SD):** 380.4±108.8 **GROUP 2** **N:** 65 **PEF AM L/min (mean±SD):** 356.4±96.2 **Total population** **Age yr. (mean±SD):** 43±14 **Males %:** 34.3 **FEV_1 % predicted (mean±SD):** NR **Duration of asthma yr. (mean±SD):** NR **Smoking status (never/past/current %):** NR	**GROUP 1** **Drug mcg/day:** FORM/BDP 24/500 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE n:** 1 **GROUP 2** **Drug mcg/day:** BDP 1000 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE n:** 1 **Reliever Tx:** salbutamol as needed **Run-in Tx:** BDP 500 mcg/d **Run-in duration:** 2 wk.	**Definition of exacerbation:** Patients requiring OCS **List of clinical outcomes reported:** **Primary** • PEF AM **Secondary** • PEF PM • FEV_1 • DTS • NTS • SABA use	**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.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Bousquet J 2007[10] **Pub status:** Journal article **No. countries:** 17 **No. centers:** 184 **Design:** randomized, parallel, double blind, double-dummy **Funding:** Industry: AstraZeneca	**Randomized:** 2,309 **Analyzed:** 2,304 **Withdrawals:** 208 **ITT analysis:** all available data **Asthma stage and severity:** symptomatic, intermittent to severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 1151 **Age yr. (mean±SD):** 40±17 **Males %:** 38 **FEV_1 % predicted (mean±SD):** 70.2±17.3 **PEF AM L/min (mean):** 330.1 **Duration of asthma yr. (mean±SD):** 14±16.5 **Smoking status (never/past/current %):** 82/13/4 (all < 10 pack-yr.) **GROUP 2** **N:** 1153 **Age yr. (mean±SD):** 39±17 **Males %:** 38 **FEV_1 % predicted (mean±SD):** 71.0±44.3 **PEF AM L/min (mean):** 329.0 **Duration of asthma yr. (mean±SD):** 13±19 **Smoking status (never/past/current %):** 82/13/5 (all < 10 pack-yr.)	**GROUP 1** **Drug mcg/day:** FORM/BUD 24/800 + PLA **Dosing:** fixed **Treatment duration:** 6 mo. **Device:** Turbuhaler® + Diskus™ **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** SAL/FP 100/1000 + PLA **Dosing:** fixed **Treatment duration:** 6 mo. **Device:** Diskus™ + Turbuhaler® **Withdraw LOE:** NR **Reliever Tx:** terbutaline as needed **Run-in Tx:** Current ICS maintenance tx + LABA if already on it **Run-in duration:** 2 wk.	**Definition of exacerbation: severe:** deterioration leading to hospitalization/ED tx and/or OCS ≥ 3 days **List of clinical outcomes reported:** **Primary** • exacerbation: time to 1st severe exacerbation • exacerbation: time to 2nd severe exacerbation **Secondary** • PEF AM • PEF PM • FEV_1 • exacerbation: rate of severe • exacerbation: time to 1st hospitalization /ED treatment • exacerbation: rate of hospitalization /ED treatments • exacerbation: total events • ACQ-5 • asthma control days • NTA • SFD • asthma symptoms • SABA use • RFD • change in ICS dose	**Study objective:** to assess efficacy of FORM/BUD plus FORM/BUD as needed to SAL/FP plus SABA as needed. **Additional details:** Each participant received 2 inhalers for maintenance: 1 Turbuhaler® either active or PLA and 1 Diskus™ either active or PLA plus 1 Turbuhaler® either FORM/BUD or PLA. **Definition of asthma control day**: day and night with no asthma symptoms, no awakenings due to asthma symptoms and no use of as-needed medication

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Boyd G 1995[73] **Pub status:** Journal article **No. countries:** 1 **No. centers:** 15 **Design:** randomized, parallel, double blind **Funding:** Industry (ND)	**Randomized:** 119 **Analyzed:** 97 **Withdrawals:** 22 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 47 **Age yr. (mean±SD):** 47±15.3 **Males %:** 40 **FEV_1 % predicted (mean±SD):** 66±18 **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_1 % predicted (mean±SD):** 66±24.8 **PEF AM L/min (mean±SD):** 289±111 **Duration of asthma:** NR **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** Usual asthma medications + SAL 200 **Dosing:** SAL was fixed; usual care NR **Treatment duration:** 12 wk. **Device:** Diskhaler® **Withdraw LOE n:** 2 **GROUP 2** **Drug mcg/day:** Usual asthma medications + PLA **Dosing:** PLA was fixed; usual care NR **Treatment duration:** 12 wk. **Device:** Diskhaler® **Withdraw LOE n:** 2 **Reliever Tx:** salbutamol as needed **Run-in Tx:** current high dose ICS (1500 mcg or equivalent) plus other current asthma therapy **Run-in duration:** 2 wk.	**Definition of exacerbation:** an acute episode requiring ED treatment or a short course of OCS. **List of clinical outcomes reported:** **Primary** • PEF AM • PEF PM **Secondary** • FEV_1 • exacerbations • FVC • DTS • NTS • SFD • SFN • SABA use	**Study objective:** To investigate the efficacy and safety of SAL in the management of chronic asthmatics currently being considered for OCS. **Additional details:** Patients carried on with current asthma treatment throughout the study.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Buhl R 2004[186] **Pub status:** Journal article **No. countries:** 1 **No. centers:** 1051 **Design:** randomized, parallel, open label **Funding:** Industry: AstraZeneca	**Randomized:** 3,297 **Analyzed:** 3,027 **Withdrawals:** 260 **ITT analysis:** yes **Asthma stage and severity:** asymptomatic after run-in (mild-moderate for inclusion) **Baseline ICS use:** non-naïve **GROUP 1** **N:** 1491 **Age yr. (mean±SD):** 37.6±10 **Males %:** 44 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 356±89.4 **Duration of asthma:** ≥ 6 mo. **Smoking status:** <10 pack-yr. and non-smoking for at least 2 yrs. pre-enrolment **GROUP 2** **N:** 1546 **Age yr. (mean±SD):** 37.3±10.2 **Males %:** 43.2 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 355±84.6 **Duration of asthma:** ≥ 6 mo. **Smoking status:** <10 pack-yr. and non-smoking for at least 2 yrs. pre-enrolment	**GROUP 1** **Drug mcg/day:** FORM/BUD 24/800 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Turbuhaler® **Withdraw LOE n:** 14 **GROUP 2** **Drug mcg/day:** FORM/BUD 12/400 **Dosing:** variable **Treatment duration:** 12 wk. **Device:** Turbuhaler® **Withdraw LOE n:** 8 **Reliever Tx:** terbutaline as needed **Run-in Tx:** FORM/BUD 24/800 mcg/d **Run-in duration:** 4 wk.	**Definition of exacerbation:** required a course of OCS and were withdrawn from the study. **List of clinical outcomes reported:** **Primary** • change in AQLQ score **Secondary** • PEF AM • PEF PM • symptom severity score (4 pt scale) • SF-36 • SABA use • NTA • SFD • asthma control days % • use of study medication • step-up tx required	**Study objective:** to assess whether adjustable dosing maintained HRQL and asthma control as effectively as fixed dosing using questionnaires and clinical measures of asthma control. **Additional details:** Patients in the variable group instructed to step up FORM/BUD to 24/800 x 1 wk. if AM PEF was < 80% of baseline, or required reliever ≥ 3 inhalations/24 hr. period, or had a nocturnal awakening due to asthma. If asthma improved stepped down to 12/400 again. If above criteria still met after 7 days they increased dose a second time to 48/1600 x 1 wk. If not controlled they contacted 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

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Buhl R 2003[72] **Pub status:** Journal article **No. countries:** 9 **No. centers:** 56 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: AstraZeneca	**Randomized:** 523 **Analyzed:** 523 **Withdrawals:** 43 **ITT analysis:** yes **Asthma stage and severity:** symptomatic- mixed asymptomatic and symptomatic, mild **Baseline ICS use:** non-naïve **GROUP 1** (FORM/BUD bid) **N:** 176 **Age yr. (mean±SD):** 44.8±14 **Males %:** 36.4 **FEV_1 % predicted (mean±SD):** 77.6±17 **PEF AM L/min (mean±SD):** 351±135 **Duration of asthma (mean±SD):** 12.3±15.5 **Smoking status (never/past/current %):** 70.5/20.5/9.0 (all < 10 pack-yr.) **GROUP 2** (FORM/BUD OD) **N:** 176 **Age yr. (mean±SD):** 42.7±14.8 **Males %:** 38 **FEV_1 % predicted (mean±SD):** 77.1±20.5 **PEF AM L/min (mean±SD):** 350±146.3 **Duration of asthma yr. (mean±SD):** 12.7±15.5 **Smoking status (never/past/current %):** 79.5/14.8/5.7 (all < 10 pack-yr.) **GROUP 3** (BUD OD) **N:** 171 **Age yr. (mean±SD):** 45.5±15 **Males %:** 39.8 **FEV_1 % predicted (mean±SD):** 77.6±24.8 **PEF AM L/min (mean±SD):** 344±129.3 **Duration of asthma yr. (mean±SD):** 14.5±15.5 **Smoking status (never/past/current %):** 74.3/17.5/8.2 (all < 10 pack-yr.)	**GROUP 1** **Drug mcg/day:** FORM/BUD 12/400 + PLA **Dosing:** fixed (bid) **Treatment duration:** 12 wk. **Device:** Turbuhaler® **Withdraw LOE n:** 4 **GROUP 2** **Drug mcg/day:** FORM/BUD 12/400 + PLA **Dosing:** fixed (OD PM) **Treatment duration:** 12 wk. **Device:** Turbuhaler® **Withdraw LOE n:** 5 **GROUP 3** **Drug mcg/day:** BUD 400 + PLA **Dosing:** fixed (OD PM) **Treatment duration:** 12 wk. **Device:** Turbuhaler® **Withdraw LOE n:** 5 **Reliever Tx:** terbutaline as needed **Run-in Tx:** BUD 400 mcg/d **Run-in duration:** 2 wk.	**Definition of exacerbation:** Mild: NTA due to asthma, or PEF ≤ 20% of baseline, or ≥ 4 inhalations of reliever/24 hr. for 2 consecutive days. Severe: deterioration requiring OCS, or PEF ≤ 30% of baseline for 2 consecutive days, or discontinuation due to worsening asthma. **List of clinical outcomes reported:** **Primary** • PEF AM **Secondary** • PEF PM • FEV_1 • asthma symptom score (0-6 scale) • asthma control days • asthma control week • SABA use • SFD • NTA • RFD • time to 1st mild exacerbation • exacerbation mild and severe incidence	**Study objective:** to examine the efficacy of FORM/BUD 6/200 mcg given bid to FORM/BUD 12/400 and BUD 400 mcg given once a day (OD) to show that one inhaler once a day is effective in patients with moderate persistent asthma. **Additional details:** To ensure blinding all patients took active drug and/or PLA twice a day. In groups 2 and 3 once a day (OD) active drug was given in the evening, PLA taken in the morning. **Definition of a well controlled asthma week**:

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Busse W 2003[137] **Pub status:** Journal article **No. countries:** 1 (United States) **No. centers:** 90 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 558 **Analyzed:** 558 **Withdrawals:** 100 **ITT analysis:** yes **Asthma stage and severity:** asymptomatic, moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 281 for 12 wk.; 155 for 24 wk. **Age yr. (mean±SD):** 38±16.3 **Males %:** 41 **FEV_1 % predicted (mean±SD):** 80.5±(9.7) **PEF AM L/min (mean±SD):** 458.0±145.8 **Duration of asthma % (≥ 15 yr.):** 5 **Smoking status (never/past/current %):** NR **GROUP 2** **N:** 277 for 12 wk.; 153 for 24 wk. **Age yr. (mean±SD):** 39±15 **Males %:** 43 **FEV_1 % predicted (mean±SD):** 80.9 (9.4) **PEF AM L/min (mean±SD):** 457.4±148.1 **Duration of asthma % (≥ 15 yr.):** 7 **Smoking status (never/past/current %):** NR	**GROUP 1** **Drug mcg/day:** SAL/FP 100/200 **Dosing:** fixed **Treatment duration:** 12-24 wk. **Device:** Diskus™ **Withdraw LOE n:** wk. 1-12. n=14; wk. 13-24 n=3 **GROUP 2** **Drug mcg/day:** FP 500 **Dosing:** fixed **Treatment duration:** 12-24 wk. **Device:** Diskus™ **Withdraw LOE n:** wk. 1-12 n= 20; wk. 13-24 n=4 **Reliever Tx:** albuterol as needed **Run-in Tx:** P1 (10-14 d) FP 500 mcg/d or equivalent; P2 (5-28 d) FP 200 mcg/d; P3 (4 wk. FP 500 mcg (to regain control)) **Run-in duration:** 12-24 wk.	**Definition of exacerbation:** worsening asthma that required non-study drugs **List of clinical outcomes reported:** **Primary** • % of pts remaining in study after 12 wk. and 24 wk. of blind therapy with no lack of efficacy. **Secondary** • PEF AM • PEF PM • FEV_1 • asthma symptom score (6 pt scale) • SFD • SABA use • NTA • RFD	**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.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Busse WW 2008[133] **Pub status:** Journal article **No. countries:** 1 **No. centers:** 145 **Design:** randomized, parallel, open label **Funding:** Industry: AstraZeneca	**Randomized:** P1: 1,222; P2: 1,169 **Analyzed:** P2: 1,215 **Withdrawals:** 157 **Analysis:** all available data **Asthma stage and severity:** stable, moderate to severe **Baseline ICS use:** non-naïve **GROUP 1 (fixed dose)** **N:** Period 1: 778; Period 2: 427 **Age yr. (mean±SD):** 39.4±15.9 **Males %:** 34 **FEV_1 % predicted (mean±SD):** 79.6±15.2 **PEF AM L/min (mean±SD):** 348.4±91.2 **Duration of asthma:** 19.6±15.6 **Smoking status:** < 20 pack-yr **GROUP 2 (adjustable dose)** **N:** Period 2: 389 **Age yr. (mean±SD):** 38.4±15.8 **Males %:** 44 **FEV_1 % predicted (mean±SD):** 79.4±16.1 **PEF AM L/min (mean±SD):** 358.5±100.7 **Duration of asthma:** 18.7±14.6 **Smoking status:** < 20 pack-yr **GROUP 3 (fixed dose)** **N:** Period 2: 406 **Age yr. (mean±SD):** 38.8±15.9 **Males %:** 43 **FEV_1 % predicted (mean±SD):** 78.1±14.3 **PEF AM L/min (mean±SD):** 350.4±93.7 **Duration of asthma:** 19.1±14.5 **Smoking status:** < 20 pack-yr	**GROUP 1** **Drug mcg/day:** FORM/BUD 24/800 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** MDI **Withdraw LOE n:** 18 **GROUP 2** **Drug mcg/day:** FORM/BUD 6-24/200-800 **Dosing:** Period 1: fixed x 1 mo.; Period 2: variable x 6 mo. **Treatment duration:** 24 wk. **Device:** MDI **Withdraw LOE n:** 19 **GROUP 3** **Drug mcg/day:** SAL/FP 100/500 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** DPI **Withdraw LOE n:** 23 **Reliever Tx:** albuterol as needed **Run-in Tx:** P1: 10-14 d remained on current asthma Tx; during P2 and P3 only study drugs allowed. **Run-in duration:** 10-14 d.	**Definition of exacerbation:** worsening asthma requiring OCS **List of clinical outcomes reported:** **Primary** • asthma control assessed by exacerbations **Secondary** • time to 1st exacerbation • number exacerbations per patient-treatment yr. • % pts. experiencing ≥1 exacerbation • FEV_1 • PEF AM • DTS (4 pt scale) • NTS (4 pt scale) • daily symptom score • SFD • awkening-free nights • SABA use • asthma control days • RFD	**Study objective:** To evaluate efficacy, tolerability, and resource use of adjustable dose FORM/BUD compared to either fixed dose FORM/BUD or SAL/FP in moderate-to-severe asthma. **Additional details:** All patients were first stabilized on fixed dose FORM/BUD. This was a 3 phase study: run-in (10-14 days); treatment x 1 mo. all on fixed dose regimens; treatment x 6 mo. on adjustable or fixed dose regimens. *Definition of asthma control day:* 24 hr. with no asthma symptoms, no NTA and no SABA use. *Adjustable dose instructions:* Patients could step-down to FORM/BUD 12/400 mcg OD if in previous 7 d: ≤ 2 inhalations/d of SABA for ≤ 2 d and no NTA. Patients could step-up to FORM/BUD 48/1600 mcg/d x 7 days if on 2 consecutive days ≥ 6 inhalations of SABA or experienced NTA. Between 7-14 days could step down to FORM/BUD 12/400 mcg/d if on 2 consecutive days: ≤ 2 inhalation/d of SABA and no NTA.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Canonica GW 2004[187] **Pub status:** Journal article **No. countries:** 1 **No. centers:** 154 **Design:** randomized, parallel, open label **Funding:** Industry: AstraZeneca	**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 **Age yr. (mean±SD):** 42.6±17 **Males %:** 48.4 **FEV_1 % 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_1 % 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 1** **Drug mcg/day:** FORM/BUD 24/400 to 800 **Dosing:** variable **Treatment duration:** 12 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **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.	**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 medications. **List of clinical outcomes reported:** **Primary** • exacerbation: frequency • change in asthma symptom severity **Secondary** • PEF % predicted • FEV_1 % predicted • SFD % • NTA #/d • symptom score (scale 0-3) • SABA use • asthma control wk. % • step-up/step-down tx. • study medication use • patient satisfaction (scale 1-10) • doctor satisfaction (scale 1-10) • days with lost activity	**Study objective:** To evaluate efficacy, tolerability, and costs of adjustable dose FORM/BUD (single inhaler) compared to fixed dosing in moderate-to-severe asthma. **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.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Chuchalin A 2008[62] **Pub status:** Journal article **No. countries:** 28 **No. centers:** 175 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 2,280 **Analyzed:** 2,258 **Withdrawals:** 315 **ITT analysis:** yes (also per protocol populations) **Asthma stage and severity:** symptomatic, mild **Baseline ICS use:** naïve **GROUP 1** **N:** 973 **Age yr. (mean±SD):** 33.8 ±15.8 **Males %:** 44 **FEV_1 % predicted (mean±SD):** 96.7±20.7 **PEF AM L/min (mean±SD):** 400.4±99.2 **Duration of asthma yr.:** ≥6 mo. **Smoking status (never/past/current %):** 77/15/9 **GROUP 2** **N:** 970 **Age yr. (mean±SD):** 33.8±16 **Males %:** 42 **FEV_1 % predicted (mean±SD):** 96.1±14.2 **PEF AM L/min (mean±SD):** 395.1±96.1 **Duration of asthma yr.:** ≥6 mo. **Smoking status (never/past/current %):** 78/15/8 **GROUP 3** **N:** 315 **Age yr. (mean±SD):** 35.0±16.5 **Males %:** 39 **FEV_1 % predicted (mean±SD):** 98.0±19.0 **PEF AM L/min (mean±SD):** **393.8±**96.4 **Duration of asthma yr.:** ≥6 mo **Smoking status (never/past/current %):** 78/14/7	**GROUP 1** **Drug mcg/day:** SAL/FP 50/100 (AM) + PLA (PM) **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** Diskus™/Accuhaler™ **Withdraw LOE n:** 7 **GROUP 2** **Drug mcg/day:** FP 100 (AM) + FP 100 (PM) **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** Diskus™/Accuhaler™ **Withdraw LOE n:** 5 **GROUP 3** **Drug mcg/day:** PLA (AM + PM) **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** Diskus™/Accuhaler™ **Withdraw LOE n:** 8 **Reliever Tx:** Salbutamol as needed **Run-in Tx:** SABA as needed **Run-in duration:** 2 wk.	**Definition of exacerbation:** Mild: AM PEF > 20% below baseline; SABA use greater than baseline on more than 3 occasions/24 hrs.; or NTA; all on ≥ 2 consecutive days. Moderate: required OCS based on AM PEF > 30% below baseline on ≥ 2 consecutive days. Severe: required hospitalization **List of clinical outcomes reported:** **Primary** • PEF AM • exacerbation: rate (moderate/severe) **Secondary** • FEV_1 • exacerbation: hospitalization/ER visits • exacerbation: outpatient/practice visits • asthma symptom score (6 pt scale) • NTA • ACQ • SABA use • asthma control • SFD % • FEV_{25-75} • well controlled asthma • totally controlled asthma	**Study objective:** to test the hypothesis that once daily SAL/FP 50/100 mcg is non-inferior to twice daily FP 100 mcg as initial therapy in mild asthma. **Additional details:** Only study drugs allowed except OCS for an exacerbation. **Definition of well controlled and totally controlled asthma**: Composite measures based on GINA and NIH guidelines

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Chuchalin AG 2002[46] **Pub status:** Journal article **No. countries:** 1 **No. centers:** NR **Design:** randomized, parallel, double blind, double dummy **Funding:** NR	**Randomized:** 333 **Analyzed:** 333 **Withdrawals:** 17 ITT analysis: yes (also per protocol populations **Asthma stage and severity:** mild-to-moderate **Baseline ICS use:** naïve **GROUP 1** **N:** 111 **Age yr. (mean±SD):** 44.1±9 **Males %:** 22.5 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 288.0±89.4 **Duration of asthma yr. (mean±SD):** ≥ 6 mo. **Smoking status (never/past/current %):** all < 10 pack-yr **GROUP 2** **N:** 114 **Age yr. (mean±SD):** 46.7±11.8 **Males %:** 28.1 **FEV1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 285.7±89.4 **Duration of asthma yr. (mean±SD):** ≥ 6 mo. **Smoking status (never/past/current %):** all < 10 pack-yr **GROUP 3** **N:** 108 **Age yr. (mean±SD):** 43.6 ±12 **Males %:** 22.2 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 304.7±92.7 **Duration of asthma yr. (mean±SD):** ≥ 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:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • PEF AM **Secondary** • FEV_1 • FVC • PEF PM • SABA use • asthma symptoms (4 pt scale) • SF-36 • AQLQ	**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 allowed.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Condemi JJ 1999[110] **Pub status:** Journal article **No. countries:** 1 **No. centers:** 36 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 437 **Analyzed:** 388 **Withdrawals:** 39 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, moderate, severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 221 **Age yr. (mean±SD):** 36.9±13.4 **Males %:** 38 **FEV_1 % predicted (mean±SD):** 60.9±11.0 **PEF AM L/min (mean±SD):** 363.6±116.0 **Duration of asthma ≥ 10yr. %:** 76 **Smoking status (never/past/current %):** 77/23/0 **GROUP 2** **N:** 216 **Age yr. (mean±SD):** 36.8±13.2 **Males %:** 40 **FEV_1 % predicted (mean±SD):** 61.8±10.9 **PEF AM L/min (mean±SD):** 36.07±111.7 **Duration of asthma ≥ 10yr. %:** 78 **Smoking status (never/past/current %):** 80/20/0	**GROUP 1** **Drug mcg/day:** 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:** 2-4 wk.	**Definition of exacerbation:** any asthma event that required treatment with OCS or parenteral CS **List of clinical outcomes reported:** **Primary** • PEF AM **Secondary** • PEF PM • FEV_1 AM • pts experiencing 1 exacerbation • pts experiencing ≥1 exacerbation • wheeze (5 pt scale) • SOB (5 pt scale) • chest tightness (5 pt scale) • cough (5 pt scale) • combined symptoms (5 pt scale) • SABA use • NTA • nights with 0 awakenings	**Study objective:** To evaluate the 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 period.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Corren J 2007[47] **Pub status:** Journal article **No. countries:** 1 **No. centers:** 56 **Design:** randomized, parallel, double blind, double-dummy **Funding:** Industry: AstraZeneca	**Randomized:** 480 **Analyzed:** 454 **Withdrawals:** 133 **ITT analysis:** all available data **Asthma stage and severity:** asymptomatic, mild-moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 123 **Age yr. (mean±SD):** 37.2±15.7 **Males %:** 37.4 **FEV_1 % predicted (mean±SD):** 70.6±10.3 **PEF AM L/min (mean±SD):**350±**95** **Duration of asthma yr. (mean±SD):** 20.2±12.5 **Smoking status:** all < 10 pack-yr **GROUP 2** **N: 1**21 **Age yr. (mean±SD):** 37.1±15.9 **Males %:** 38 **FEV_1 % predicted (mean±SD):** 70.0±10.1 **PEF AM L/min (mean±SD**): 353±82 **Duration of asthma yr. (mean±SD):** 19.5±13.0 **Smoking status:** all < 10 pack-yr **GROUP 3** **N:** 114 **Age yr. (mean±SD):** 35.3±16.0 **Males %:** 36.8**7.9**.1 **FEV_1 % predicted (mean±SD):** 70.6±10.1 **PEF AM L/min (mean±SD):** 359±87 **Duration of asthma yr. (mean±SD):** 19.7± 12.3 **Smoking status:** all < 10 pack-yr **GROUP 4** **N:** 122 **Age yr. (mean±SD):** 36.1±14.5 **Males %:** 38.5 **FEV_1 % predicted (mean±SD):** 69.7±9.8 **PEF AM L/min (mean±SD):** 350±93 **Duration of asthma:** 20.8±13.7 **Smoking status:** all < 10 pack-yr	**GROUP 1** **Drug mcg/day:** FORM/BUD 24/400 + PLA **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE n:** 9 **GROUP 2** **Drug mcg/day:** BUD 400 + PLA **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE n:** 8 **GROUP 3** **Drug mcg/day:** FORM 24 + PLA **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Turbuhaler® **Withdraw LOE n:** 21 **GROUP 4** **Drug mcg/day:** PLA + PLA **Dosing:** **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE:** 40 **Reliever Tx:** albuterol as needed **Run-in Tx:** PLA. All current asthma medications discontinued **Run-in duration:** 1-3 wk.	**Definition of exacerbation:** worsening asthma requiring ED treatment, hospitalization, or non-study drugs. **List of clinical outcomes reported:** **Primary** • FEV_1 AM • FEV_1 12 hr. mean **Secondary** • PEF AM • PEF PM • DTS (4 pt scale) • NTS (4 pt scale) • asthma symptom score (4 pt scale) • SABA use • worsening asthma • awakening free nights • SFD	**Study objective:** To compare efficacy and tolerability of FORM/BUD combined to FORM and BUD and PLA alone. **Additional details:** All groups received an MDI and a Turbuhaler®. Only study medications allowed. **Criteria for worsening asthma**: • A decrease in AM FEV1 ≥ 20% of baseline or a decrease to < 45% predicted. • ≥ 12 uses of SABA/d on ≥ 3 of 7 consecutive days. • A decrease in AM PEF ≥ 20% of baseline on ≥ 3 of 7 consecutive days. • Night awakenings requiring SABA on ≥ 2 of 7 consecutive nights. • Exacerbation requiring ED treatment, hospitalization, or non-study drugs.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Creticos PS 1999[55] **Pub status:** Journal article **No. countries:** 1 (United States) **No. centers:** 1 **Design:** randomized, parallel **Funding:** NR	**Randomized:** 46 **Analyzed:** NR **Withdrawals:** NR **ITT analysis**: not clear **Asthma stage and severity:** symptomatic, mild-moderate **Baseline ICS use:** naïve **GROUP 1** **N:** NR **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** NR **Duration of asthma yr. (mean±SD):** NR **Smoking status (never/past/current %):** NR **GROUP 2** **N:** NR **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** NR **Duration of asthma yr. (mean±SD):** NR **Smoking status (never/past/current %):** NR **GROUP 3** **N:** NR **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** NR **Duration of asthma yr. (mean±SD):** NR **Smoking status (never/past/current %):** NR **Total population** **N:** 46 **Age yr. (mean):** 35 **Males %:** 43.5 **FEV_1 % predicted (mean):** all ≥ 65	**GROUP 1** **Drug mcg/day:** SAL/TAA 100/800 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** NR **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** TAA 800 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** NR **Withdraw LOE:** NR **GROUP 3** **Drug mcg/day:** SAL 100 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** NR **Withdraw LOE:** NR **Reliever Tx:** NR **Run-in Tx:** observational period **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • methacholine sensitivity **Secondary** • FEV_1	**Study objective:** to examine effects of primary therapy with TAA compared to SAL alone and to SAL plus TAA in symptomatic asthma **Additional details:** Very little data reported

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Dahl R 2006[128] **Pub status:** Journal article **No. countries:** 18 **No. centers:** 178 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 1,397 **Analyzed:** 1,391 (ITT) **Withdrawals:** 133 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 697 **Age yr. (mean±SD):** 47.1±16.0 **Males %:** 41 **FEV_1 % predicted (mean±SD):** 78.5±18.2 **PEF AM L/min (mean±SD):** 348.4±111.47 **Duration of asthma:** 6 mo. to ≥ 25 yr **Smoking status (never/past/current %):** all < 10 pack-yr **GROUP 2** **N:** 694 **Age yr. (mean±SD):** 45.6±18.3 **Males %:** 44 **FEV_1 % predicted (mean±SD):** 78.7±17.9 **PEF AM L/min (mean±SD):** 357.6±122.45 **Duration of asthma yr. (mean±SD):** 6 mo. to ≥ 25 yr **Smoking status (never/past/current %):** all < 10 pack-yr	**GROUP 1** **Drug mcg/day:** FORM/BUD 24/800 + PLA **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** Turbuhaler® **Withdraw LOE:** 2 **GROUP 2** **Drug mcg/day:** SAL/FP 100/500 + PLA **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** Diskus™/Accuhaler™ **Withdraw LOE:** 5 **Reliever Tx:** salbutamol as required **Run-in Tx:** current ICS 1000-2000 mcg/d. No LABAs x 4 wk. prior to study **Run-in duration:** 2 wk.	**Definition of exacerbation:** Mild: AM PEF > 20% below baseline; SABA use greater than baseline on more than 3 occasions/24 hrs.; or NTA; all on ≥ 2 consecutive days. Moderate: required OCS 40-60 mg/d x 7-10 days based on AM PEF > 30% below baseline on ≥ 2 consecutive days or clinical deterioration assessed by investigator. Severe: required hospitalization **List of clinical outcomes reported:** **Primary** • exacerbation: rate/24 weeks **Secondary** • PEF AM • PEF AM % predicted • FEV_1 • exacerbation requiring OCS • exacerbation requiring hospital admission • DTS • NTS • SABA use • SFD • SFN • RFD • well-controlled asthma week	**Study objective:** To compare the efficacy of FORM/BUD 24/800 mcg/d to SAL/FP 100/500 mcg/d in patients with persistent asthma currently on ICS 1000-2000 mcg/d. **Additional details:** To ensure blinding each group received both inhalers *Well controlled asthma week defined as:* at least 2 of 3 of the following: symptom score > 1 on no more than 2 days; no more than 2 days of SABA use (maximum 4 x/wk.); AM PEF ≥ 80% predicted every day plus all of the following: no NTA, exacerbations, ED visits, or treatment related AEs forcing a change in therapy.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: DiFranco A 1999[54] **Pub status:** Journal article **No. countries:** 1 (Italy) **No. centers:** 1 **Design:** randomized, parallel, open label, single blind **Funding:** NR	**Randomized:** 33 **Analyzed:** 24 **Withdrawals:** 9 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, mild **Baseline ICS use:** naïve **GROUP 1** **N:** 10 **Age yr. (mean±SD):** 32±8.5 **Males %:** 91 **FEV_1 % predicted (median±SD):** 99±16.5 **PEF AM L/min (mean±SD):** NR **Duration of asthma yr. (mean±SD):** 10±5.8 **Smoking status (never/past/current %):** 91/9/0 **GROUP 2** **N:** 5 **Age yr. (mean±SD):** 42±13.5 **Males (%):** 27.3 **FEV_1 % predicted (mean±SD):** 92±10.8 **PEF AM L/min (mean±SD):** NR **Duration of asthma yr. (mean±SD):** 10±7.3 **Smoking status (never/past/current %):** 36.4/54.5/9 **GROUP 3** **N:** 9 **Age yr. (mean±SD):** 26±11.8 **Males %:** 63.6 **FEV_1 % 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	**GROUP 1** **Drug mcg/day:** SAL/BDP 100/1000 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** MDI **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** BDP 1000 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** MDI **Withdraw LOE:** NR **GROUP 3** **Drug mg/day:** nedocromil sodium 16 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** MDI **Withdraw LOE:** NR **Reliever Tx:** NR **Run-in Tx:** SABA as needed **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • FEV_1 % pred **Secondary** • PEF • asthma symptom score • PC_{20}	**Study objective:** To compare efficacy of SAL/BDP to BDP alone and NS alone. **Additional details:** 2 participants withdrew due to asthma exacerbation. Group not reported.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Fitzgerald JM 2005[11] **Pub status:** Journal article **No. countries:** 15 **No. centers:** 91 **Design:** randomized, parallel, double blind, double dummy **Funding:** Government, institution, industry: GlaxoSmithKline	**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_1 % 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_1 % predicted (mean±SD):** 82±21 **Mean PEF AM (mean±SD):** 357±103 **Duration of asthma (mean±SD):** 197±57 **Smoking status:** <10 pack-yr.	**GROUP 1** **Drug mcg/day:** FORM/BUD 24/800, 12/400, 6 /200 **Dosing:** variable **Treatment duration:** 52 wk. **Device:** Turbuhaler® **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.	**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 control weeks	**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).

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Fitzgerald JM 1999[90] **Pub status:** Journal article **No. countries:** 1 (Canada) **No. centers:** 15 **Design:** randomized, parallel, double blind **Funding:** Industry: Novartis	**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 **FEV_1 % 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 **FEV_1 % 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 **FEV_1 % predicted (mean±SD):** 79.7±16.4 **Mean PEF AM (mean±SD):** 438±86 **Duration of asthma (mean±SD):** NR **Smoking status:** non-smokers	**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 **Reliever Tx:** albuterol prn **Run-in Tx:** PLA dry powder 4x/day; albuterol prn **Run-in duration:** 2 wk.	**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_{20} **Secondary** • change in FEV_1 • FEV_1 • asthma symptom score • daytime SABA use • nighttime SABA use • frequency of exacerbation days	**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.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Fowler SJ 2002[77] **Pub status:** Journal article **No. countries:** 1 (Scotland) **No. centers:** 1 **Design:** randomized, parallel, double blind, 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_1 % predicted (mean±SD):** NR **Mean PEF AM (mean±SD):** NR **Duration of asthma:** NR **Smoking status:** NR **GROUP 2** **N:** 20 **Age:** 16-70 **Males %:** NR **FEV_1 % 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® **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_{20} **Secondary** • PEF % predicted • PEF AM • PEF PM • PEF_{25-75} • FEV_1 • FEV_1 % 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

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Greening AP 1994[111] **Pub status:** Journal article **No. countries:** 1 (United Kingdom) **No. centers:** 1 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 429 **Analyzed:** 426 **Withdrawals:** 136 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, intermittent to severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 220 **Age yr. (mean±SD):** 48±15 **Males %:** 46 **FEV_1 % predicted:** NR **Mean PEF AM (mean±SD):** 349±109 **Duration of asthma (median [range]):** 11.1 yr. (0.7-53) **Smoking status – never/prev/current (n [%]):** 104(47) / 57(26) / 59(27) **GROUP 2** **N:** 206 **Age yr. (mean±SD):** 47±15 **Males %:** 41 **FEV_1 % predicted:** NR **Mean PEF AM (mean±SD):** 339±99 **Duration of asthma (median [range]):** 11 yr. (0.1-62.6) **Smoking status – never/prev/current (n [%]):** 106(51) / 46(22) / 54(26)	**GROUP 1** **Drug mcg/day:** SAL/BDP 100 /400 **Dosing:** fixed **Treatment duration:** 26 wk. **Device:** diskhaler **Withdraw LOE:** NR **GROUP 2** **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.	**Definition of exacerbation:** Mild = increased use of relief medication. Moderate = requiring a short course of oral corticosteroids. Severe = requiring hospital admission. **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 • self-reported symptom frequency • NTA • SABA use • AE **Secondary** No secondary outcome measures reported	**Study objective:** To compare two options in a randomized controlled trial – an increase in the inhaled corticosteroid dose and the addition of salmeterol xinafoate**.**

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Grutters J 1999[59] **Pub status:** Journal article **No. countries:** 1 (The Netherlands) **No. centers:** 2 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 40 **Analyzed:** 40 **Withdrawals:** 0 **ITT analysis: yes** **Asthma stage and severity:** asymptomatic, intermittent-moderate **Baseline ICS use:** naïve **GROUP 1** **N:** 12 **Age yr. (mean±SD):** 27± 20.8 **Males %:** 6 (50) **FEV_1 % predicted (mean±SD):** 79±17.3 **Mean PEF AM (mean±SD):** NR **Duration of asthma:** NR **Smoking status:** NR **GROUP 2** **N:** 15 **Age yr. (mean±SD):** 26±19.4 **Males %:** 62 **FEV_1 % predicted (mean±SD):** 86±15.5 **Mean PEF AM (mean±SD):** NR **Duration of asthma:** NR **Smoking status:** NR **GROUP 3** **N:** 13 **Age yr. (mean±SD):** 31±25.2 **Males %:** 38 **FEV_1 % predicted (mean±SD):** 79±10.8 **Mean PEF AM (mean±SD):** NA **Duration of asthma:** NR **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** SAL/BDP 100/800 **Dosing:** fixed **Treatment duration:** 8 wk. **Device:** Diskhaler® **Withdraw LOE:** 0 **GROUP 2** **Drug mcg/day:** BDP 800 **Dosing:** fixed **Treatment duration:** 8 wk. **Device:** Diskhaler® **Withdraw LOE:** 0 **GROUP 3** **Drug mcg/day:** SAL 100 **Dosing:** fixed **Treatment duration:** 8 wk. **Device:** Diskhaler® **Withdraw LOE:** 0 **Reliever Tx:** salbutamol 400 mcg prn **Run-in Tx:** SAL prn **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • FEV_1 % predicted **Secondary** • response to allergens • inflammatory responses	**Study objective:** To investigate whether regular antiasthma treatment including salmeterol could modulate the priming-sensitive cytotoxic mechanisms of human eosinophils.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Ind PW 2004[188] **Pub status:** Journal article **No. countries:** 1 (United Kingdom) **No. centers:** 365 **Design:** randomized, parallel, open label **Funding:** Industry: AstraZeneca	**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_1 % 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_1 % predicted:** NR **PEF AM (mean±SD):** NR **Duration of asthma:** NR **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** FORM/BUD 18/640 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Turbuhaler® **Withdraw LOE:** 8 **GROUP 2** **Drug mcg/day:** FORM/BUD 9-36/320-1,280 **Dosing:** variable **Treatment duration:** 12 wk. **Device:** Turbuhaler® **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.	**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	**Study objective:** To examine the effect of a symptom-driven, self-management plan in a large asthma population receiving budesonide/formoterol 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.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Ind PW 2003[76] **Pub status:** Journal article **No. countries:** 6 **No. centers:** 100 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 502 **Analyzed:** 496 **Withdrawals:** 64 **ITT analysis: no** **Asthma stage and severity:** symptomatic, intermittent to severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 171 **Age yr. (mean±SD):** 44.8±15.6 **Males %:** 41 **FEV_1 % predicted:** NR **PEF AM (mean±SD):** 347±93 **Duration of asthma:** 12 (0.2-64) (median(range)) **Smoking status – prev/current (n [%]):** 48(40)/23(13) **GROUP 2** **N:** 160 **Age yr. (mean±SD):** 43.9±14.9 **Males %:** 50 **FEV_1 % predicted:** NR **PEF AM (mean±SD):** 357±104 **Duration of asthma (median [range]):** 11 (0.4-65) **Smoking status – prev/current (n [%]):** 48 (29)/ 39 (24) **GROUP 3** **N:** 165 **Age yr. (mean±SD):** 45.7±15.2 **Males %:** 49 **FEV_1 % predicted:** NR **PEF AM (mean±SD):** 347±101 **Duration of asthma (median [range]):** 15 (1-68) **Smoking status – prev/current (n [%]):** 51 (32)/25 (16)	**GROUP 1** **Drug mcg/day:** SAL/FP 100/500 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** MDI **Withdraw LOE:** 12 **GROUP 2** **Drug mcg/day:** FP 1000 mcg **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** MDI **Withdraw LOE:** NR **GROUP 3** **Drug mcg/day:** FP 500 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** MDI **Withdraw LOE:** NR **Reliever Tx:** salbutamol prn, unblended FP 250 mcg, oral prednisolone for use in an exacerbation **Run-in Tx:** FP 250 bid and salbutamol prn **Run-in duration:** 4 wk.	**Definition of exacerbation:** Mild = requiring clinically significant increase in relief medication. Moderate = requiring the use of additional corticosteroid. Severe = requiring emergency hospital treatment. **List of clinical outcomes reported:** **Primary** • PEF AM **Secondary** • PEF PM • total exacerbations • number mild exacerbations • number moderate exacerbations • number severe exacerbations • SFD • SFN • medication free days	**Study objective:** To see whether the benefit of adding salmeterol was superior to that of doubling the dose of FP to 500 mcg bid, while also including a control group who continued treatment with low-dose FP (250 mcg bid).

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Jenkins C 2000[80] **Pub status:** Journal article **No. countries:** NR **No. centers:** 44 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 353 **Analyzed:** 353 **Withdrawals:** 59 **ITT analysis:** yes **Asthma stage and severity:** moderate to severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 180 **Age (mean [range]):** 45 (16-75) **Males %:** 50 **FEV_1 % predicted (mean [range]):** 68 (33-105) **PEF AM (mean±SD):** NR **Duration of asthma** (n(%) 0-1yr./1-5yr./5-10yr./>10yr.)**:** 10(5)/34(19)/31(17)/105(58) **Smoking status:** NR **GROUP 2** **N:** 143 **Age (mean [range]):** 48 (14-80) **Males %:** 50 **FEV_1 % predicted (mean [range]):** 72 (37-109) **PEF AM (mean±SD):** NR **Duration of asthma** (n(%) 0-1yr./1-5yr./5-10yr./>10yr.)**:** 11(6)/28(16)/28(16)/106(62) **Smoking status:** NR	**GROUP 1** **Drug/mcg per d.:** SAL/FP 100/500 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** Diskhaler® **Withdraw LOE:** 7 **GROUP 2** **Drug/mcg per d.:** BUD 1600 + PLA **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** Turbuhaler® **Withdraw LOE:** 9 **Reliever Tx:** salbutamol prn **Run-in Tx:** usual ICS and salbutamol prn **Run-in duration:** 2 wk.	**Definition of exacerbation:** Severe = deterioration in asthma requiring emergency hospital treatment. Moderate = requiring administration of additional inhaled corticosteroids, bronchodilators and/or oral corticosteroids. Mild = a deterioration in asthma requiring an increase in the use of relief medication which the physician considered to be clinically relevant. **List of clinical outcomes reported:** **Primary** • PEF AM **Secondary** • PEF PM • PEF % diurnal variation • FEV_1 • FEV_1 % predicted • number exacerbations • SFD • SFN • RFD • SAE	**Study objective:** to compare the efficacy and tolerability of a SAL/FP combination (SFC 50/250 mcg bid) with a three-fold higher microgram dose (3:1 ratio) of inhaled corticosteroid (budesonide 1600 mcg/day) in patients with moderate to severe persistent asthma remaining symptomatic on a moderate to high corticosteroid dose (800-1200 mcg/day.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Jenkins C 2006[93] **Pub status:** Journal article **No. countries:** 6 **No. centers:** 54 **Design:** randomized, parallel, double blind **Funding:** Industry: AstraZeneca	**Randomized:** 456 **Analyzed:** 451 **Withdrawals:** 57 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 222 **Age yr. (mean [range]):** 46 (13-79) **Males %:** 36 **FEV_1 % predicted:** **PEF AM (mean±SD):** NR **Duration of asthma (mean [range]):** 8 (1-56) **Smoking status:** NR **GROUP 2** **N:** 114 **Age yr. (mean [range]):** 47 (12-79) **Males %:** 40 **FEV_1 % predicted:** NR **PEF AM (mean±SD):** NR **Duration of asthma (mean [range]):** 10 yr. (1-66) **Smoking status:** NR **GROUP 3** **N:** 115 **Age yr. (mean [range]):** 46 (13-74) **Males %:** 43 **FEV_1 % predicted:** NR **PEF AM (mean±SD):** NR **Duration of asthma (mean [range]):** 8 yr. (1-61) **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** FORM/BUD 36/1600 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Turbuhaler® **Withdraw LOE:** **GROUP 2** **Drug mcg/day:** FORM/BUD (separate inhalers) 36/1600 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** NR **Withdraw LOE:** **GROUP 3** **Drug mcg/day:** BUD 1600 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** NR **Withdraw LOE:** **Reliever Tx:** terbutaline 0.5 mcg prn **Run-in Tx:** current ICS therapy **Run-in duration:** 2 wk.	**Definition of exacerbation:** Mild exacerbation day – a day with one of the following: ≥20% decrease in morning PEF from baseline; night-time awakening(s) due to asthma; or an increase of ≥4 inhalations of reliever medication over a 24-hr period compared with baseline. Mild exacerbation – two consecutive mild exacerbation days of the same type. **List of clinical outcomes reported:** **Primary** • PEF AM **Secondary** • PM PEF • FEV_1 % predicted • exacerbations • DTS • NTS • total daily symptom score (0-6) • nighttime SABA use • daytime SABA use • SFD • RFD	**Study objective:** To assess the efficacy and safety of a higher dose of BUD/FORM in patients with persistent symptomatic asthma.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Johansson G 2001[112] **Pub status:** Journal article **No. countries:** 6 **No. centers:** 39 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 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 **FEV_1 % 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 **FEV_1 % 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® **Withdraw LOE:** 0 **GROUP 2** **Drug mcg/day:** BUD 800 + PLA **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskhaler® **Withdraw LOE:** 1 **Reliever Tx:** salbutamol prn **Run-in Tx:** current ICS and salbutamol **Run-in duration:** 2 wk.	**Definition of exacerbation:** Mild = increased relief medication use. Moderate = additional corticosteroids (inhaled and/or oral). Severe = emergency hospital treatment. **List of clinical outcomes reported:** **Primary** • PEF AM **Secondary** • PEF PM • PEF diurnal variation • FEV_1 • number of exacerbations • DTS • NTS • SFD • SFN • SABA use • AE	**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.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Kavuru M 2000[81] **Pub status:** Journal article **No. countries:** 1 (United States) **No. centers:** 42 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 356 **Analyzed:** 335 **Withdrawals:** 126 **ITT analysis:** yes **Asthma stage and severity:** asymptomatic, intermittent to moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 87 **Age yr. (mean [range]):** 38 (12-70) **Males %:** 59 **FEV_1 % predicted (mean):** 64 **PEF AM (mean±SD):** 393±98.9 **Duration of asthma:** NR **Smoking status:** NR **GROUP 2** **N:** 85 **Age yr. (mean [range]):** 39 (12-67) **Males %:** 52 **FEV_1 % predicted (mean):** 64 **PEF AM (mean±SD):** 374±104.2 **Duration of asthma:** NR **Smoking status:** NR **GROUP 3** **N:** 86 **Age yr. (mean [range]):** 37 (12-67) **Males %:** 51 **FEV_1 % predicted (mean):** 64 **PEF AM (mean±SD):** 369±88.1 **Duration of asthma:** NR **Smoking status:** NR **GROUP 4** **N:** 77 **Age yr. (mean [range]):** 35 (12-66) **Males %:** 51 **FEV_1 % predicted (mean):** 64 **PEF AM (mean±SD):** 382±102.7 **Duration of asthma:** NR **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** SAL/FP 100/200 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskus® **Withdraw LOE:** 3 **GROUP 2** **Drug mcg/day:** FP 200 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** diskhaler **Withdraw LOE:** 9 **GROUP 3** **Drug mcg/day:** SAL 100 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** diskhaler **Withdraw LOE:** 30 **GROUP 4** **Drug mcg/day:** PLA **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** single drugs **Withdraw LOE:** 38 **Reliever Tx:** albuterol prn **Run-in Tx:** PLA **Run-in duration:** 2 wk.	**Definition of exacerbation:** Clinical exacerbation – requiring emergency treatment, hospitalization, or asthma medication not allowed by protocol. **List of clinical outcomes reported:** **Primary** • mean change FEV_1 • probability of remaining in study over time **Secondary** • mean change in PEF PM • % days no symptoms • % nights no awakenings • asthma symptoms 0-5 • SABA use	**Study objective:** To compare the efficacy and safety of SAL/FP 50 mcg/100 mcg in a combination dry powder product administered twice daily with that of FP or SAL at the same doses in patients previously treated with low doses of inhaled corticosteroids or SAL.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Kelsen SG 1999[114] **Pub status:** Journal article **No. countries:** 1 (United States) **No. centers:** 34 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 483 **Analyzed:** 476 **Withdrawals:** 97 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 236 **Age yr. (mean±SD):** 42.2±13.8 **Males %:** 43 **FEV_1 % predicted (mean±SD):** 64.93±10.1 **PEF AM (mean±SD):** NR **Duration of asthma:** NR **Smoking status:** non-smoking **GROUP 2** **N:** 240 **Age yr. (mean±SD):** 42.0±12.4 **Males %:** 35 **FEV_1 % predicted (mean±SD):** 64.14±10.1 **PEF AM (mean±SD):** NR **Duration of asthma:** NR **Smoking status:** non-smoking	**GROUP 1** **Drug mcg/day:** SAL/BDP 100 /400 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** MDI **Withdraw LOE:** **GROUP 2** **Drug mcg/day:** BDP 800 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** MDI **Withdraw LOE:** **Reliever Tx:** albuterol **Run-in Tx:** BDP 400 mcg/day and albuterol prn **Run-in duration:** 2 wk.	**Definition of exacerbation:** Asthma exacerbation = any event requiring treatment with oral or parenteral corticosteroids or any other asthma medication not allowed as concurrent therapy during study participation. **List of clinical outcomes reported:** **Primary** • FEV_1 **Secondary** • PEF PM • DTS • exacerbations • daytime albuterol use • nightime awakenings • nighttime albuterol use	**Study objective:** To evaluate the efficacy of SAL administered via metered-dose inhaler in the management of asthma in adults symptomatic while receiving inhaled BDP at a dosage less than 400 mcg daily compared with doubling the dose of BDP.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Kemp JP 1998[82] **Pub status:** Journal article **No. countries:** 1 (United States) **No. centers:** 44 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 506 **Analyzed:** NR **Withdrawals:** 72 **ITT analysis:** yes **Asthma stage and severity:** mixed asymptomatic and symptomatic, intermittent to severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** NR **Age yr. (mean±SE):** 42±1.0 **Males %:** 45 **FEV_1 % predicted:** NA **PEF AM (mean±SE):** 372±7 **Duration of asthma:** NR **Smoking status:** NR **GROUP 2** **N:** NR **Age yr. (mean±SE):** 41.6±1.0 **Males %:** 48 **FEV_1 % predicted:** 63±1 **PEF AM (mean±SE):** 369±6 **Duration of asthma:** NR **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** SAL/BDP SAL/Flunisolide, SAL/TAA 84/252-840, 84/1000-2000, 84/600-1600 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE:** <1% **GROUP 2** **Drug mcg/day:** BDP, Flunisolide, TAA 252-840, 1000-2000, 600-1600 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE:** 4% **Reliever Tx:** albuterol prn **Run-in Tx:** current ICS + albuterol prn **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • mean change in AQLQ **Secondary** • mean change in PEF AM • mean change in PEF PM • mean change from BL in diurnal variation • mean change in FEV1 • DTS • NTS • SFD • Reliever use	**Study objective:** To evaluate the impact of salmeterol on disease-specific quality of life with the AQLQ, as well as the efficacy and safety of salmeterol in patients with stable asthma who were symptomatic despite daily use of ICS.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Kerwin EM 2008[61] **Pub status:** Journal article **No. countries:** 2 (Canada, United States) **No. centers:** 103 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 844 **Analyzed:** 844 **Withdrawals:** 140 **ITT analysis:** yes – all who were randomized and received at least one dose of double-blind study medication **Asthma stage and severity:** symptomatic, intermittent-severe **Baseline ICS use:** naïve **GROUP 1** **N:** 210 **Age yr. (mean±SD):** 33.4±12.9 **Males %:** 40 **FEV_1 % predicted:** 74.4±10.8 **PEF AM (mean±SD):** 348±5.5 **Duration of asthma:** > 3 mo **Smoking status:** NR **GROUP 2** **N:** 210 **Age yr. (mean±SD):** 33.5±13.4 **Males %:** 50 **FEV_1 % predicted:** 72.8±10.3 **PEF AM (mean±SD):** 349±5.6 **Duration of asthma:** > 3 mo **Smoking status:** NR **GROUP 3** **N:** 212 **Age yr. (mean±SD):** 31.7±12.7 **Males %:** 47 **FEV_1 % predicted:** 74.5±10.5 **PEF AM (mean±SD):** 348±5.7 **Duration of asthma:** > 3 mo **Smoking status:** NR **GROUP 4** **N:** 212 **Age yr. (mean±SD):** 33±13.7 **Males %:** 48 **FEV_1 % predicted:** 73.2±10.8 **PEF AM (mean±SD):** 344±5.0 **Duration of asthma:** > 3 mo **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** SAL/FP 50/250 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskus® **Withdraw LOE:** 4 **GROUP 2** **Drug mcg/day:** SAL/FP 100/200 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskus® **Withdraw LOE:** 4 **GROUP 3** **Drug mcg/day:** FP 250 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskus® **Withdraw LOE:** 6 **GROUP 4** **Drug mcg/day:** PLA **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** single drugs **Withdraw LOE:** 17 **Reliever Tx:** albuterol **Run-in Tx:** albuterol prn + PLA **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • PEF PM % predicted **Secondary** • PEF PM • PEF AM • 2 hr post-dose PM PEF • FEV_1 • withdrawal due to exacerbation • 24-h symptom score • SABA use • withdrawal due to worsening asthma	**Study objective:** To assess the effectiveness of FL/SAL via a single inhaler (FSC) administered once daily compared with FP once daily, FSC twice daily, or placebo.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Kips JC 2000[138] **Pub status:** Journal article **No. countries:** 3 **No. centers:** 3 **Design:** randomized, parallel, double blind **Funding:** Industry: AstraZeneca	**Randomized:** 60 **Analyzed:** NR **Withdrawals:** NR **ITT analysis:** yes **Asthma stage and severity:** asymptomatic, intermittent to severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** NR **Age yr. (mean [range]):** 34.7 (19-59) **Males %:** 41.4 **FEV_1 % predicted (mean±SE):** 84.4±3.6 **PEF AM (mean±SE):** 414.7±22.3 **Duration of asthma:** ≥6 mo. **Smoking status:** NR **GROUP 2** **N:** NR **Age yr. (mean [range]):** 37.6 (19-69) **Males %:** 38.7 **FEV_1 % predicted (mean±SE):** 82.2±2.9 **PEF AM (mean±SE):** 396.3±18.6 **Duration of asthma:** ≥6 mo. **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** FORM/BUD 24/200 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** BUD 800 + PLA **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **Reliever Tx:** terbutaline **Run-in Tx:** BUD 800 mcg bid + terbutaline prn **Run-in duration:** 4 wk.	**Definition of exacerbation:** Mild – 1) morning or evening PEF >20% below baseline; 2) rescue terbutaline use of more than four inhalations per 24h above baseline; 3) awakenings due to asthma. Severe – if OCS were required either as judged by the investigator or after a decrease in morning or evening peak flow by more than 30% below baseline on two consecutive days. **List of clinical outcomes reported:** **Primary** • no primary clinical outcomes **Secondary** • FEV_1 % predicted • mild exacerbations • severe exacerbations • episode-free days	**Study objective:** To compare in patients with asthma the effect of a 1-yr treatment with budesonide (100 mcg, twice daily) plus the LA β2-agonist formoterol (12 mcg, twice daily) versus budesonide (400 mcg, twice daily) on markers of airway inflammation in induced sputum.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Koenig SM 2008[95] **Pub status:** Journal article **No. countries:** 3 **No. centers:** 55 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 466 **Analyzed:** 466 **Withdrawals:** 145 **ITT analysis:** no **Asthma stage and severity:** NR, moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 156 **Age yr. (mean [range]):** 34.8 (12-81) **Males %:** 38 **FEV_1 % predicted (mean±SD):** 77±119.9 **Mean PEF AM (mean±SD):** 401±168.6 **Duration of asthma:** > 3 mo **Smoking status:** NR **GROUP 2** **N:** 156 **Age yr. (mean [range]):** 34.8 (12-81) **Males %:** 36 **FEV_1 % predicted (mean±SD):** 79±114.9 **Mean PEF AM (mean±SD):** 409±167.4 **Duration of asthma:** > 3 mo **Smoking status:** NR **GROUP 3** **N:** 154 **Age yr. (mean [range]):** 33.2 (12-72) **Males %:** 49 **FEV_1 % predicted (mean±SD):** 79±119.1 **Mean PEF AM (mean±SD):** 407±161.3 **Duration of asthma:** > 3 mo **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** SAL/FP (BHR) Class 1: PLA; Class 2 to 4: 100/200; Class 3: 100/500; Class 4: 100/1000 **Dosing:** variable **Treatment duration:** 40 wk. **Device:** diskhaler **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** FP Class 1: PLA; Class 2: 200; Class 3: 500; Class 4: 1000 **Dosing:** variable **Treatment duration:** 40 wk. **Device:** diskhaler **Withdraw LOE:** NR **GROUP 3** **Drug mcg/day:** FP Class 1: PLA; Class 2: 200; Class 3: 500; Class 4: 1000 **Dosing:** variable **Treatment duration:** 40 wk. **Device:** diskhaler **Withdraw LOE:** NR **Reliever Tx:** albuterol **Run-in Tx:** continued treatment with SABA, anticholinergic, or ICS **Run-in duration:** 2 wk.	**Definition of exacerbation:** Exacerbation – worsening asthma for which treatment with medication other than the double-blind study drugs or study-provided albuterol was necessary, and was treated with the prednisone **List of clinical outcomes reported:** **Primary** • average daily ICS dose **Secondary** • PEF AM • PEF PM • pre-dose FEV_1 • SFD • RFD • SFD • NTA • SABA use	**Study objective:** To determine whether adding a LABA to an ICS would control bronchial hyperresponsiveness (BHR) at an overall lower dose of ICS when titration of medication was based upon the assessment of routine clinical measures with or without the measurement of BHR.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Koopmans JG 2006[78] **Pub status:** Journal article **No. countries:** 1 (The Netherlands) **No. centers:** 1 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**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_1 % 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_1 % predicted (mean±SD):** 93.1±16.1 **Mean PEF AM (mean±SD):** 422±102 **Duration of asthma:** NA **Smoking status:** all non-smoking	**GROUP 1** **Drug mcg/day:** SAL/FP 100/500 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** Diskus® **Withdraw LOE:** 0 **GROUP 2** **Drug mcg/day:** FP 500 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** Diskus® **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.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • No primary clinical outcomes **Secondary** • PEF PM • FEV_1 % predicted • DTS • NTS	**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.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Kuna P 2007[129] **Pub status:** Journal article **No. countries:** 16 **No. centers:** 235 **Design:** randomized, parallel, double blind **Funding:** Industry: AstraZeneca	**Randomized:** 3,335 **Analyzed:** 3,321 **Withdrawals:** 149 **ITT analysis:** no **Asthma stage and severity:** symptomatic, intermittent to moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 1,103 **Age yr. (mean±SD):** 38±17 **Males %:** 43 **FEV_1 % predicted (mean±SD):** 72±14 **Mean PEF AM (mean):** 337 **Duration of asthma:** NR **Smoking status – never/prev/current (n):** 873/178/56 **GROUP 2** **N:** 1,099 **Age yr. (mean±SD):** 38±17 **Males %:** 41 **FEV_1 % predicted (mean±SD):** 73±14 **Mean PEF AM (mean):** 335 **Duration of asthma:** NR **Smoking status – never/prev/current (n):** 865/169/71 **GROUP 3** **N:** 1,119 **Age yr. (mean±SD):** 38±17 **Males %:** 43 **FEV_1 % predicted (mean±SD):** 73±14 **Mean PEF AM (mean):** 338 **Duration of asthma:** NR **Smoking status – never/prev/current (n):** 904/165/54	**GROUP 1** **Drug mcg/day:** FORM/BUD 12/400 **Dosing:** variable **Treatment duration:** 26 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** FORM/BUD 24/800 **Dosing:** fixed **Treatment duration:** 26 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 3** **Drug mcg/day:** SAL/FP 100/500 **Dosing:** fixed **Treatment duration;** 26 wk. **Device:** MDI **Withdraw LOE:** NR **Reliever Tx:** terbutaline prn **Run-in Tx:** regular ICS and terbutaline **Run-in duration:** 2 wk.	**Definition of exacerbation:** Severe – deterioration in asthma resulting in hospitalization or ER treatment, or the need for oral steroids ≥3 days (as judged by the investigator). Mild – two consecutive mild exacerbation days. Mild exacerbation day – a day with any one of the following: morning PEF ≥20% below baseline, daily as-needed medication use ≥2 inhalations above baseline or a night with an asthma-related awakening. **List of clinical outcomes reported:** **Primary** • time to first severe exacerbation **Secondary** • PEF PM • FEV_1 • total no. severe exacerbations • total no. mild exacerbations • symptom score • SABA use • NTA • SFD • RFD	**Study objective:** To compare BUD/FORM for maintenance and relief with SAL/FP and a fixed maintenance dose of BUD/FORM, both with terbutaline for relief **Additional Details:** SMART® study

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Kuna P 2006[45] **Pub status:** Journal article **No. countries:** 8 **No. centers:** 61 **Design:** randomized, parallel, double blind **Funding:** Industry: AstraZeneca	**Randomized:** 617 **Analyzed:** 616 **Withdrawals:** 61 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, mild,moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 202 **Age yr. (mean [range]):** 45.8 (18-80) **Males %:** 41 **FEV_1 % predicted (mean [range]):** 79.3 (37-115) **PEF AM (mean [range]):** 356 (115-648) **Duration of asthma (mean [range]):** 11.5 (1-63) **Smoking status:** ≤10pack-yr **GROUP 2** **N:** 207 **Age yr. (mean [range]):** 43.9 (19-80) **Males %:** 38 **FEV_1 % predicted (mean [range]):** 77.9 (23-123) **PEF AM (mean [range]):** 351 (173-692) **Duration of asthma (mean [range]):** 12.2 (0-50) **Smoking status:** ≤10 pack-yr **GROUP 3** **N:** 207 **Age yr. (**mean (range))**:** 45.1 (18-78) **Males %:** 44 **FEV_1 % predicted (mean [range]):** 78.3 (38-119) **PEF AM (mean [range]):** 368 (200-500) **Duration of asthma (mean [range]):** 10.6 (1-58) **Smoking status:** ≤10pack-yr	**GROUP 1** **Drug mcg/day:** FORM/BUD 12/200 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Turbuhaler® **Withdraw LOE:** 10 **GROUP 2** **Drug mcg/day:** FORM/BUD 12/200 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Turbuhaler® **Withdraw LOE:** 5 **GROUP 3** **Drug mcg/day:** BUD 200 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Turbuhaler® **Withdraw LOE:** 11 **Reliever Tx:** terbutaline sulfate or another preferred SABA prn **Run-in Tx:** BUD 200 mcg/day **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • PEF AM **Secondary** • PEF PM • FEV_1 • symptoms score 0-3 • % medication free days • NTA • asthma-control days	**Study objective:** To compare the efficacy and safety of a low dose of BUD/FORM (80/4.5 mcg, 2 inhalations) administered once daily with that of twice-daily BUD/FORM (80/4.5 mcg, 1 inhalation administered in the morning and the evening) and a corresponding once-daily dose of BUD (200 mcg, 1 inhalation in the evening) in patients with mild to moderate asthma.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Lalloo UG 2003[113] **Pub status:** Journal article **No. countries:** 7 **No. centers:** 51 **Design:** randomized, parallel, double blind **Funding:** Industry: AstraZeneca	**Randomized:** 467 **Analyzed:** 467 **Withdrawals:** 37 **ITT analysis:** yes **Asthma stage and severity:** intermittent-moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 230 **Age yr. (mean [range]):** 42 (18-77) **Males %:** 44 **FEV_1 % predicted (mean [range]):** 82 (38-117) **PEF AM (mean [range]):** 362 (153-665) **Duration of asthma ((mean [range]):** 12 yr. (0-47) **Smoking status:** < 10 pack/years-yr **GROUP 2** **N:** 237 **Age yr. (mean [range]):** 40 (18-78) **Males %:** 41 **FEV_1 % predicted (mean [range]):** 81 (42-137) **PEF AM (mean [range]):** 362 (109-643) **Duration of asthma (mean [range]):** 11 yr. (0-53) **Smoking status:** < 10 pack-yr	**GROUP 1** **Drug mcg/day:** FORM/BUD 12/200 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** BUD 400 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** NR **Withdraw LOE:** **Reliever Tx:** terbutaline or salbutamol (patient preference) **Run-in Tx:** BUD 100 mcg bid **Run-in duration:** 2 wk.	**Definition of exacerbation:** Mild = two consecutive mild exacerbation days (of the dame criterion). Severe = nighttime awakening due to asthma, a 20% decrease in PEF from baseline, or more than four inhalations of reliever medication over a 24-hr period. **List of clinical outcomes reported:** **Primary** • mean change PEF AM • mean change PEF PM **Secondary** • mean change in FEV_1 • mean change in FEV_1 % predicted • DTS • NTS • asthma aggravation • Reliever use • nightime awakenings • FVC	**Study objective:** to evaluate the efficacy and safety of low-dose budesonide/formoterol, 80/4.5 mcg bid in a single inhaler compared with an increased dose of budesonide, 200 mcg bid, in adult patients with mild-to-moderate asthma not fully controlled on low doses of ICS.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Langton Hewer S 1995[83] **Pub status:** Journal article **No. countries:** 1 (United Kingdom) **No. centers:** 1 **Design:** randomized, parallel, double blind **Funding:** Institution	**Randomized:** 23 **Analyzed:** 23 **Withdrawals:** 2 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 11 **Age yr. (mean [range]):** 15 (12-17) **Males %:** 55 **FEV_1 % predicted:** NR **PEF AM (mean±SD):** NR **Duration of asthma:** 13 **Smoking status:** NR **GROUP 2** **N:** 12 **Age yr. (mean [range]):** 14 (12-16) **Males %:** 83 **FEV_1 % predicted:** Fig 1 **PEF AM (mean±SD):** NR **Duration of asthma:** NR **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** SAL/ICS 200/(ND) high dose **Dosing:** fixed **Treatment duration:** 8 wk. **Device:** diskhaler **Withdraw LOE:** 0 **GROUP 2** **Drug mcg/day:** ICS (ND) high dose **Dosing:** fixed **Treatment duration:** 8 wk. **Device:** diskhaler **Withdraw LOE:** 0 **Reliever Tx: NR** **Run-in Tx:** current dose ICS (ND) **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 **Secondary** • FEV_1 • FEV_1 % predicted AM • nighttime symptom score • exacerbations • SFD • SFN	**Study objective:** To evaluate the efficacy and safety of SAL 100 mcg bid in a group of children considered to have chronic severe asthma.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Lemanske RF 2001[79] **Pub status:** Journal article **No. countries:** 1 (United States) **No. centers:** 6 **Design:** randomized, parallel, triple blind, double dummy **Funding:** Government and Industry (various)	**Randomized:** 167 **Analyzed:** 167 **Withdrawals:** 23 **ITT analysis: yes** **Asthma stage and severity:** mixed asymptomatic and symptomatic, mild **Baseline ICS use:** non-naïve **GROUP 1** **N:** 74 **Age yr. (mean±SD):** 35.7±12.25 **Males %:** 53 **FEV_1 % predicted (mean±SD):** 73.81±(10.43) **PEF AM (mean±SD):** 445.6±124.2 **Duration of asthma:** NR **Smoking status:** <10 pack-yr and no smoking in past year **GROUP 2** **N:** 74 **Age yr. (**mean±SD**):** 34.23±10.8 **Males %:** 47 **FEV_1 % predicted (mean±SD):** 73.78±11.24 **PEF AM (mean±SD):** 425.3±125.3 **Duration of asthma:** NR **Smoking status:** <10 pack/yr. and no smoking in past year **GROUP 3** **N:** 19 **Age yr. (mean±SD):** 35.58±14.39 **Males %:** 42 **FEV_1 % 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	**GROUP 1** **Drug mcg/day:** SAL/TAA 100/800 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** MDI **Withdraw LOE:** 4 **GROUP 2** **Drug mcg/day:** SAL/TAA 100/400 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** MDI **Withdraw LOE:** 12 **GROUP 3** **Drug mcg/day:** TAA 400 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** MDI **Withdraw LOE:** 1 **Reliever Tx:** albuterol **Run-in Tx:** TAA 400 mcg bid and albuterol prn **Run-in duration:** 6 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • Time to treatment failure **Secondary** • PEF PM • FEV_1 • DTS • NTS • PC_{20}	**Study objective:** To determine whether ICS therapy can be reduced or eliminated in patients with persistent asthma after adding a long-acting β_2-agonist to their treatment regimen. **Additional Details:** Triamcinolone reduction phase weeks 3-10, triamcinolone elimination phase weeks 11-18.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Leuppi JD 2003[189] **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_1 % 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_1 % 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® **Withdraw LOE:** 1 **GROUP 2** **Drug mcg/day:** FORM/BUD, 12-48 /400-1600 **Dosing:** variable **Treatment duration:** 12 wk. **Device:** Turbuhaler® **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_1 • 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**

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Li X 1999[86] **Pub status:** Journal article **No. countries:** 1 (Australia) **No. centers:** NR **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 50 **Analyzed:** 45 **Withdrawals:** 5 **ITT analysis: no** **Asthma stage and severity:** symptomatic, mild-moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 13 **Age yr. (mean [range]):** 38 (20-70) **Males %:** 61.5 **FEV_1 % predicted (median [range]):** 84 (63-106) **PEF AM (mean [range]):** 474 (301-625) **Duration of asthma:** NR **Smoking status:** all nonsmokers **GROUP 2** **N:** 16 **Age yr. (mean [range]):** 42 (22-63) **Males %:** 68.8 **FEV_1 % predicted (median [range]):** 80 (61-102) **PEF AM (mean [range]):** 420 (341-531) **Duration of asthma:** NR **Smoking status:** all nonsmokers **GROUP 3** **N:** 16 **Age yr. (mean [range]):** 33 (22-68) **Males %:** 43.8 **FEV_1 % predicted (median [range]):** 83 (61-109) **PEF AM (mean [range]):** 404 (280-623) **Duration of asthma:** NR **Smoking status:** all nonsmokers	**GROUP 1** **Drug mcg/day:** SAL/BUD/BDP 200-500/ 100/100-500 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** diskhaler **Withdraw LOE:** 2 **GROUP 2** **Drug mcg/day:** FP/BUD/BDP 200-500/200/100-500 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** diskhaler **Withdraw LOE:** 0 **GROUP 3** **Drug mcg/day:** ICS 100-500 **Dosing:** fixed **Treatment duration;** 12 wk. **Device:** diskhaler **Withdraw LOE:** 1 **Reliever Tx:** albuterol prn **Run-in Tx:** ICS at pre-study dose up to 500 mcg BDP or BUD + albuterol 200 mcg prn **Run-in duration:** 2-6 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • bronchial biopsy results **Secondary** • exacerbation leading to withdrawal • PD_{20}	**Study objective:** To determine the effects of 12-wk treatment with SAL on "allergic" inflammation of the airways, as well as clinical status, in a clinically relevant group.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Lundbäck B 2006[84] **Pub status:** Journal article **No. countries:** 1 (Sweden) **No. centers:** 3 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 282 **Analyzed:** 282 **Withdrawals:** 19 **ITT analysis:** no **Asthma stage and severity:** symptomatic, mild-moderate **Baseline ICS use:** naïve & non-naïve **GROUP 1** **N:** 95 **Age yr. (mean±SD):** 39.9±11.9 **Males %:** 34 **FEV_1 % predicted (mean):** 92.1 **PEF AM (mean±SD):** NR **Duration of asthma:** NR **Smoking status (% current):** 14 **GROUP 2** **N:** 92 **Age yr. (mean±SD):** 39.1±12.0 **Males %:** 42 **FEV_1 % predicted (mean):** 93 **PEF AM (mean±SD):** NR **Duration of asthma:** NR **Smoking status (% current):** 12 **GROUP 3** **N:** 95 **Age yr. (mean±SD):** 40.7±12.3 **Males %:** 37 **FEV_1 % predicted (mean):** 94.9 **PEF AM (mean±SD):** NR **Duration of asthma:** NR **Smoking status (% current):** 17	**GROUP 1** **Drug mcg/day:** SAL/FP 100/500 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** diskhaler **Withdraw LOE:** 0 **GROUP 2** **Drug mcg/day:** FP 500 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** diskhaler **Withdraw LOE:** 0 **GROUP 3** **Drug mcg/day:** SAL 100 **Dosing:** fixed **Treatment duration;** 52 wk. **Device:** diskhaler **Withdraw LOE:** 0 **Reliever Tx:** salbutamol dry powder (0.2 mg) or salbutamol aerosol (0.1 mg) **Run-in Tx:** P1: previous therapy; P2: ICS reduced to BUD 400 mcg **Run-in duration:** 8 wk.	**Definition of exacerbation:** any deterioration in asthma that required an increase in rescue medication use (beta-agonist) over that used during the run-in period of >6 puffs/day for ≥2 consecutive days, or and increase of ≥2 doses/day in regular inhaled medication (study medication or additional ICS) for ≥2 days by the patient's own decision, or ≥2 days when asthma symptoms prevented the patient's work or normal activities. **List of clinical outcomes reported:** **Primary** • % pts required increase in study medication **Secondary** • PEF AM • PEF diurnal variation • FEV_1 • FVC • no. pts with ≥ 2 exacerbations • SFN • SFD • PC_{20} • RFD • RFN	**Study objective:** To assess asthma control using salmeterol plus FP in combination (SFC) versus salmeterol or FP as monotherapy in patients with mild to moderate asthma.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Lundborg M 2006[190] **Pub status:** Journal article **No. countries:** 1 (Sweden) **No. centers:** 53 **Design:** randomized, parallel, open label **Funding:** Industry: AstraZeneca	**Randomized:** 491 **Analyzed:** 489 **Withdrawals:** 61 **ITT analysis:** no **Asthma stage and severity:** mixed asymptomatic and symptomatic (75% stable, symptomatic5% unstable), intermittent, moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** NR **Age yr. (mean±SD):** 39.7±19.6 **Males %:** 43 **FEV_1 % predicted (mean±SD):** 95.7±13.7 **PEF AM (mean±SD):** NR **Duration of asthma (mean±SD):** NR **Smoking status:** ≤ 10 pack-yr **GROUP 2** **N:** NR **Age yr. (mean±SD):** 38.2±20.6 **Males %:** 49 **FEV_1 % predicted (mean±SD):** 96.2±14.7 **PEF AM (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 **FEV_1 % predicted (mean±SD):** 96.5±15.2 **PEF AM (mean±SD):** NR **Duration of asthma (mean±SD):** NR **Smoking status:** ≤ 10 pack-yr	**GROUP 1** **Drug mcg/day:** FORM/BUD 6/200 **Dosing:** variable (also relief med) **Treatment duration:** 24 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** FORM/BUD 9/400 **Dosing:** variable (also relief med) **Treatment duration:** 24 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 3** **Drug mcg/day:** FORM/BUD 18/800 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **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 wk.	**Definition of exacerbation:** One or several of the following: an asthma-related serious adverse event, treatment at a medical care centre with parenteral or nebulised bronchodilators, use of ICS or OCS due to worsening of asthma and/or withdrawal from the study because of need of added asthma maintenance therapy. **List of clinical outcomes reported:** **Primary** • PEF AM • Asthma Control Questionnaire **Secondary** • time to first exacerbation • exacerbation rate over 6 mo. • symptom score • no. inhalations of extra FORM/BUD (Groups A & B) or FORM (Group C) • Asthma Treatment Questionnaire • % asthma controlled days	**Study objective:** To evaluate efficacy and cost-effectiveness of FORM/BUD maintenance (one dose 1-2x daily) plus additional doses as needed (SMART®) compared with a higher fixed dose of FORM/BUD with FORM as needed in patients with persistent asthma.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Mitchell C 2003[115] **Pub status:** Journal article **No. countries:** 1 (Australia) **No. centers:** 16 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: Novartis	**Randomized:** 203 **Analyzed:** 201 **Withdrawals:** 19 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, intermittent to severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 100 **Age yr. (mean±SD):** 43.9±14.9 **Males %:** 45.1 **FEV_1 % predicted (mean±SD):** 71.83±11.56 **PEF AM (mean±SD):** 352.2±119.8 **Duration of asthma yr. (mean±SD):** 26.5±15.9 **Smoking status: G1 (current and previous smokers %):** 51.9 **GROUP 2** **N:** 101 **Age yr. (mean±SD):** 43.86±15.4 **Males %:** 43.6 **FEV_1 % predicted (mean±SD):** 72.37±11.16 **PEF AM (mean±SD):** 349.7±103.0 **Duration of asthma yr. (mean±SD):** 29.4±14.7 **Smoking status (current and previous smokers %):** 46.5	**GROUP 1** **Drug mcg/day:** FORM/BDP 24/1000 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Aerolizer **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** BDP 2000 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Aerolizer **Withdraw LOE:** NR **Reliever Tx:** salbutamol **Run-in Tx:** BDP 500 mcg bid + salbutamol prn **Run-in duration:** 2-4 wk.	**Definition of exacerbation:** Mild = asthma symptom score of 3 and increased use of rescue medication. Moderate = treatment with a course or oral corticosteroids and/or nebulised β2-andrenoceptor agonists. Severe = hospitalization caused by an asthma exacerbation if the adverse event was considered to be related to the study medication. **List of clinical outcomes reported:** **Primary** • PEF AM **Secondary** • FEV_1 • DTS • NTS • % pts symptomatic • daytime SABA use	**Study objective:** To compare the effect of the addition of the LABA formoterol to medium-high doses of ICS with that of doubling the dose of ICS, in patients with poorly-controlled, moderate-to-severe asthma. **Additional Details: NA**

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Molimard M 2001[85] **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_1 % 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_1 % 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 β_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 • FEV_1 • 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.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Morice AH 2007[96] **Pub status:** Journal article **No. countries:** 8 **No. centers:** 62 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: AstraZeneca	**Randomized:** 680 **Analyzed:** 668 **Withdrawals:** 79 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, moderate-severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 223 **Age yr. (mean [range]):** 39 (11-78) **Males %:** 38.9 **FEV_1 % predicted (mean [range]):** 69 (50-90) **PEF AM (mean [range]):** 321 (93-668) **Duration of asthma (mean [range]):** 9 yr. (1-63) **Smoking status – current (n (%)):**11 (5) **GROUP 2** **N:** 229 **Age yr. (mean [range]):** 40 (12-78) **Males %:** 40.2 **FEV_1 % predicted (mean [range]):** 71 (39-92) **PEF AM (mean [range]):** 326 (89-715) **Duration of asthma (mean [range]):** 8 yr. (1-58) **Smoking status – current (n (%)):**13 (6) **GROUP 3** **N:** 216 **Age yr. (mean [range]):** 40 (12-79) **Males %:** 31.3 **FEV_1 % 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 (%)):** 14 (6)	**GROUP 1** **Drug mcg/day:** FORM/BUD 18/800 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Turbuhaler® **Withdraw LOE:** 2 **GROUP 2** **Drug mcg/day:** FORM/BUD 18/800 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE:** 11 **GROUP 3** **Drug mcg/day:** BUD 800 **Dosing:** fixed **Treatment duration;** 12 wk. **Device:** MDI **Withdraw LOE:** 15 **Reliever Tx:** terbutaline prn **Run-in Tx:** current ICS; stopped previous LABA use **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • PEF AM **Secondary** • PEF PM • FEV_1 • symptom score • SABA use • NTA • SFD • RFD • asthma control days • AQLQ	**Study objective:** To compare the efficacy and safety of a novel hydrofluoroalkane (HFA) pressurized metered-dose inhaler (pMDI) formulation of BUD/FORM with that of budesonide pMDI and **Additional Details:** Comparing HFA pressurized MDI with a DPI

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Murray JJ 1999[117] **Pub status:** Journal article **No. countries:** 1 (United States) **No. centers:** 35 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 514 **Analyzed:** 514 **Withdrawals:** 107 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, moderate-severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 260 **Age yr. (mean±SD):** 42.2±12.9 **Males %:** 41 **FEV_1 % predicted (mean±SD):** 65.2±10.5 **PEF AM (mean±SD):** 390.2±95.1 **Duration of asthma:** NR **Smoking status:** NR **GROUP 2** **N:** 254 **Age yr. (mean±SD):** 41.9±14.3 **Males %:** 45 **FEV_1 % predicted (mean±SD):** 64.0±10.8 **PEF AM (mean±SD):** 381.6±95.6 **Duration of asthma:** NR **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** SAL/BDP 100/400 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** MDI **Withdraw LOE:** 5 **GROUP 2** **Drug mcg/day:** BDP 800 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** MDI **Withdraw LOE:** 5 **Reliever Tx:** albuterol prn **Run-in Tx:** BDP 200 mcg bid + albuterol prn **Run-in duration:** 2 wk.	**Definition of exacerbation:** events requiring treatment with any asthma medication excluded during study participation, including oral and parenteral corticosteroids. **List of clinical outcomes reported:** **Primary** • PEF AM • FEV_1 **Secondary** • PEF PM • total exacerbations • exacerbation leading to hospitalization • asthma symptom score • SFD • SABA use • diurnal varation PEF AM • diurnal variation PEF PM • RFD	**Study objective:** To determine whether the addition of salmeterol to existing ICS therapy provides greater therapeutic benefit than doubling the dose of inhaled corticosteroids in symptomatic patients with asthma.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Murray JJ 2004[64] **Pub status:** Journal article **No. countries:** 1 (United States **No. centers:** 33 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 267 **Analyzed:** 267 **Withdrawals:** 39 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, mild-severe **Baseline ICS use:** naïve **GROUP 1** **N:** 88 **Age yr. (mean [range]):** 36 (12-75) **Males %:** 47 **FEV_1 % predicted (mean):** 66 **PEF AM (mean±SD):** 347.9±92.9 **Duration of asthma:** ≥6 mo **Smoking status:** <10 pack-yr **GROUP 2** **N:** 89 **Age yr. (mean [range]):** 32 (12-64) **Males %:** 51 **FEV_1 % predicted (mean):** 65 **PEF AM (mean±SD):** 358±100 **Duration of asthma:** ≥6 mo **Smoking status:** <10 pack-yr **GROUP 3** **N:** 90 **Age yr. (mean [range]):** 34 (12-58) **Males %:** 40 **FEV_1 % predicted (mean):** 66 **PEF AM (mean±SD):** 349±97.7 **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:** Diskus® **Withdraw LOE:** 4 **GROUP 2** **Drug mcg/day:** FP 200 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskus® **Withdraw LOE:** 2 **GROUP 3** **Drug mcg/day:** SAL 100 **Dosing:** fixed **Treatment duration;** 12 wk. **Device:** Diskus® **Withdraw LOE:** 5 **Reliever Tx:** albuterol **Run-in Tx:** albuterol **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • FEV_1 AUC **Secondary** • PEF AM • PEF PM • asthma symptom score • SABA use • SFD • SFN	**Study objective:** To compare the efficacy and safety of initiating maintenance therapy with an inhaled, LABA and an ICS administered from a single device with that of the individual agents alone.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Nathan RA 2006[94] **Pub status:** Journal article **No. countries:** 1 (United States) **No. centers:** 45 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 365 **Analyzed:** 365 **Withdrawals:** 122 **ITT analysis: yes** **Asthma stage and severity:** symptomatic, intermittent to severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 94 **Age yr. (mean [range]):** 38.8 (13-69) **Males %:** 39 **FEV_1 % predicted (mean±SD):** 68.3±11.6 **PEF AM (mean±SD):** 342.6±93.1 **Duration of asthma:** NR **Smoking status:** no pts smoked in last year and <10 pack-yr. **GROUP 2** **N:** 91 **Age yr. (mean [range]):** 39.1 (12-82) **Males %:** 37 **FEV_1 % predicted (mean±SD):** 69.0±10.5 **PEF AM (mean±SD):** 344.4±91.6 **Duration of asthma:** NR **Smoking status:** no pts smoked in last year and <10 pack-yr. **GROUP 3** **N:** 91 **Age yr. (mean [range]):** 37.5 (12-73) **Males %:** 38 **FEV_1 % predicted (mean±SD):** 68.5±11.4 **PEF AM (mean±SD):** 344.3±88.7 **Duration of asthma:** NR **Smoking status:** no pts smoked in last year and <10 pack-yr. **GROUP 4** **N:** 89 **Age yr. (mean [range]):** 41.1 (12-76) **Males %:** 44 **FEV_1 % predicted (mean±SD):** 67.5±12.3 **PEF AM (mean±SD):** 347.4±93.4 **Duration of asthma:** NR **Smoking status:** no pts smoked in last year and <10 pack-yr.	**GROUP 1** **Drug mcg/day:** SAL/FP 100/500 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE:** 7 **GROUP 2** **Drug mcg/day:** FP 500 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE:** 11 **GROUP 3** **Drug mcg/day:** SAL 100 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE:** 23 **GROUP 4** **Drug mcg/day:** PLA **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** single drugs **Withdraw LOE:** 48 **Reliever Tx:** albutarol prn **Run-in Tx:** current ICS therapy and albuterol as needed **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • PEF AM AUC **Secondary** • PEF PM • daily symptom score • SABA use • NTA • SFN • SFD	**Study objective:** To compare the efficacy and tolerability of the combination of FP and SAL delivered via a single HFA MDI with those of its 2 components alone delivered via a CFC MDI and placebo delivered via HFA MDI in adolescent and adult patients with persistent asthma that were not controlled by medium doses (equivalent to FP 500-800 mcg/day) of ICS **Additional Details:** Compares HFA to CFC propellant

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Nelson HS 2003[57] **Pub status:** Journal article **No. countries:** 1 (United States) **No. centers:** 33 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 283 **Analyzed:** 283 **Withdrawals:** 26 **ITT analysis:** no **Asthma stage and severity:** symptomatic, intermittent-severe **Baseline ICS use:** naïve **GROUP 1** **N:** 95 **Age yr. (mean [range]):** 29.2 (12-77) **Males %:** 52 **FEV_1 % predicted:** 67.2 **PEF AM (mean±SD):** 356.4±88.0 **Duration of asthma:** >6 mo. **Smoking status:** NR **GROUP 2** **N:** 97 **Age yr. (mean [range]):** 33.6 (12-76) **Males %:** 53 **FEV_1 % predicted:** 64.7 **PEF AM (mean±SD):** 361.4±87.5 **Duration of asthma:** >6 mo. **Smoking status:** NR **GROUP 3** **N:** 91 **Age yr. (mean [range]):** 34.3 (12-67) **Males %:** 53 **FEV_1 % predicted:** 66.0 **PEF AM (mean±SD):** 363.8±86.0 **Duration of asthma:** >6 mo. **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** SAL/FP 100/200 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE:** 1 **GROUP 2** **Drug mcg/day:** FP 200 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE:** 3 **GROUP 3** **Drug mcg/day:** SAL 100 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE:** 7 **Reliever Tx:** albuterol prn **Run-in Tx:** PLA MDI + albuterol prn **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • FEV_1 AUC • **Secondary** • PEF PM • FEV_1 • daily symptom score (scale 0-5) • SABA use • SFD • RFD • nights with no awakenings	**Study objective:** To compare the efficacy and safety of twice-daily FP 100 mcg and SAL 50 mcg combined in a CFC-free MDI with the individual agents alone, each delivered through an MDI containing CFC propellants, in patients with persistent asthma previously uncontrolled with as-needed SABA alone. **Additional Details:** SAL/FP (CFC-free) compared to individual agents through MDI containing CFC propellants.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Nielsen LP 1999[139] **Pub status:** Journal article **No. countries:** 1 (Denmark) **No. centers:** multicenter (ND) **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 34 **Analyzed:** NR **Withdrawals:** NR **ITT analysis:** yes **Asthma stage and severity:** asymptomatic, mild-moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** NR **Age yr. (mean):** 45 **Males %:** 33 **FEV_1 % predicted (mean):** 86.1 **PEF AM (mean±SD):** NR **Duration of asthma yr. (mean):** 15.4 **Smoking status (current n [%]):** 5 (33) **GROUP 2** **N:** NR **Age yr. (mean):** 43 **Males %:** 53 **FEV_1 % predicted (mean):** 86.7 **PEF AM (mean±SD):** NR **Duration of asthma yr. (mean):** 12.9 **Smoking status (current n [%)]:** 9 (47.4)	**GROUP 1** **Drug mcg/day:** SAL/BDP 100/800-1,600 **Dosing:** variable **Treatment duration:** NR **Device:** Diskhaler® **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** BDP 800-1,600 + PLA **Dosing:** variable **Treatment duration:** NR **Device:** Diskhaler® **Withdraw LOE:** NR **Reliever Tx:** salbutamol prn **Run-in Tx:** P1: switched to BDP at doses equivalent to 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.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • PEF AM • PEF PM • FEV_1 **Secondary** • symptom score • DTS • NTS • SFD • SABA use • MAD	**Study objective:** To determine whether SAL had steroid-sparing properties in stable asthma patients already receiving maintenance ICS **Additional Details:** Assessment of MAD (defined as the dose one step above the dose resulting in unstable asthma).

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Noonan M 2006[92] **Pub status:** Journal article **No. countries:** 1 (United States) **No. centers:** 84 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: AstraZeneca	**Randomized:** 596 **Analyzed:** 585 **Withdrawals:** 225 **ITT analysis:** yes **Asthma stage and severity:** NR, moderate, severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 121 **Age yr. (mean±SD):** 41.8±15.5 **Males %:** 35.5 **FEV_1 % predicted (mean±SD):** 67.5±11.5 **PEF AM (mean):** 341 **Duration of asthma (mean±SD):** 23.1±15.1 **Smoking status:** ≤10 pack-yr history **GROUP 2** **N:** 113 **Age yr. (mean±SD):** 40.3±14.7 **Males %:** 43.5 **FEV_1 % predicted (mean±SD):** 66.9±10.9 **PEF AM (mean):** 338 **Duration of asthma (mean±SD):** 21.7±13.4 **Smoking status:** ≤10 pack-yr. **GROUP 3** **N:** 109 **Age yr. (mean±SD):** 40.7±14.2 **Males %:** 34.9 **FEV_1 % predicted (mean±SD):** 70.0±10.5 **PEF AM (mean):** 342 **Duration of asthma (mean±SD):** 23.2±16.0 **Smoking status:** ≤10 pack-yr. **GROUP 4** **N:** 118 **Age yr. (mean±SD):** 40.0±16.4 **Males %:** 35.0 **FEV_1 % predicted (mean±SD):** 67.5±11.5 **Mean PEF AM (mean):** 339 **Duration of asthma (mean±SD):** 21.7±15.3 **Smoking status:** ≤10 pack-yr.	**GROUP 1** **Drug mcg/day:** FORM/BUD 18/800 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** FORM/BUD 18/800 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** DPI **Withdraw LOE:** NR **GROUP 3** **Drug mcg/day:** BUD 800 + PLA **Dosing:** fixed **Treatment duration;** 12 wk. **Device:** MDI **Withdraw LOE:** NR **GROUP 4** **Drug mcg/day:** FORM 18 + PLA **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** separate drug **Withdraw LOE:** NR **Reliever Tx:** salbutamol prn **Run-in Tx:** single blind BUD (pMDI) 320 mcg/day. Rescue salbutamol as needed. **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** • FEV_1 12-hr post dose • FEV_1 12-hr predose **Secondary** • PM PEF • exacerbations • DTS (4-pt score) • NTS • NTA	**Study objective:** To compare the efficacy and safety of FORM/BUD pressurized MDI with BUD pMDI, FORM DPI, BUD plus FORM in separate inhalers (BUD pMDI + FORM DPI) and PLA **Additional Details:** Comparing pMDI and DPI inhalers

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: O'Byrne PM 2005[105] **Pub status:** Journal article **No. countries:** 22 **No. centers:** 246 **Design:** randomized, parallel, double blind **Funding:** Industry: AstraZeneca	**Randomized:** 2,760 **Analyzed:** 2,760 (ITT) **Withdrawals:** 83 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, intermittent-severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 925 **Age yr. (mean [range]):** 35 (4-77) **Males %:** 45.5 **FEV_1 % predicted (mean [range]):** 73 (43-108) **PEF AM (mean±SD):** NR **Duration of asthma yr. (mean [range]):** 9 (0-63) **Smoking status:** NR **GROUP 2** **N:** 909 **Age yr. (mean [range]):** 36 (4-79) **Males %:** 43.3 **FEV_1 % predicted (mean [range]):** 73 (46-108) **PEF AM (mean±SD):** NR **Duration of asthma yr. (mean [range]):** 9 (0-65) **Smoking status:** NR **GROUP 3** **N:** 926 **Age yr. (mean [range]):** 36 (4-79) **Males %:** 44.9 **FEV_1 % predicted (mean [range]):** 73 (49-100) **PEF AM (mean±SD):** NR **Duration of asthma yr. (mean [range]):** 9 (0-69) **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** FORM/BUD, 12/200 **Dosing:** variable **Treatment duration:** 48 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** FORM/BUD, 12/200 **Dosing:** fixed **Treatment duration:** 48 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 3** **Drug mcg/day:** BUD 640 mcg **Dosing:** fixed **Treatment duration:** 48 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **Reliever Tx:** Group 1: FORM/BUD 6/100 mcg prn; Group 2: FF/BUD 6/100 mcg prn, terbutaline 0.4 mcg prn; Group 3: BUD + terbutaline 0.4 mcg prn **Run-in Tx:** ND (pre-randomization treatment ICS 400-1,000 ug) **Run-in duration:** >10 d.	**Definition of exacerbation:** Severe = deterioration in asthma resulting in hospitalization/emergency room treatment, oral steroid treatment (or an increase in ICS [via a separate inhaler] and/or other additional treatment for children aged 4-11 years), or morning PEF of 70% or less of baseline on 2 consecutive days. Mild = 2 consecutive days with either a morning PEF of 80% or less of baseline, as-needed use two or more inhalation per day above baseline, or awakenings caused by asthma. **List of clinical outcomes reported:** **Primary** • decrease to ≤ 70% of baseline • time to first exacerbation • no. severe exacerbations • exacerbation requiring ED/hospital • time to second severe exacerbation • time to third exacerbation. • Exacerbation requiring OCS **Secondary** • PM L/min • DTS • NTS • SFD • control days • daytime SABA use • nighttime SABA use • change in ICS dose • RFD • NTA • mild exacerbation days	**Study objective:** To determine if FORM/BUD used for regular maintenance therapy and symptom relief would further reduce exacerbations and improve overall asthma control compared with traditional LABA/ICS therapy.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: O'Byrne PM 2001[58] **Pub status:** Journal article **No. countries:** 17 **No. centers:** 198 **Design:** randomized, parallel, double blind **Funding:** Industry: AstraZeneca	**Randomized:** 1,970 **Analyzed:** 1,947 **Withdrawals:** 301 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, intermittent-mild **Baseline ICS use:** naïve **GROUP 1** **N:** NR **Age yr. (mean Stratum A/ mean Stratum B):** 31.2/36.5 **Males %:** 36.8/ 44.6 **FEV_1 % predicted (mean±SE):** 89.1±0.97/ 86.4±0.91 **PEF AM (mean±SE):** 416±7.5/429±7.1 **Duration of asthma:** NR **Smoking status:** NR **GROUP 2** **N:** NR **Age yr. (mean Stratum A/ mean Stratum B):** 36.8 **Males %:** 41.0 **FEV_1 % predicted (mean±SE):** 86.5±0.92 **PEF AM (mean±SE):** 412±6.5 **Duration of asthma:** NR **Smoking status:** NR **GROUP 3** **N:** NR **Age yr.** (mean Stratum A/ mean Stratum B)**:** 30.6/38.1 **Males %:** 40.8/ 41.6 **FEV_1 % predicted (mean±SE):** 90.1±0.94/ 86.3±0.94 **PEF AM (mean±SE):** 421±7.4/419±7.1 **Duration of asthma:** NR **Smoking status:** NR **GROUP 4** **N:** NR **Age yr. (mean Stratum A/ mean Stratum B):** 37.5 **Males %:** 42.6 **FEV_1 % predicted (mean±SE):** 87.0±0.93 **PEF AM (mean±SE):** 416±6.5 **Duration of asthma:** NR **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** FORM/BUD 12/200 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** FORM/BUD 12/400 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 3** **Drug mcg/day:** BUD 200 **Dosing:** fixed **Treatment duration;** 52 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 4** **Drug mcg/day:** BUD 400 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** single drugs **Withdraw LOE:** NR **Reliever Tx: NR** **Run-in Tx:** PLA (group 1, ICS naïve) or BUD 100 mcg bid (ICS maintenance) **Run-in duration:** 4 wk.	**Definition of exacerbation:** Severe = need for treatment with oral corticosteroids, as judged by the investigator, or hospital admission or emergency treatment for worsening asthma, or a decrease in morning PEF > 25% from baseline (the mean values during the last 14 d. of the run-in) on two consecutive days. **List of clinical outcomes reported:** **Primary** • time to first severe exacerbation • poorly controlled asthma days **Secondary** • PEF AM • FEV_1 % predicted • rate per year of severe exacerbations • rescue inhalations • SFD • NTA	**Study objective:** To determine whether regular treatment with low doses of BUD, with or without low doses of FORM, would reduce severe asthma exacerbations and improve asthma control compared with placebo.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Overbeek SE 2005[70] **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_1 % 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_1 % 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® **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® **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** • FEV_1 % predicted • PC_{20}	**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[132] **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_1 % 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_1 % 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® **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 • FEV_1 • FVC • no. mild/mod/severe 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® DPI **Additional Details:** Comparison of pMDI and DPI inhalers

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Papi A 2007[134] **Pub status:** Journal article **No. countries:** NR **No. centers:** 12 **Design:** randomized, parallel, double blind **Funding:** Industry: Chiesi Pharmaceutical	**Randomized:** 228 **Analyzed:** 225 **Withdrawals:** 3 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, moderate-severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 115 **Age yr. (mean±SD):** 47.3±12.6 **Males %:** 45.2 **FEV_1 % predicted (mean±SD):** 67.7±9.57 **PEF AM (mean±SD):** 287.2±99.1 **Duration of asthma (median [range]):** 10.1 (8.6) **Smoking status:** <10 pack-yr. **GROUP 2** **N:** 113 **Age yr. (mean±SD):** 49.7±10.2 **Males %:** 42.5 **FEV_1 % predicted (mean±SD):** 66.9±9.59 **PEF AM (mean±SD):** 275.1±92.6 **Duration of asthma (median [range]):** 8.7 (7.7) **Smoking status:** <10 pack-yr	**GROUP 1** **Drug mcg/day:** FORM/BDP 24/400 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE:** 0 **GROUP 2** **Drug mcg/day:** SAL/FP 100/500 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE:** 0 **Reliever Tx:** OCS in case of exacerbations; salbutamol prn **Run-in Tx:** current ICS (≤1,000 mcg/day) **Run-in duration:** 2 wk.	**Definition of exacerbation:** Mild = ≥2 consecutive days with: morning PEF more than 20% below the baseline value, or use of more than three additional inhalations of rescue salbutamol for a 24 hr period when compared with baseline, or a night-time asthma symptoms score ≥3. Severe = morning PEF more than 30% below the baseline value on ≥2 consecutive days, or a deterioration in asthma requiring administration of oral corticosteroids. **List of clinical outcomes reported:** **Primary** • PEF AM **Secondary** • mean change in PEF PM • mean change in FEV_1 • FVC • DTS • NTS • Reliever use • SFD	**Study objective:** To compare a new fixed combination of extrafine BDP and FORM, with the fixed combination FP and SAL

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Pauwels RA 1997[140] **Pub status:** Journal article **No. countries:** 9 **No. centers:** 71 **Design:** randomized, parallel, double blind **Funding:** Industry: Astra Draco	**Randomized:** 852 **Analyzed:** 852 **Withdrawals:** 158 **ITT analysis:** yes **Asthma stage and severity:** asymptomatic, intermittent to severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 210 **Age yr. (mean [range]):** 41 (18-68) **Males %:** 49.5 **FEV_1 % predicted (mean):** 75.7 **PEF AM (mean):** 399 **Duration of asthma (minimum):** ≥6 mo. **Smoking status:** NR **GROUP 2** **N:** 213 **Age yr. (mean [range]):** 42 (18-70) **Males %:** 50.7 **FEV_1 % predicted (mean):** 75.8 **PEF AM (mean):** 397 **Duration of asthma (minimum):** ≥6 mo **Smoking status:** NR **GROUP 3** **N:** 215 **Age yr. (mean [range]):** 42 (17-70) **Males %:** 47.4 **FEV_1 % predicted (mean):** 76.3 **PEF AM (mean):** 394 **Duration of asthma (minimum):** ≥6 mo. **Smoking status:** NR **GROUP 4** **N:** 214 **Age yr. (mean [range]):** 44 (18-70) **Males %:** 47.7 **FEV_1 % predicted (mean):** 75.4 **PEF AM (mean):** 381 **Duration of asthma (minimum):** ≥6 mo **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** FORM/BUD 24/200 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** Turbuhaler® **Withdraw LOE:** total (across all groups): 30 **GROUP 2** **Drug mcg/day:** BUD 200 + PLA **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 3** **Drug mcg/day:** FORM/BUD 24/800 **Dosing:** fixed **Treatment duration;** 52 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 4** **Drug mcg/day:** BUD 800 + PLA **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** separate drug **Withdraw LOE:** NR **Reliever Tx:** terbutaline prn **Run-in Tx:** BUD 800 mcg bid + terbutaline prn **Run-in duration:** 4 wk.	**Definition of exacerbation:** Severe – requiring treatment with oral glucocorticoids, as judged by the investigator or a decrease in the PEF as measured in the morning to more than 30% below the BL value on 2 consecutive days. Mild – days when one of the following occurred: a PEF AM >20% below the BL value; the use of >3 additional inhalations of terbutaline per 24 hours as compared with the BL period; or awakening at night due to asthma. **List of clinical outcomes reported:** **Primary** • mild exacerbations • severe exacerbations **Secondary** • FEV_1 • withdrawals due to exacerbations • pts without severe exacerbation • DTS • NTS • daytime SABA use • nighttime SABA use • episode-free days • NTA	**Study objective:** To evaluate the effects of adding inhaled FORM to both lower and higher doses of BUD.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Pearlman DS 2004[74] **Pub status:** Journal article **No. countries:** 2 (United States, Puerto Rico) **No. centers:** 36 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 360 (181 CE arms) **Analyzed:** 279 (160 CE arms) **Withdrawals:** 81 (21 CE arms) **ITT analysis:** no **Asthma stage and severity:** symptomatic, intermittent-mild **Baseline ICS use:** naïve & non-naïve **GROUP 1** **N:** 85 **Age yr. (mean [range]):** 32.8 (12-63) **Males %:** 38 **FEV_1 % predicted (mean±SD):** 68.1±11.1 **PEF AM (mean±SD):** 376.1±75.6 **Duration of asthma:** NR **Smoking status:** NR **GROUP 2** **N:** 75 **Age yr. (mean [range]):** 34.7 (12-74) **Males %:** 42 **FEV_1 % predicted (mean±SD):** 67.1±11.3 **PEF AM (mean±SD):** 369.2±76.2 **Duration of asthma:** NR **Smoking status:** NR	**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 • FEV_1 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 β_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[123] **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_1 % 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_1 % 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 FEV_1 % 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.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Peters 2008[101] **Pub status:** Industry report **No. countries:** 1 (United States) **No. centers:** 77 **Design:** randomized, parallel, double blind **Funding**: Industry: AstraZeneca	**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_1 % 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_1 % 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_1 % predicted (mean±SD):** 72.7±13.59 **PEF AM L/min (mean±SD):** NR **Duration of asthma (mean±SD):** 24.4 yr. ±15.48 **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** FORM/BUD 18/800 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** MDI **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** FORM/BUD 36/1600 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** MDI **Withdraw LOE:** NR **GROUP 3** **Drug mcg/day:** BUD 1600 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** MDI **Withdraw LOE:** NR **Reliever Tx:** albuterol prn **Run-in Tx:** BUD 800 mcg (single blind); albuterol prn **Run-in duration:** 2 wk.	**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** • FEV_1 • no. pts with ≥1 exacerbation • DTS • SFD • asthma control days • RFD • Use of other asthma tx • missed work/school due to asthma	**Study objective:** To examine long-term safety of BUD/FORM via pMDI in pts with moderate to severe asthma.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Pohl WR 2006[141] **Pub status:** Journal article **No. countries:** 1 **No. centers:** 16 **Design:** randomized, parallel, double blind **Funding:** Industry: AstraZeneca	**Randomized:** 133 **Analyzed:** 126 **Withdrawals:** 24 **ITT analysis: yes –** all patients with efficacy measurement on treatment (n=126) **Asthma stage and severity:** intermittent to severe **Baseline ICS use:** naïve & non-naïve **GROUP 1** **N:** 65 **Age yr. (mean (range)):** 45 (20-80) **Males %:**59 **FEV_1 % predicted (mean (range)):** 65 (39-85) **PEF AM (mean±SD):** NR **Duration of asthma yr. (mean (range)):** 10 (0-35) **Smoking status – documented smoking habit n(%):** 24 (38) **GROUP 2** **N:** 68 **Age yr. (mean (range)):** 45 (20-82) **Males %:** 48 **FEV_1 % predicted (mean (range)):** 67 (35-88) **PEF AM (mean±SD):** NR **Duration of asthma yr.** (**mean (range)):** 4.5 (0-30) **Smoking status – documented smoking habit n(%):** 21 (33)	**GROUP 1** **Drug mcg/day:** FORM/BUD, 18 (wk 1-4), 9-18 (wk 5-8), 6-18 (wk 9-20) mcg/640 (wk 1-4), 320-640 (wk 5-8), 200-640 (wk 9-20) mcg **Dosing:** fixed (wk fixed-4), variable (wk 5-variable0) **Treatment duration:** 20 wk. **Device:** Turbuhaler® **Withdraw LOE:** **GROUP 2** **Drug mcg/day:** BUD, 1280 (wk 1-4), 640-1280 (wk 5-8), 320-1280 (wk 9-20) mcg **Dosing:** fixed (wk fixed-4), variable (wk 5-variable0) **Treatment duration:** 20 wk. **Device:** Turbuhaler® **Withdraw LOE:** **Reliever Tx:** Terbutaline prn **Run-in Tx:** no run-in **Run-in duration:** 20 wk.	**Definition of exacerbation:** Severe = requiring one or more of: hospitalization; nebulized β_2-agonits; oral steroids; or withdrawal owing to lack of efficacy or a life-threatening/fatal condition. **List of clinical outcomes reported:** **Primary** • Composite: no. patients experiencing treatment failure (treatment failure defined as (a) hospitalizatio n; (b) nebulized beta2-agonists; (c) oral steroids; (d) withdrawal due to no efficacy or fatal condition.) **Secondary** • mean change in PEF PM • mean change in FEV_1 • % days pts required use • treatment satisfaction • dose of medication	**Study objective:** To examine the effects of adjustable maintenance dosing with budesonide/formoterol (160/4.5 mcg) or higher-dose budesonide (320 mcg); the ICS dose per inhalation was 2-fold higher in patients treated with budesonide than in those treated with budesonide/formoterol. **Additional Details:** Fixed dosing weeks 1-4, adjustable dosing regimen (2-4 inhalations/dy) weeks 4-8, adjustable dosing regimen (1-4 inhalations/dy) from week 8.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Price D 2002[91] **Pub status:** Journal article **No. countries:** 2 (United Kingdom, Ireland) **No. centers:** 152 **Design:** randomized, parallel, double blind **Funding:** Industry: AstraZeneca	**Randomized:** 663 **Analyzed:** 663 **Withdrawals:** 37 **ITT analysis:** yes **Asthma stage and severity:** asymptomatic, mild **Baseline ICS use:** naïve **GROUP 1 (Part 1)** **N:** 332 **Age yr. (mean±SD):** 38.9±16.7 **Males %:** 41 **FEV_1 % predicted:** NR **PEF AM L/min (mean±SD):** 402.2±94.8 **Duration of asthma:** <1yr - >5yrs **Smoking status:** NR **GROUP 2 (Part 1)** **N:** 331 **Age yr. (mean±SD):** 37.7±16.1 **Males %:** 43 **FEV_1 % predicted:** NR **PEF AM L/min (mean±SD):** 404.1±93.5 **Duration of asthma:** <1yr - >5yrs **Smoking status:** NR **GROUP 1 (Part 2)** **N:** 250 **Age yr. (mean±SD):** 37.2±16.0 **Males %:** 39 **FEV1 % predicted:** NR **PEF AM L/min (mean±SD):** 441.2±106.7 **Duration of asthma:** <1yr - >5yrs **Smoking status:** NR **GROUP 2 (Part 2)** **N:** 255 **Age yr. (mean±SD):** 38.3±16.7 **Males %:** 42 **FEV_1 % predicted:** NR **PEF AM L/min (mean±SD):** 439.6 ±101.7 **Duration of asthma:** <1yr - >5yrs **Smoking status:** NR	**GROUP 1 (Part 1)** **Drug mcg/day:** FORM/BUD 18/800 **Dosing:** fixed **Treatment duration:** 4 wk. **Device:** Turbohaler **Withdraw LOE:** NR **GROUP 2 (Part 1)** **Drug mcg/day:** BUD 800 + PLA **Dosing:** fixed **Treatment duration:** 4 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 1 (Part 2)** **Drug mcg/day:** FORM/BUD 18/400 **Dosing:** fixed **Treatment duration;** 26 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 2 (Part 2)** **Drug mcg/day:** BUD 400 + PLA **Dosing:** fixed **Treatment duration:** 26 wk. **Device:** Turbohaler® **Withdraw LOE:** NR **Reliever Tx:** SABA as needed **Run-in Tx:** <400 mcg/d BUD or BDP via MDI or <200 mcg/d via Turbuhaler® **Run-in duration:** 7-14 d	**Definition of exacerbation:** Any combination of the following for 2 consecutive days: PEF <80% baseline, SABA use 4 inhalations above baseline post-Part 1, night awakening due to asthma **List of clinical outcomes reported:** **Primary** time until 3 consecutive days with symptom score of 0 (Part 1) time to first mild exacerbation (Part 2) **Secondary** time to first severe exacerbation frequency of mild and severe exacerbations % of pts free of exacerbations during 6 mo. treatment time to first poorly controlled day frequency of poorly controlled days	**Study objective:** To determine the effect of adding formoterol to a lower dose budedsonide (400 mcg qd) on the time to first mild asthma exacerbation (Part 2). **Additional details:** Study consisted of two randomization periods: Part 1 to determine effect of adding formoterol to a moderate dose of budesonide (400 mcg bid) on length of time to achieve asthma control. Treatment period lasted 4 wk. Part 2 described above. Patients achieving asthma control by end of Part 1 re-randomized to Part 2 treatment.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Rabe KF 2006[122] **Pub status:** Journal article **No. countries:** 9 **No. centers:** 77 **Design:** randomized, parallel, double blind **Funding:** Industry: AstraZeneca	**Randomized:** 697 **Analyzed:** 696 **Withdrawals:** 58 **ITT analysis:** all randomized (1 pt lost) **Asthma stage and severity:** symptomatic, mild to moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 354 **Age yr. (mean±SD):** 38±16.75 **Males %:** 41 **FEV_1 % predicted (mean±SD):** 75±18 **PEF AM L/min (mean±SD):** 345±142.5 **Duration of asthma, yr. (mean±SD):** 10±17.25 **Smoking status % (never/occasional/habitual):** 93/3/4 **GROUP 2** **N:** 342 **Age yr. (mean±SD):** 38±16.75 **Males %:** 36 **FEV_1 % predicted (mean±SD):** 75±14.25 **PEF AM L/min (mean±SD):** 335**±** 151.75 **Duration of asthma, yr. (mean±SD):** 10±15 **Smoking status % (never/occasional/habitual):** 92/4/4	**GROUP 1** **Drug mcg/day:** FF/BUD 9/160 **Dosing:** fixed **Treatment duration:** 26 wk. **Device:** DPI **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** BUD 320 **Dosing:** fixed **Treatment duration:** 26 wk. **Device:** DPI **Withdraw LOE:** NR **Reliever Tx:** Terbutaline as needed **Run-in Tx:** BUD 100 mcg bid + terbutaline as needed **Run-in duration:** 14-18 d	**Definition of exacerbation:** hospitalization/ED treatment due to asthma worsening, need for OCS, ≥30% decrease from baseline PEF AM for 2 consecutive days. **List of clinical outcomes reported:** **Primary** PEF AM PEF PM **Secondary** FEV_1 % predicted total daily asthma symptom score (scale 0-3) RFD SFD NTA asthma control days (combined SFD and RFD)	**Study objective:** To compare the efficacy and safety of FORM/BUD for both maintenance and symptom relief with that of double the dose of BUD (320 mcg) and terbutaline over 6 mo.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Ringdal N 2002[130] **Pub status:** Journal article **No. countries:** 11 **No. centers:** NR **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 428 **Analyzed:** 379 **Withdrawals:** 49 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, moderate to severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 189 **Age yr. (mean±SD):** 46.5±14 **Males %:** 40 **FEV_1 % predicted (mean±SD):** 69.2±10.7) **PEF AM L/min (mean±SD):** 349±101 **Duration of asthma:** **Smoking status:** <10 pack-yr. **GROUP 2** **N:** 190 **Age yr. (mean±SD):** 48.1±13.9 **Males %:** 49 **FEV_1 % predicted:** 69±10.1 **PEF AM L/min (mean±SD):** 348±101 **Duration of asthma:** **Smoking status:** <10 pack-yr.	**GROUP 1** **Drug mcg/day:** SAL/FP 100/500 + 2 placebo Turbuhalers® **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskus®r **Withdraw LOE:** 2 **GROUP 2** **Drug mcg/day:** FORM/BUD, 24/1600 + PLA Diskus **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Turbuhaler® **Withdraw LOE:** 4 **Reliever Tx:** salbutamol **Run-in Tx:** pre-study ICS **Run-in duration:** 2 wk.	**Definition of exacerbation:** severe = deterioration in asthma requiring emergency hospital treatment **List of clinical outcomes reported:** **Primary** PEF AM **Secondary** PEF PM PEF PM % diurnal variation FEV_1 exacerbation rate DTS score NTS score salbutamol use night time awakening withdrawals	**Study objective:** To demonstrate similar efficacy between SAL/FP 100/500 in one Diskus vs. FORM/BUD 24/1600 in two Turbuhalers®

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Rojas RA 2007[60] **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_1 % 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_1 % 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: SAM30007 2005[146] **Pub status:** Industry report **No. countries:** 1 (Denmark) **No. centers:** 5 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 61 **Analyzed:** 61 **Withdrawals:** 6 **ITT analysis:** yes **Asthma stage and severity:** asymptomatic, moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 29 **Age yr (mean±SD):** 38.2±11.4 **Males %:** 52 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 470.4±121.7 **Duration of asthma:** NR **Smoking status:** NR **GROUP 2** **N:** 32 **Age yr (mean±SD):** 36.2±11.8 **Males %:** 53 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 469±119.5 **Duration of asthma:** NR **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** SAL/FP NR/1000, 500, 200; 100 (dose-scaling) **Dosing:** fixed **Treatment duration:** 24 **Device:** NR **Withdraw LOE:** 0 **GROUP 2** **Drug mcg/day:** FP 1000 500, 200; 100 (dose-scaling) **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** NR **Withdraw LOE:** 0 **Reliever Tx:** NR **Run-in Tx:** BUD 1500-2000 mcg or equivalent **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** minimum acceptable dose time to uncontrolled asthma **Secondary** PEF AM PEF PM FEV_1 AM DTS score NTS score reliever use (# days with no relief medication)	**Study objective:** To determine whether FP in combination with SAL allowed dose-titration to a lower ICS dose than FP alone while maintaining asthma control. **Additional details:** Dose reduction design: Initial Tx dose was administered for 6 wk. After each 6-wk. period, subjects whose asthma was controlled were given the next dose down for a further 6 wk. and so on until subjects were no longer receiving study medication.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAM30013 2005[126] **Pub status:** Industry report **No. countries:** 1 (Canada) **No. centers:** 40 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 237 **Analyzed:** 237 **Withdrawals:** 11 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, mild, moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 121 **Age yr (mean±SD):** 37.7±14.1 **Males %:** 30 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 335.6±105.2 **Duration of asthma:** NR **Smoking status:** NR **GROUP 2** **N:** 116 **Age yr (mean±SD):** 36.4±14.9 **Males %:** 40 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 349.1±98.0 **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:** FP 500 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE:** 0 **Reliever Tx:** NR **Run-in Tx:** Open label FP 200 mcg/d **Run-in duration:** 6 wk.	**Definition of exacerbation:** NA **List of clinical outcomes reported:** **Primary** PEF AM **Secondary** PEF PM FEV_1	**Study objective:** To compare the efficacy of SAL/FP 50/100 mcg bid with FP 250 mcg bid in the treatment of mild to moderate asthmatics who remain uncontrolled on FP 100 bid.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAM40008 2004[145] **Pub status:** Industry report **No. countries:** 10 **No. centers:** 34 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 186 **Analyzed:** 186 **Withdrawals:** 172 **ITT analysis:** yes **Asthma stage and severity:** asymptomatic, severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 93 **Age yr (mean±SD):** 48.4±15.1 **Males %:** 52 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 386 **Duration of asthma:** NR **Smoking status:** NR **GROUP 2** **N:** 93 **Age yr (mean±SD):** 50.9±16.1 **Males %:** 43 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 339 **Duration of asthma:** NR **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** SAL/FP 100/1000, 500, 200, no drug **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** diskhaler **Withdraw LOE:** 67/93 **GROUP 2** **Drug mcg/day:** FP/1000, 500, 200, no drug **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** diskhaler **Withdraw LOE:** 74/93 **Reliever Tx:** NR **Run-in Tx:** NR **Run-in duration:** NR	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** minimum acceptable dose % pts with acceptable control time to treatment failure **Secondary** PEF AM PEF PM FEV_1 no. of exacerbations SFD SFN RFD minimum dose at which asthma remained ideally controlled	**Study objective:** To determine the ability of SAL/FP to allow tapering of the ICS dose in subjects currently taking BUD 1,500-2,000 mcg; and to determine if control can be maintained with a lower mcg of SAL/FP than FP alone. **Additional details:** Dose reduction design: Initial Tx dose was administered for 6 wk. After each 6-wk. period, subjects whose asthma was controlled were given the next dose down for a further 6 wk. and so on until subjects were no longer receiving study medication.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAM40010 2004[136] **Pub status:** Industry report **No. countries:** 6 **No. centers:** 50 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 373 **Analyzed:** 373 **Withdrawals:** 11 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, mild-severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 183 **Age yr (mean±SD):** 41.9±15.4 **Males %:** 44 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 353±90 **Duration of asthma:** ≥ 6 mo () **Smoking status:** NR **GROUP 2** **N:** 190 **Age yr (mean±SD):** 42.9±16.2 **Males %:** 37 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 346±89 **Duration of asthma:** ≥ 6 mo. **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** FORM/BUD 9/400 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** 6 **Withdraw LOE:** 0/190 **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.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** PEF AM **Secondary** PEF PM PEF diurnal variation PEF AM % predicted FEV_1 no. pts with exacerbations 24-hr. periods with symptom score ≥2 24-hr. periods with no relief medication SFD SFN	**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.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAM40034 2004[66] **Pub status:** Industry report **No. countries:** 3 **No. centers:** 27 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 154 **Analyzed:** 154 **Withdrawals:** 9 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, mild-severe **Baseline ICS use:** naïve **GROUP 1** **N:** 75 **Age yr (mean±SD):** 36.8±11.6 **Males %:** 36 **FEV_1 % 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_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 453±74.7 **Duration of asthma:** NR **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** SAL/FP 100/200 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** diskhaler **Withdraw LOE:** 0/75 **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.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** PEF AM **Secondary** PEF PM time to 3 d. consecutive of PEF higher than at randomization FEV_1 % asthma control days % pts with asthma control time to 1st treatment wk with asthma control	**Study objective:** To compare efficacy and safety of SAL/FP 50/100 mcg bid in patients who were taking SABA only but required further management.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAM40036 2004[65] **Pub status:** Industry report **No. countries:** 9 **No. centers:** 74 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 577 **Analyzed:** 577 **Withdrawals:** 34 **ITT analysis:** yes **Asthma stage and severity:** asymptomatic, mild-moderate **Baseline ICS use:** naïve **GROUP 1** **N:** 288 **Age yr (mean±SD):** 37.2±15.6 **Males %:** 40.3 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 381±97.1 **Duration of asthma:** NR **Smoking status:** NR **GROUP 2** **N:** 289 **Age yr (mean±SD):** 36.0±15.7 **Males %:** 45.7 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 388±92.9 **Duration of asthma:** NR **Smoking status:** NR	**GROUP 1** **Drug/mcg/day:** SAL/FP 50/100 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** diskhaler **Withdraw LOE:** 0 **GROUP 2** **Drug/mcg/day:** BUD 400 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** 6 **Withdraw LOE:** 0 **Reliever Tx:** salbutamol prn **Run-in Tx:** salbutamol prn **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** PEF AM **Secondary** PEF PM FEV_1 FEF_{25-75} DTS NTS Reliever use (daytime and nighttime)	**Study objective:** To demonstrate that once daily treatment with SAL/FP 50/100 mcg at night is at least as effective as BUD 400 mcg at night over 12-wk. period.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAM40048 2005[135] **Pub status:** Industry report **No. countries:** 1 **No. centers:** 27 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 248 **Analyzed:** 248 **Withdrawals:** 13 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 121 **Age yr (mean±SD):** 47±13 **Males %:** 38 **FEV_1 % 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 **Age yr (mean±SD):** 49±14 **Males %:** 47 **FEV_1 % predicted (mean±SD):** 65.6±7.94 **PEF AM L/min (mean±SD):** 301.33±103.94 **Duration of asthma:** NR **Smoking status:** NR	**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:** FORM/BUD 12/400 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Turbuhaler **Withdraw LOE:** 0 **Reliever Tx:** NR **Run-in Tx:** NR **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** FEV_1 % predicted **Secondary** PEF AM PEF PM FEV_1 DTS NTS % RFD % SFD	**Study objective:** To determine if SAL/FP 50/250 is superior to FORM/BUD 6/200 in efficacy and tolerability over 12 wk.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAM40065 2007[99] **Pub status:** Industry report **No. countries:** 3 **No. centers:** 51 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 449 **Analyzed:** 449 **Withdrawals:** 127 **ITT analysis:** yes **Asthma stage and severity:** asymptomatic, mild-severe **Baseline ICS use:** naïve & non-naïve **GROUP 1** **N:** 150 **Age yr (mean±SD):** 34.6±15.2 **Males %:** 35.3 **FEV_1 % predicted (mean±SD):** 83.1 **PEF AM L/min (mean±SD):** 373.3±219.2 **Duration of asthma:** ≥3 mo **Smoking status:** NR **GROUP 2** **N:** 150 **Age yr (mean±SD):** 34.2±13.9 **Males %:** 37.3 **FEV_1 % predicted (mean±SD):** 80.6 **PEF AM L/min (mean±SD):** 403.3±214.1 **Duration of asthma:** ≥3 mo **Smoking status:** NR **GROUP 3** **N:** 149 **Age yr (mean±SD):** 33.5±13.3 **Males %:** 38.3 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 378.6±17.2 **Duration of asthma:** ≥3 mo **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** SAL/FP 100/200-1000 **Dosing:** fixed **Treatment duration:** 40 wk. **Device:** diskhaler **Withdraw LOE:** 2 **GROUP 2** **Drug mcg/day:** FP (BHR) 200-1000 + PLA **Dosing:** fixed **Treatment duration:** 40 wk. **Device:** diskhaler **Withdraw LOE:** 2 **GROUP 3** **Drug mcg/day:** FP 200-1000 + PLA **Dosing:** fixed **Treatment duration:** 40 wk. **Device:** diskhaler **Withdraw LOE:** 1 **Reliever Tx:** NR **Run-in Tx:** Usual pre-study tx **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** mean ICS dose **Secondary** PEF AM FEV_1 reliever use SFD	**Study objective:** To determine whether asthma control and reduced bronchiol hyperresponsiveness could be achieved and maintained at a lower dose of ICS with SAL/FP Diskus™ or FP Diskus™ in adult and adolescent subjects with persistent asthma.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAM40090 2005[144] **Pub status:** Industry report **No. countries:** 1 (Canada) **No. centers:** 79 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**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_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 404.2±117.93 **Duration of asthma:** ≥ 3 mo. **Smoking status:** NR **GROUP 2** **N:** 241 **Age yr (mean±SD):** 40.0±15.0 **Males %:** 43 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 397.4±114.26 **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 **Reliever Tx:** salbutamol prn **Run-in Tx:** open label FP 500 mcg/day **Run-in duration:** 2 wk.	**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).

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAM40120 2005[53] **Pub status:** Industry report **No. countries:** 1 **No. centers:** 10 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**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_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 309±46 **Duration of asthma:** NR **Smoking status (pack-yr± SD):** 42±24 **GROUP 2** **N:** 10 **Age yr (mean±SD):** 59±10 **Males %:** 60 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 282±79 **Duration of asthma:** NR **Smoking status (pack-yr± SD):** 35±18	**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 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Evohaler™ **Withdraw LOE:** 0/8 **Reliever Tx:** SABA (ND) **Run-in Tx:** FP 200-400 or equivalent **Run-in duration:** ≥1 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** PEF AM **Secondary** PEF PM EQ5D % RFD % RFN % SFD mini-AQLQ	**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 problems the study was terminated after 18 subjects recruited. Only primary endpoint analyzed.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAS30002 2008[124] **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_1 % 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_1 % 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[68] **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_1 % 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_1 % 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[67] **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_1 % 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 2** **N:** 182 **Age yr (mean±SD):** 40.8±14.74 **Males %:** 42 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 336.2±106.2 **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 **Reliever Tx:** salbutamol **Run-in Tx:** SABA only **Run-in duration:** >1 wk.	**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.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAS40026 2006[49] **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_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 458±122.9 **Duration of asthma:** >6 mo. **Smoking status:** ≤10 pack-yr **GROUP 2** **N:** 311 **Age yr (mean±SD):** 39.2±14.9 **Males %:** 34.9 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 437±139.3 **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 **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).	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** asthma stability (% subjects remaining at 12 wk.) **Secondary** PEF AM FEV_1 % 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.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAS40036 2005[102] **Pub status:** Industry report **No. countries:** 1 **No. centers:** 85 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 483 **Analyzed:** 483 **Withdrawals:** 166 **ITT analysis:** yes **Asthma stage and severity:** asymptomatic, mild-severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 172 **Age yr (mean±SD):** 40.4±13.4 **Males %:** 39 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 401.5±107.5 **Duration of asthma:** >6 mo. **Smoking status:** NR **GROUP 2** **N:** 152 **Age yr (mean±SD):** 41.7±14.9 **Males %:** 38.8 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 386.0±106.0 **Duration of asthma:** >6 mo. **Smoking status:** NR **GROUP 3** **N:** 159 **Age yr (mean±SD):** 42±14.5 **Males %:** 45.4 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 394.4±104.7 **Duration of asthma:** >6 mo. **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** SAL/FP 100/200 **Dosing:** fixed **Treatment duration:** 16 wk. **Device:** diskhaler **Withdraw LOE:** 10 **GROUP 2** **Drug mcg/day:** SAL 100 **Dosing:** fixed **Treatment duration:** 16 wk. **Device:** diskhaler **Withdraw LOE:** 34 **GROUP 3** **Drug mcg/day:** FP 200 **Dosing:** fixed **Treatment duration;** 16 wk. **Device:** diskhaler **Withdraw LOE:** 64 **Reliever Tx:** albuterol prn **Run-in Tx:** Current ICS use (2 wk). If not controlled, then open label SAL/FP100/200 mcg bid until control achieved (4 wk) **Run-in duration:** 6 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** PEF AM **Secondary** FEV_1 % SFD % RFD patient satisfaction	**Study objective:** To evaluate whether study subjects who were stable on SAL/FP could maintain long-term superior asthma control when continued on SAL/FP compared with “step-down” therapy to FP 100 mcg bid, SAL 50 mcg bid or monteleukast 10 mg qd.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SAS40068 2005[69] **Pub status:** Industry report **No. countries:** 1 (Canada) **No. centers:** 58 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 532 **Analyzed:** 532 **Withdrawals:** 99 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, mild **Baseline ICS use:** naïve **GROUP 1** **N:** 262 **Age yr (mean±SD):** 34.8±14.27 **Males %:** 13.7 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 395.3±102.3 **Duration of asthma:** NR **Smoking status:** NR **GROUP 2** **N:** 270 **Age yr (mean±SD):** 34.3±14.2 **Males %:** 13.3 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 392.5±102.9 **Duration of asthma:** NR **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** SAL/FP 100/200 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** Diskus® **Withdraw LOE:** 1 **GROUP 2** **Drug mcg/day:** FP 200 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** Diskus® **Withdraw LOE:** 1 **Reliever Tx:** NR **Run-in Tx:** NR **Run-in duration:** NR	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** PEF AM **Secondary** FEV_1 AM exacerbation rate % SFD % RFD	**Study objective:** To evaluate the efficacy of the SAL/FP Diskus® 50/100 mcg bid compared with the FP Diskus® 100 mcg bid in adult and adolescents with mild asthma.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Schermer TR 2007[142] **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_1 % 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_1 % 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™ **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** FP 500 or 1000 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskus™ **Withdraw LOE:** NR **Reliever Tx:** salbutamol prn **Run-in Tx:** FP (open-label) via Diskus™ + salbutamol **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** mean change FEV_1 % 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[119] **Pub status:** Journal article **No. countries:** 18 **No. centers:** 211 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: AstraZeneca	**Randomized:** 1,890 **Analyzed:** 1,890 **Withdrawals:** 317 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, moderate-severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 942 **Age yr (mean [range]):** 43 (12-79) **Males %:** 41.5 **FEV_1 % 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:** NR **GROUP 2** **N:** 943 **Age yr (mean [range]):** 43 (11-80) **Males %:** 42.9 **FEV_1 % 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 no. severe exacerbations DTS NTS nighttime awakenings SABA use change in ICS dose RFD asthma-control days treatment days with OCS	**Study objective:** To compare SMART® (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
Author Year: Self T 1998[143] **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_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 386±76 **Duration of asthma:** 83% childhood onset **Smoking status:** NR **GROUP 2** **N:** 10 **Age yr (mean [range]):** 46.6 (22-68) **Males %:** 0 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 388±107 **Duration of asthma:** 67% 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 **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.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** % reduction in ICS dose **Secondary** PEF FEV_1 AQLQ SABA use	**Study objective:** To determine is SAL facilitates step-down therapy in pts receiving moderate to high dose ICS.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SFA103153 2007[100] **Pub status:** Industry report **No. countries:** 1 (United States) **No. centers:** 59 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 475 **Analyzed:** 475 **Withdrawals:** 155 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, mild-severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 239 **Age yr (mean±SD):** 31.5±13.5 **Males %:** 40.2 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 342±91.2 **Duration of asthma:** NR **Smoking status:** NR **GROUP 2** **N:** 236 **Age yr (mean±SD):** 32.2±13.6 **Males %:** 36.4 **FEV_1 % predicted (mean±SD):** NR **PEF AM L/min (mean±SD):** 340±99.9 **Duration of asthma:** NR **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** SAL/FP 100/200 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** Diskus™ **Withdraw LOE:** 6 **GROUP 2** **Drug mcg/day:** FP 200 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** Diskus™ **Withdraw LOE:** 9 **Reliever Tx:** albuterol **Run-in Tx:** FP 250 mcg bid **Run-in duration:** 4 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** exacerbation rate **Secondary** PEF AM FEV_1 SFD RFD	**Study objective:** To demonstrate that SAL/FP 50/100 mcg is superior to FP 100 in controlling asthma exacerbation rate in subjects of African American descent. **Additional details:** All subjects of African American descent

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Shapiro G 2000[87] **Pub status:** Journal article **No. countries:** 1 (United States) **No. centers:** 42 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 84 **Analyzed:** 81 **Withdrawals:** 13 **ITT analysis:** yes **Asthma stage and severity:** asymptomatic, moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 81 **Age (mean [range]):** 38 (12-69) **Males (%):** 48 **FEV_1 % predicted:** NR **Mean PEF AM (mean±SD):** 367±99 **Duration of asthma:** ≥ 6 mo. **Smoking status:** none smoked in previous year or had history >10 pack/year **GROUP 2** **N:** 81 **Age (mean [range]):** 40 (12-67) **Males %:** 54 **FEV_1 % predicted:** NR **Mean PEF AM (mean±SD):** 374±75.6 **Duration of asthma:** ≥ 6 mo. **Smoking status:** none smoked in previous year or had history >10 pack/year **GROUP 3** **N:** 84 **Age (mean [range]):** 39 (12-68) **Males %:** 49 **FEV_1 % predicted:** NR **Mean PEF AM (mean±SD):** 372±92.6 **Duration of asthma:** ≥ 6 mo. **Smoking status:** none smoked in previous year or had history >10 pack/year **GROUP 4** **N:** 90 **Age (mean [range]):** 38 (12-69) **Males %:** 41 **FEV_1 % 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.	**GROUP 1** **Drug mcg/day:** SAL/FP 100 500 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** diskhaler **Withdraw LOE:** 3 **GROUP 2** **Drug mcg/day:** FP 500 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskus® **Withdraw LOE:** 18 **GROUP 3** **Drug mcg/day:** SAL 100 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskus® **Withdraw LOE:** 32 **GROUP 4** **Drug mcg/day:** PLA **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** single drugs **Withdraw LOE:** 56 **Reliever Tx:** albuterol prn **Run-in Tx:** medium dose of ICS + PLA **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** mean change PEF AM AUC FEV_1 12 hr serial relative to day 1 probability of pts remaining in study without being withdrawn for worsening asthma **Secondary** mean change in PEF PM SABA use (puffs/day) nighttime awakenings requiring SABA	**Study objective:** To compare the efficacy and safety of SAL/FP 50/250 mcg in a combination dry-powder product administered twice daily through the Diskus device with that of FP and SAL alone in patients previously treated with low to medium dose ICS.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SLGA5021 2005[125] **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_1 % 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_1 % 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.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SLGF75 2005[103] **Pub status:** Industry report **No. countries:** 1 (Italy) **No. centers:** 7 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 46 **Analyzed:** 46 **Withdrawals:** 4 **ITT analysis:** yes – subjects randomized and with at least one dose of administered study drug. Per-protocol population – all subjects of ITT without any major protocol violation were used for secondary efficacy analysis. **Asthma stage and severity:** NR, intermittent, mild, moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 14 **Age (mean± SD):** 41.7±16.3 **Males %:** 36 **FEV_1 % predicted:** NR **Mean PEF AM (mean±SD):** NR **Duration of asthma:** >6 mo. **Smoking status:** NR **GROUP 2** **N:** 17 **Age (mean±SD):** 42±10.6 **Males %:** 71 **FEV_1 % predicted:** NR **Mean PEF AM (mean±SD):** NR **Duration of asthma:** >6 mo. **Smoking status:** NR **GROUP 3** **N:** 15 **Age (mean±SD):** 32.9±13.1 **Males %:** 60 **FEV_1 % predicted:** NR **Mean PEF AM (mean±SD):** NR **Duration of asthma:** >6 mo. **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** SAL/FP 100/200 **Dosing:** fixed **Treatment duration:** 3 mo. **Device:** diskhaler **Withdraw LOE:** 0 **GROUP 2** **Drug mcg/day:** FP 200 **Dosing:** fixed **Treatment duration:** 3 mo. **Device:** diskhaler **Withdraw LOE:** 0 **GROUP 3** **Drug mcg/day:** FP 500 **Dosing:** fixed **Treatment duration;** 3 mo. **Device:** diskhaler **Withdraw LOE:** 0 **Reliever Tx:** salbutamol prn **Run-in Tx:** FP 100 mcg bid; salbutamol prn **Run-in duration:** 4 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** NR **Secondary** PEF AM/PM variation PEF PM	**Study objective:** To demonstrate a higher efficacy of two treatments (SAL 50 mcg + low-dose FP or high-dose FP bid) compared with FP 100 mcg bid in naïve subjects with mild-moderate asthma **Additional details:** No reported data for secondary outcomes because study was interrupted.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: SLGQ97/SLGB4010 2005[104] **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_1 % 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_1 % 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_1 % 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 FEV_1 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[147] **Pub status:** Industry report **No. countries:** 1 (France) **No. centers:** 56 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 188 **Analyzed:** 168 **Withdrawals:** 31 **ITT analysis:** yes **Asthma stage and severity:** asymptomatic, NR **Baseline ICS use:** non-naïve **GROUP 1** **N:** 83 **Age (mean±SD):** 41.1±13.8 **Males %:** 44.6 **FEV_1 % predicted (mean±SD):** 91.8±13.5 **Mean PEF AM (median±SD):** 441.5±79.1 **Duration of asthma:** NR **Smoking status:** NR **GROUP 2** **N:** 85 **Age (mean±SD):** 39.5±14.9 **Males %:** 37.6 **FEV_1 % predicted (mean±SD):** 91.6±20.6 **Mean PEF AM (median±SD):** 442.9±95.8 **Duration of asthma:** NR **Smoking status:** NR	**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 **Reliever Tx:** NR **Run-in Tx:** NR-assumed current ICS use (BDP 800-1000 mcg) **Run-in duration:** NR	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** PEF AM **Secondary** PEF PM FEV_1 % 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.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Ställberg B 2003[191] **Pub status:** Journal article **No. countries:** 1 (Sweden) **No. centers:** 94 **Design:** randomized, parallel, open label **Funding:** Industry: AstraZeneca	**Randomized:** 1,034 **Analyzed:** 977 **Withdrawals:** 57 **ITT analysis:** no **Asthma stage and severity:** mixed asymptomatic and symptomatic, moderate **Baseline ICS use:** non-naïve **GROUP 1** **N:** 486 **Age (mean±SD):** 44±17 **Males %:** 39 **FEV_1 % 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) **GROUP 2** **N:** 491 **Age (mean±SD):** 44±16 **Males %:** 41 **FEV_1 % 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)	**GROUP 1** **Drug mcg/day:** FORM/BUD 18/400 or 800 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** Turbuhaler® **Withdraw LOE:** **GROUP 2** **Drug mcg/day:** FORM/BUD 18/200-1600 **Dosing:** variable **Treatment duration:** 24 wk. **Device:** Turbuhaler® **Withdraw LOE:** **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.	**Definition of exacerbation:** one or more of the following (as judged by the investigator): use of oral corticosteroids for treatment due to worsening of asthma; treatment at a medical care unit due to worsening of asthma; an asthma-related SAE; withdrawal due to a need to use non-study asthma medication **List of clinical outcomes reported:** **Primary** symptom score time to 1st exacerbation **Secondary** asthma free days SABA use nighttime wakenings	**Study objective:** To examine the potential clinical benefits of a guided adjustable-dosing regimen with BUD/FORM in a single inhaler over a six-month period based on patient assessment of their asthma, compared with a fixed-dosing regimen. **Additional details:** Step-up or step-down therapy determined by specific criteria (Table 1)

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Strand AM 2004[63] **Pub status:** Journal article **No. countries:** 1 (Denmark) **No. centers:** 45 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 150 **Analyzed:** 150 **Withdrawals:** 24 **ITT analysis: no** **Asthma stage and severity:** symptomatic, mild-severe **Baseline ICS use:** naïve **GROUP 1** **N:** 78 **Age (mean±SD):** 39±15 **Males %:** 49 **FEV_1 % predicted:** NR **Mean PEF AM (mean±SD):** 380±117 **Duration of asthma (n [%] ≥ 10 yrs):** 13 (13) **Smoking status – never/past/current (n):** 42/26/32 **GROUP 2** **N:** 72 **Age (mean±SD):** 38±15 **Males %:** 38 **FEV_1 % predicted:** NR **Mean PEF AM** (**mean±SD**)**:** 397±109 **Duration of asthma (n [%] ≥ 10 yr.):** 11 (10) **Smoking status – never/past/current (n):** 31/24/46	**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.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** SFD (24-hr period) **Secondary** PEF PM DTS NTS SFN % RFD %	**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[88] **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_1 % 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_1 % predicted (mean±SD):** 66±16 **Mean PEF AM (mean±SD):** 382±101.4 **Duration of asthma:** NA **Smoking status – current (n[%]):** 12 (10.5)	**GROUP 1** **Drug mcg/day:** FORM/ICS 48 /range <400 to ≥1600 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** Turbuhaler® **Withdraw LOE:** 1 **GROUP 2** **Drug mcg/day:** ICS range <400 to ≥1600 + PLA **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** Tubuhaler® **Withdraw LOE:** 6 **Reliever Tx:** terbutaline prn **Run-in Tx:** current tx + terbutaline prn. **Run-in duration:** 4 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** total asthma score **Secondary** PEF PM FEV_1 exacerbations requiring OCS use SABA use	**Study objective:** To investigate the efficacy and safety of FORM in asthmatic subjects already using ICS

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: van Noord JA 1999[120] **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_1 % 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_1 % 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 FEV_1 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

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: van Noord JA 2001[97] **Pub status:** Journal article **No. countries:** 13 **No. centers:** 61 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: GlaxoSmithKline	**Randomized:** 509 **Analyzed:** 503 **Withdrawals:** 62 **ITT analysis:** yes **Asthma stage and severity:** symptomatic, intermittent to severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 173 **Age (mean [range]):** 48 (12-82) **Males %:** 40 **FEV_1 % predicted (mean):** 71 **Mean PEF AM (mean):** 327 **Duration of asthma (mean±SD):** 88±50 **Smoking status – prev/current (n[%]):** 15(9)/ 50(31) **GROUP 2** **N:** 159 **Age (mean [range]):** 47 (15-81) **Males %:** 40 **FEV_1 % predicted (mean):** 73.6 **Mean PEF AM (mean):** 341 **Duration of asthma (mean±SD):** 84±52 **Smoking status – prev/current (n[%]):** 12(7)/ 54(36) **GROUP 3** **N:** 171 **Age (mean [range]):** 46 (14-79) **Males %:** 42 **FEV_1 % 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)	**GROUP 1** **Drug mcg/day:** SAL/FP 100/1000 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI (HFA) **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** SAL/FP 100/1000 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskus™ **Withdraw LOE:** NR **GROUP 3** **Drug mcg/day:** FP 1000 + PLA **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** MDI **Withdraw LOE:** NR **Reliever Tx:** salbutamol prn **Run-in Tx:** usual ICS **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** PEF AM **Secondary** PEF PM PEF PM % predicted diurnal variation in PEF % predicted FEV_1 FEV_1 % predicted SFD SFN RFD	**Study objective:** To demonstrate equivalent efficacy and comparable tolerability of two inhaled combined formulations of SAL/FP 50/500 mcg bid in asthma patients

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Vermetten FA 1999[121] **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_1 % 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_1 % 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

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Vogelmeier C 2005[131] **Pub status:** Journal article **No. countries:** 16 **No. centers:** 246 **Design:** randomized, parallel, open label **Funding:** Industry: AstraZeneca	**Randomized:** 2,143 **Analyzed:** 2,135 **Withdrawals:** 269 **ITT analysis: yes** **Asthma stage and severity:** , **Baseline ICS use:** non-naïve **GROUP 1** **N:** NR **Age (mean [range]):** 45 (12-80) **Males %:** 42.3 **FEV_1 % predicted (mean [range]):** 73 (39-115) **Mean PEF AM (mean±SD):** NR **Duration of asthma (mean [range]):** 13 yr. (1-75) **Smoking status:** NR **GROUP 2** **N:** NR **Age (mean [range]):** 45 (12-84) **Males %:** 39.9 **FEV_1 % predicted (mean [range]):** 73 (28-100) **Mean PEF AM (mean±SD):** NR **Duration of asthma (mean [range]):** 12 yr. (0-74) **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** FORM/BUD 18/800 **Dosing:** variable **Treatment duration:** 52 wk. **Device:** Turbuhaler® **Withdraw LOE:** NR **GROUP 2** **Drug mcg/day:** SAL/FP 100/500 **Dosing:** fixed **Treatment duration:** 52 wk. **Device:** Diskus® **Withdraw LOE:** NR **Reliever Tx:** salbutamol prn **Run-in Tx:** usual ICS and LABA, if appropriate **Run-in duration:** 2 wk.	**Definition of exacerbation:** Severe – a deterioration in asthma, resulting in hospitalization/ER treatment, oral steroids for ≥3 days or an unscheduled visit (i.e. patient initiated) leading to treatment change. **List of clinical outcomes reported:** **Primary** time to 1st severe exacerbation **Secondary** FEV_1 pre-SABA FEV_1 post-SABA no. severe exacerbations no. days with exacerbation 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	**Study objective:** To assess the effectiveness of BUD/FORM for maintenance plus relief with a control group using SAL/FP for maintenance plus SABA for relief.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Wallin A 2003[116] **Pub status:** Journal article **No. countries:** 1 (Sweden) **No. centers:** 1 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 56 **Analyzed:** 46 **Withdrawals:** 10 **ITT analysis: no** **Asthma stage and severity:** symptomatic, moderate-severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 14 **Age (mean±SD):** 43±16 **Males %:** 61.1 **FEV_1 % predicted (mean±SD):** 80±16 **Mean PEF AM (median):** 441 **Duration of asthma (mean months±SD):** 206±130 **Smoking status:** NR **GROUP 2** **N:** 16 **Age (mean±SD):** 42±12 **Males %:** 42.1 **FEV_1 % predicted (mean±SD):** 91±20 **Mean PEF AM (median):** NR **Duration of asthma (mean months±SD):** 176±169 **Smoking status:** NR **GROUP 3** **N:** 16 **Age (mean±SD):** 40±15 **Males %:** 47.4 **FEV_1 % predicted (mean±SD):** 92±12 **Mean PEF AM (median):** 456 **Duration of asthma (mean months±SD):** NA **Smoking status:** NR	**GROUP 1** **Drug mcg/day:** SAL/FP 100/400 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskus®/Accuhaler® **Withdraw LOE:** 0 **GROUP 2** **Drug mcg/day:** FP 400 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Diskus®/Accuhaler® **Withdraw LOE:** 1 **GROUP 3** **Drug mcg/day:** FP 1000 **Dosing:** fixed **Treatment duration;** 12 wk. **Device:** Diskus®/Accuhaler® **Withdraw LOE:** 1 **Reliever Tx:** salbutamol **Run-in Tx:** BUD 800-1,200/d or FP 400-500/d or BDP 800-1000/d **Run-in duration:** 2-4 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** No primary clinical outcomes **Secondary** PEF PM FEV_1 no. pts experiencing exacerbation exacerbations leading to withdrawal	**Study objective:** To test the hypothesis that the addition of SAL to a low dose FP has a steroid-sparing effect and does not result in a worsening of bronchial inflammation compared to doubling the dose of ICS.

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Woolcock A 1996[118] **Pub status:** Journal article **No. countries:** 14 **No. centers:** 72 **Design:** randomized, parallel, double blind **Funding:** Industry: GlaxoSmithKline	**Randomized:** 738 **Analyzed:** 628 **Withdrawals:** 89 **ITT analysis: yes/no** **Asthma stage and severity:** symptomatic, moderate-severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 218 **Age (median [range]):** 44 (18-79) **Males %:** 51 **FEV_1 % predicted (mean):** 72 **Mean PEF AM (mean):** 383 **Duration of asthma:** NR **Smoking status – never/past/current (n(%)):** 133 (55)/65 (27)/45 (19) **GROUP 2** **N:** 194 **Age (median [range]):** 46 (19-75) **Males %:** 51 **FEV_1 % predicted (mean):** 71 **Mean PEF AM (mean):** 381 **Duration of asthma:** NR **Smoking status – never/past/current (n(%)):** 112 (46)/94 (39)/38 (16) **GROUP 3** **N:** 216 **Age (median [range]):** 42 (12-72) **Males %:** 54 **FEV_1 % predicted (mean):** 75 **Mean PEF AM (mean):** 388 **Duration of asthma:** NR **Smoking status – never/past/current (n(%)):** 138 (55)/80 (32)/33 (13)	**GROUP 1** **Drug mcg/day:** SAL/BDP 100/1000 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** MDI **Withdraw LOE:** 2/243 **GROUP 2** **Drug mcg/day:** SAL/BDP 200/1000 **Dosing:** fixed **Treatment duration:** 24 wk. **Device:** MDI **Withdraw LOE:** 2/244 **GROUP 3** **Drug mcg/day:** BDP 2000 **Dosing:** fixed **Treatment duration;** 24 wk. **Device:** MDI **Withdraw LOE:** 5/251 **Reliever Tx:** salbutamol (MDI 100 mcg/actuation) or dry powder (400 mcg/blister) **Run-in Tx:** P1: for pts on BDP 1000µg/d = 1wk; for pts on 800µg/d=4wk.; P2:all received 1000µg/d x 1wk **Run-in duration:** 1 or 4 wk.	**Definition of exacerbation:** Exacerbation – any worsening of asthma symptoms requiring a change in prescribed therapy, other than increased use of rescue medication. **List of clinical outcomes reported:** **Primary** PEF AM PEF PM **Secondary** FEV_1 FEV_1 % predicted no. pts experiencing exacerbation time to first exacerbation DTS NTS RFD RFN SFD SFN nights no awakenings QoL score need for additional ICS PC_{20}	**Study objective:** to compare the efficacy and safety of the coprescription of SAL 50 mcg twice daily or 100 mcg twice daily with BDP 500 mcg twice daily (SAL 50 and SAL 100) with BDP 1,000 mcg twice daily (BDP 1,000) in patients with asthma not controlled by BDP 500 mcg twice daily (or the equivalent).

Study	Participant characteristics	Treatment characteristics	Clinical outcomes reported	Notes
Author Year: Zetterstrom O 2001[89] **Pub status:** Journal article **No. countries:** 6 **No. centers:** 59 **Design:** randomized, parallel, double blind, double dummy **Funding:** Industry: AstraZeneca	**Randomized:** 362 **Analyzed:** 362 **Withdrawals:** 53 **ITT analysis: yes** **Asthma stage and severity:** NR, mild-severe **Baseline ICS use:** non-naïve **GROUP 1** **N:** 123 **Age (mean [range]):** 46.5 (18-78) **Males %:** 53 **FEV_1 % predicted:** NR **Mean PEF AM (mean±SD):** NR **Duration of asthma (mean):** 19.1 yr. **Smoking status – never/past/current (n):** 72/40/11 **GROUP 2** **N:** 115 **Age (mean [range]):** 44.7 (18-77) **Males %:** 50 **FEV_1 % predicted:** NR **Mean PEF AM (mean±SD):** NR **Duration of asthma (mean):** 16.9 **Smoking status – never/past/current (n):** 69/33/13 **GROUP 3** **N:** 124 **Age (mean [range]):** 48.5 (21-78) **Males %:** 50 **FEV_1 % predicted:** NR **Mean PEF AM (mean±SD):** NR **Duration of asthma (mean):** 17.1 yr. **Smoking status – never/past/current (n):** 79/38/7	**GROUP 1** **Drug mcg/day:** FORM/BUD 18/800 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Turbuhaler® **Withdraw LOE:** 5 **GROUP 2** **Drug mcg/day:** FORM/BUD 18/800 **Dosing:** fixed **Treatment duration:** 12 wk. **Device:** Turbuhaler ® **Withdraw LOE:** 8 **GROUP 3** **Drug mcg/day:** BUD 800 **Dosing:** fixed **Treatment duration;** 12 wk. **Device:** Turbuhaler® **Withdraw LOE:** 14 **Reliever Tx:** terbutaline sulphate or salbutamol **Run-in Tx:** usual ICS **Run-in duration:** 2 wk.	**Definition of exacerbation:** NR **List of clinical outcomes reported:** **Primary** PEF AM **Secondary** PEF PM FVC symptom score (0-6) NTA SFD RFD SABA use	**Study objective:** FORM/BUD in a single inhaler was compared with BUD alone, and with concurrent administration of BUD and FORM from separate inhalers, in patients with asthma, not controlled with inhaled glucocorticosteroids alone **Additional details:** Comparison of the original Turbuhaler (BUD alone) measured metered dose with the new Turbuhaler® (single inhaler therapy) has a dose counter, an externally tapered mouthpiece, and measures dose as delivered dose

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 ≥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[53]was specifically designed to assess the efficacy of SAL/FP in asthmatics with a smoking history of ≥10 pack-years.

b) Assessment of compliance

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.

c) 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 SMART®)	5
Treatment duration	
<6 mo.	81 (75.7)
6–12 mo.	25 (23.4)
>12 mo.	0
Unclear	1 (0.9)
Participant characteristics	
Age yr. (range)	4-87
Studies with only participants ≥18 yr.	39 (36.4)
Asthma severity	
Mild	9 (8.4)

Table 1: Characteristics of included studies (N=107) (continued)	
Moderate	17 (15.9)
Severe	3 (2.8)
Intermittent-mild	3 (2.8)
Intermittent-moderate	8 (74.8)
Intermittent-severe	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[†]	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	
Reported at least one measure as primary outcome	
Pulmonary function	67 (62.6)
Asthma control	40 (37.4)
Health-related quality of life	4 (3.7)
Reported at least one measure as secondary outcome	
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

[†]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[29,46,54-70] 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 ≥1 mo. prior to the treatment period). Eleven trials[29,56,57,60-64,66,67,69] compared SAL/FP vs FP, three compared FORM/BUD vs BUD,[46,58,70] two compared SAL/BDP vs BDP,[54,59] one compared SAL/FP vs BUD,[65] one compared SAL/FP vs BDP,[69] and one compared SAL/TAA vs TAA.[55] 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.[29,46,54-61,63,64,67,69,70] The remaining four trials[62,65,66,68] compared LABA/ICS with a higher dose (double or greater) of ICS. The age of included participants was ≥18 years in 5 (26.3%) studies.[46,59,63,66,70] In terms of asthma severity, three trials[54,62,69] included only participants with mild asthma, and two[60,67] included only participants with moderate asthma. The remaining trials examined participants covering a range of asthma severity: intermittent to mild (1 trial),[56] intermittent to moderate (1 trial),[59] intermittent to severe (3 trials),[57,61,70] mild to moderate (4 trials),[46,55,58,65] and mild to severe (5 trials).[29,63,64,66,68] Treatment duration also varied across studies: 8 wk (2 trials),[59,70] 12 wk (10 trials),[46,56,57,59,61,64-68] 26 wk (3 trials),[55,63,69] and 52 wk (4 trials).[29,54,58,62] 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[54,55,59] 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. Double-blinding 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 ≥3) of almost all studies, no sensitivity analyses were conducted.

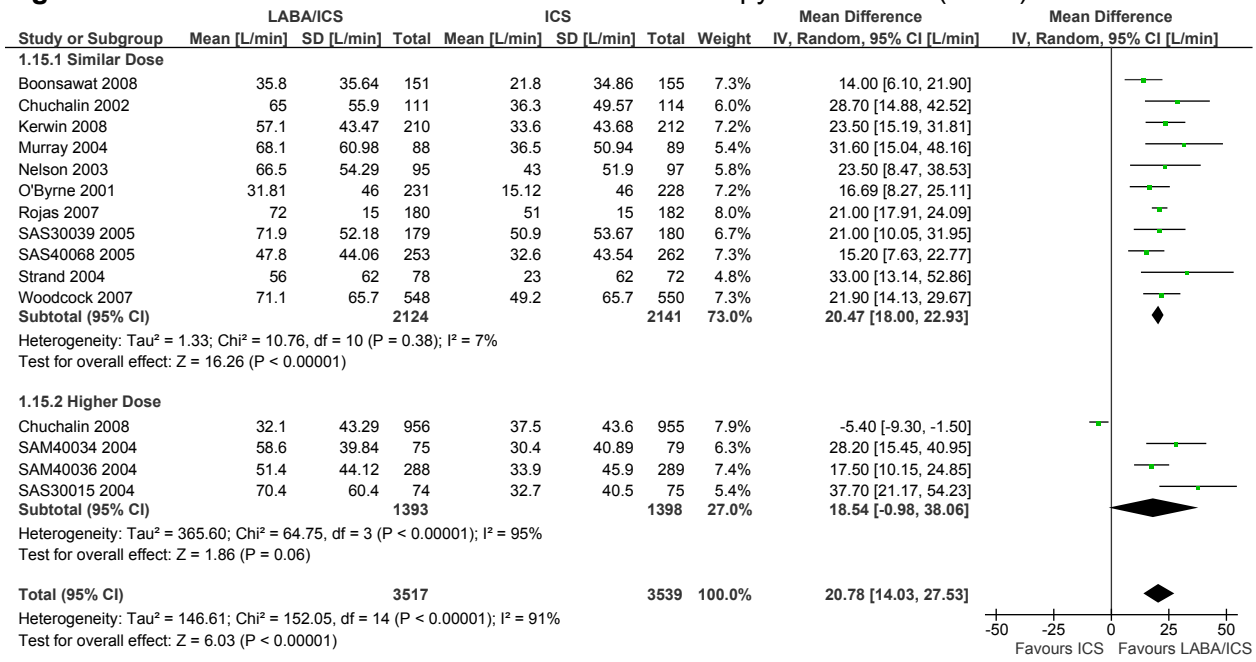
Table 3: Methodological quality of steroid naïve participants

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[39,46,56-58,60-69] 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).

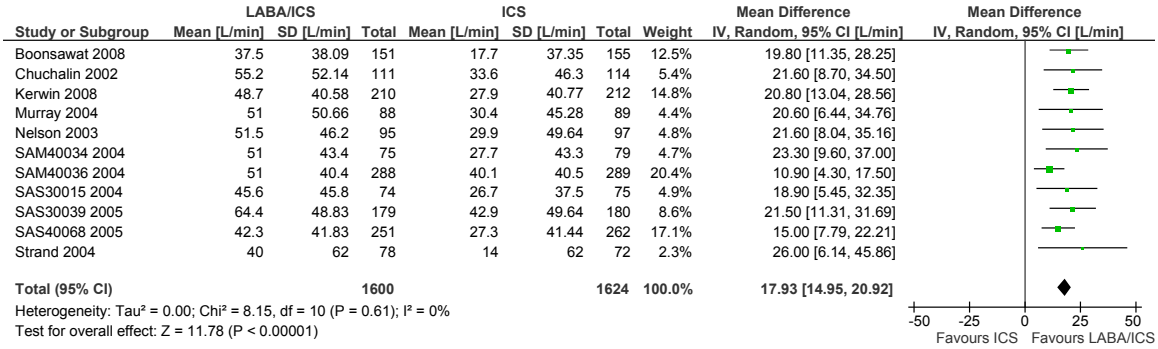
Figure 1: The effect of LABA/ICS versus ICS monotherapy on PEF AM (L/min)



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[62] 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[65] and mild to severe[66,68]).

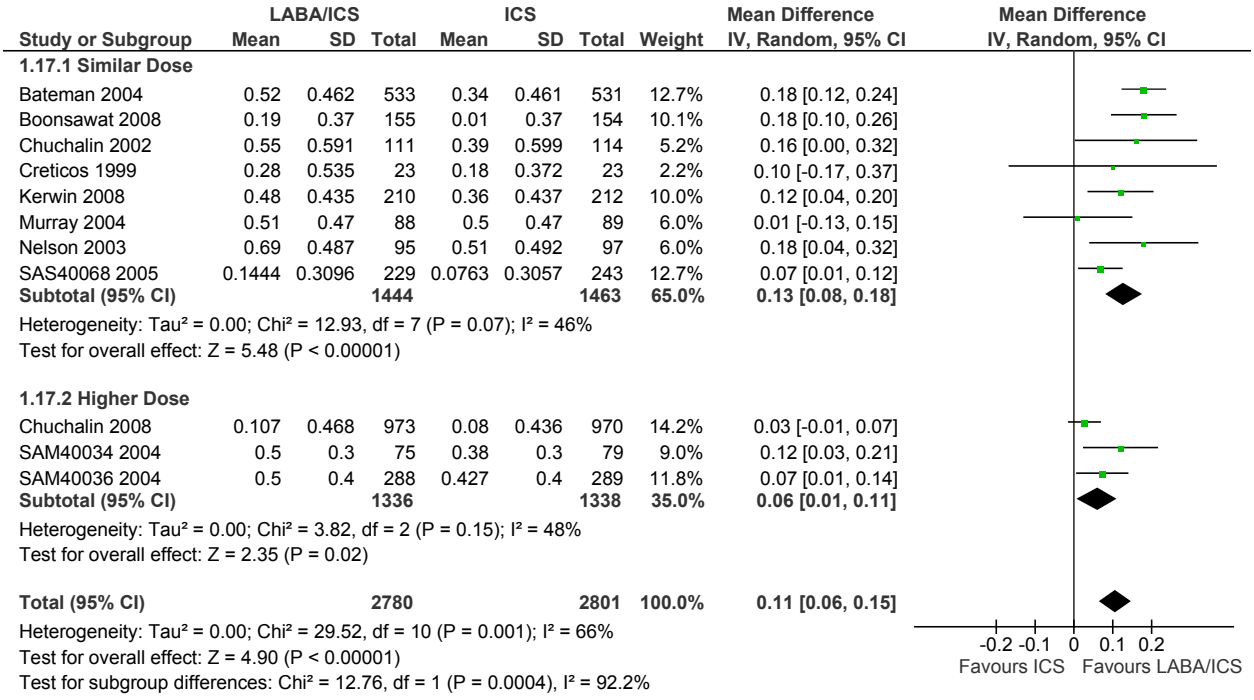
PEF PM: Eleven trials[46,56,57,61,63-69] involving 3,224 participants (LABA/ICS = 1,600, ICS = 1,624) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on PEF PM (L/min) (Figure 2). The combined result indicated a statistically significant 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).

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



FEV$_1$ (absolute): Eleven trials[29,46,55-57,61,62,64-66,69] 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$_1$ (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^2=66%); however, the pooled result demonstrated heterogeneity and the 965% CI did not include a priori defined clinical significance (MCID=0.23 L).

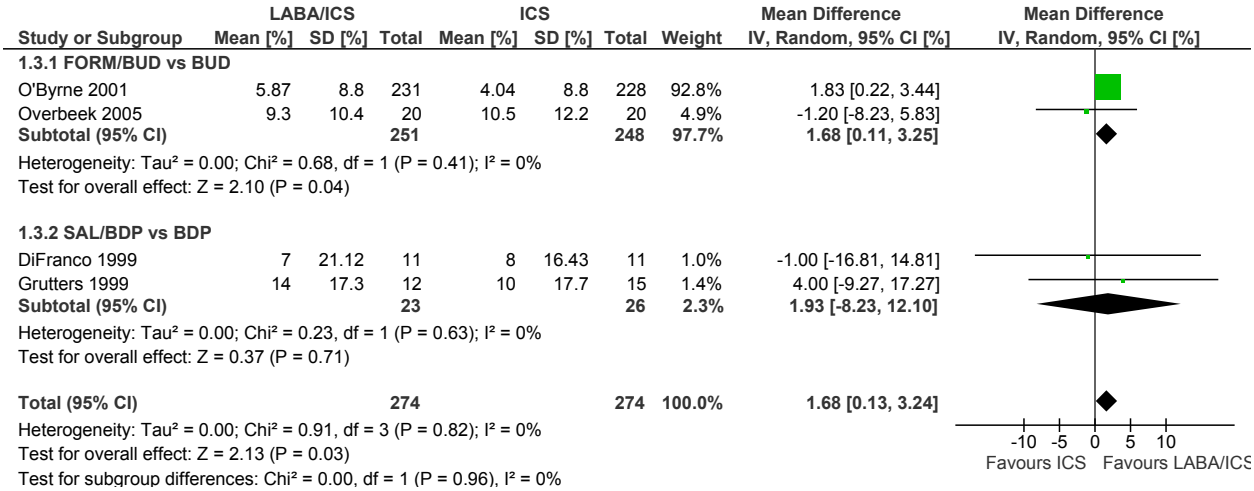
Figure 3: The effect of LABA/ICS versus ICS monotherapy on FEV$_1$ (absolute) (L)



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$_1$ % predicted: Four trials[54,58,59,70] 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%).

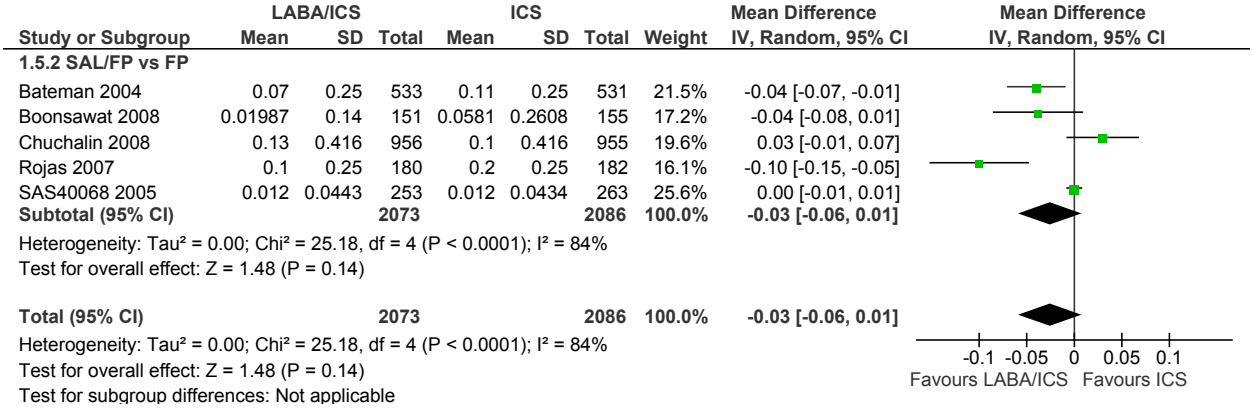
Figure 4: The effect of LABA/ICS versus ICS monotherapy on FEV$_1$ % predicted



c) Asthma symptom control measures

Total number of exacerbations: Five trials[29,56,60,62,69] 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[60] (WMD = -0.10; 95% CI: -0.15 to -0.05) compared medium-dose FP (500 mcg/d) in a population with moderate asthma. Three trials[56,62,69] compared low-dose FP (100–200 mcg/d) and one trial[29] 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.[29]

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

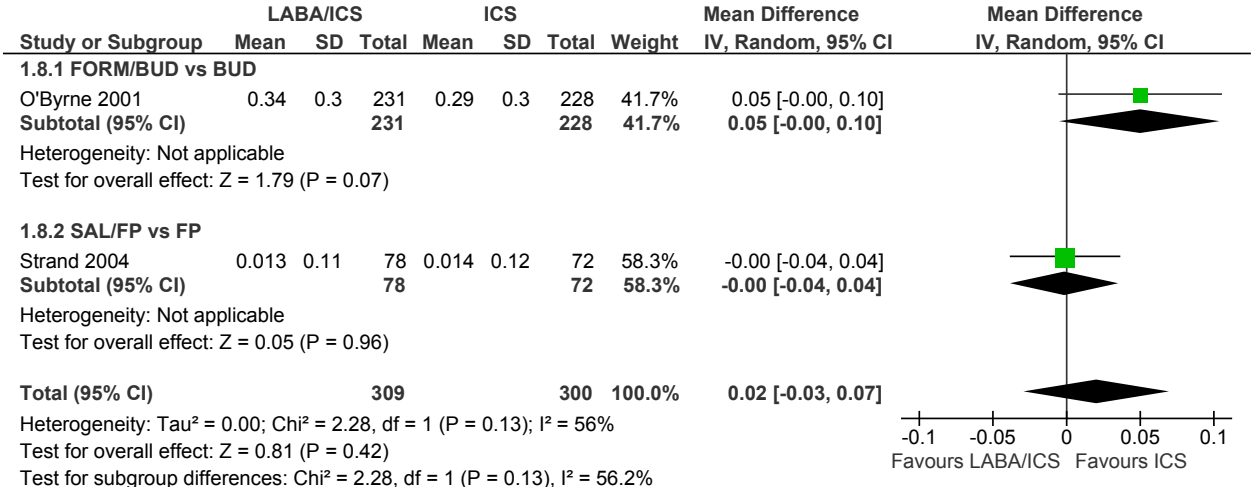


Time to first exacerbation: One trial[68] involving 156 participants (SAL/FP = 78, BDP = 78) provided data on the effects of SAL/FP compared with BDP on time to first exacerbation. The combined result indicated a statistically significant difference favouring SAL/FP (Hazard ratio = 0.44 (95% CI: 0.24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

Percent participants experiencing ≥1 exacerbation: One trial[68] 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).

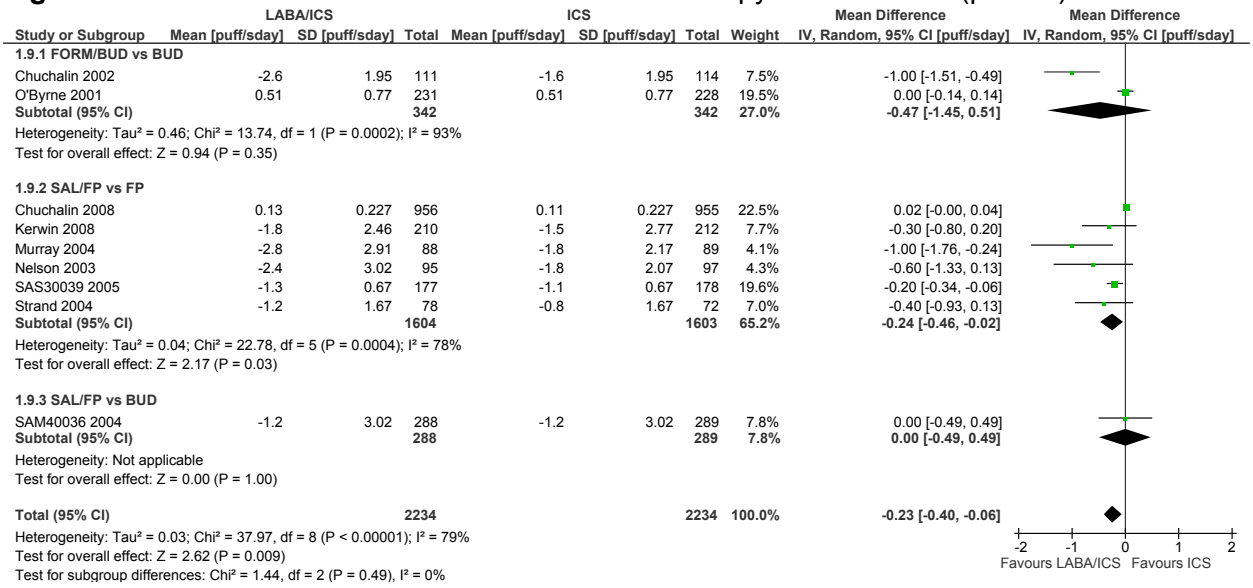
Number of severe exacerbations: Two trials[58,63] involving 609 participants (SAL/FP = 309, FP = 300) provided data for a meta-analysis of the effects of SAL/FP combination therapy compared with FP monotherapy number of severe exacerbations (Figure 6). The combined result failed to identify a statistically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

Figure 6: The effect of LABA/ICS versus ICS monotherapy on no. severe exacerbations



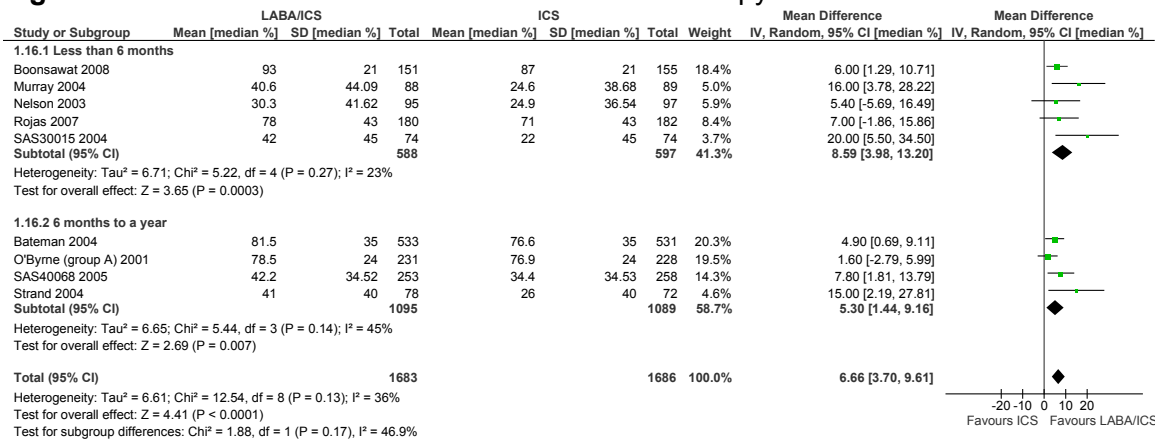
Short-acting beta$_2$-agonist (SABA) use: Nine trials[46,57,58,61-65,67] involving 4,468 participants (LABA/ICS = 2,234, ICS = 2,234) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on use of SABA reliever medication (puffs/d) (Figure 7). 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^2=79%).

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



Symptom-free days (SFD): Nine trials[29,56-58,60,63,64,68,69] 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^2=36%).

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

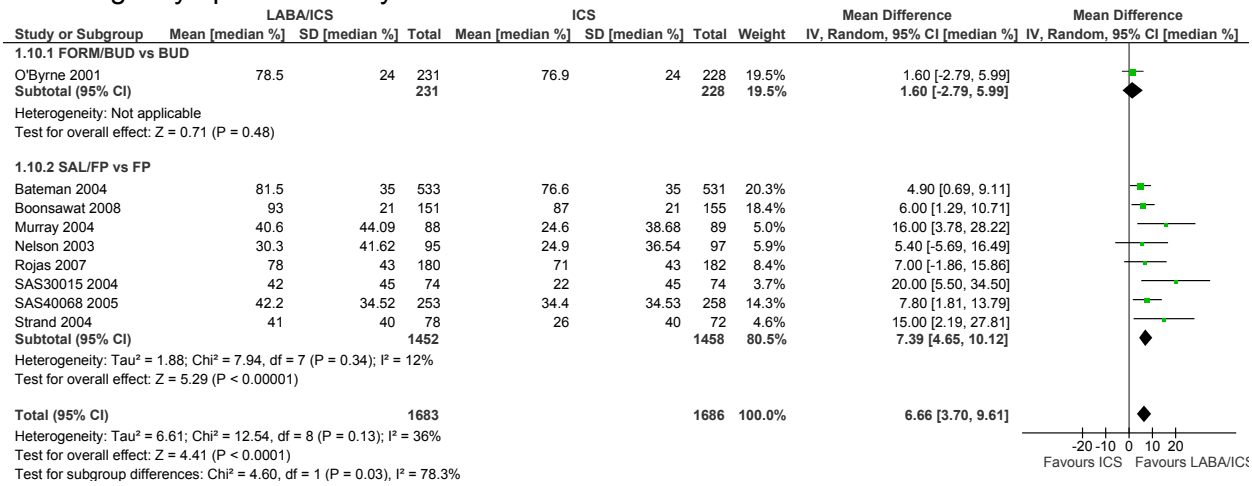


A subgroup analysis based on the duration of the treatment period (<6 mo. vs 6–12 mo.) indicated little change in the magnitude and precision of the point estimate for shorter follow-ups (WMD=8.59; 95% CI: 3.98 to 13.20; I^2=23%). Four of the studies[56,57,60,64] compared SAL/FP with FP and one study[58] 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,[56] intermittent to severe,[57] mild to severe[64,68] and moderate.[60]

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[29,63,69] compared SAL/FP with FP and one study[58] 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,[69] mild to moderate,[58] and mild to severe.[29,63]

Proportion of participants achieving symptom-free day (SFD): Nine trials[29,56-58,60,63,64,68,69] 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).

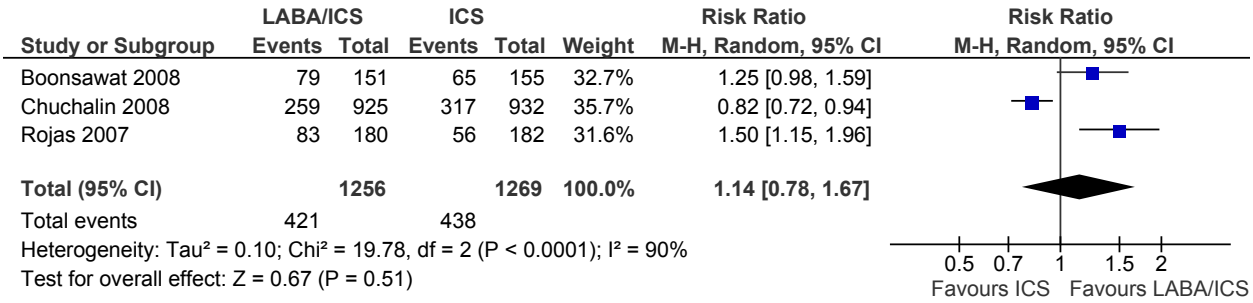
Figure 9: The effect of LABA/ICS versus ICS monotherapy on proportion of participants achieving a symptom-free day



Participants achieving optimal control: Three trials[56,60,62] 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^2 = 90%).

All three trials compared SAL/FP with FP. Two trials[56,60] compared LABA/ICS to a similar dose of ICS, and one trial[62] 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,[56] mild,[62] and moderate.[60] Two trials[56,60] had a treatment duration of 12 wk. In contrast, the trial[62] with a result favouring ICS had a treatment duration of 52 wk.

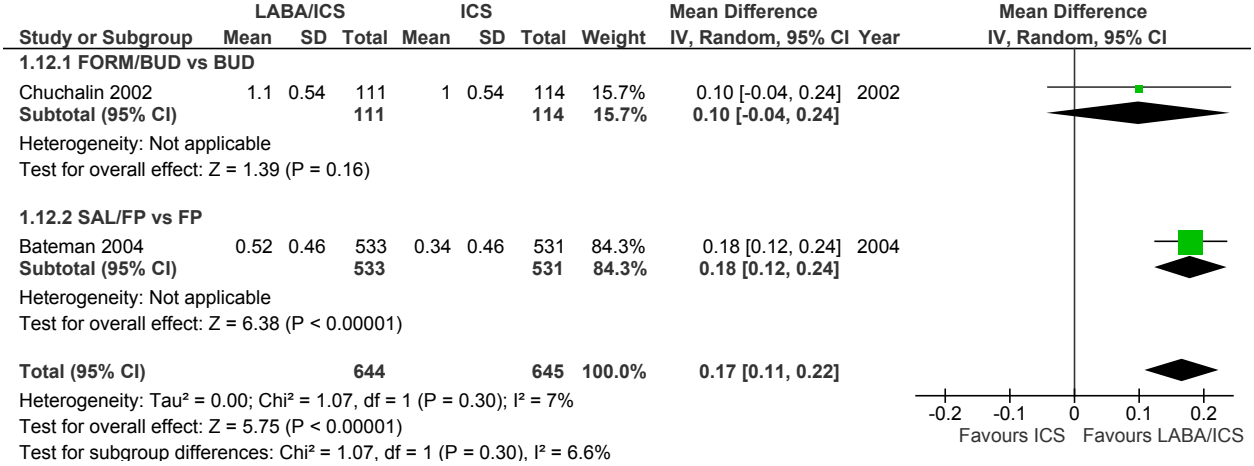
Figure 10: The effect of LABA/ICS versus ICS monotherapy on no. participants achieving optimal control



e) Health-related quality of life measures

Asthma quality of life questionnaire (AQLQ): Two trials[29,46] 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 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.

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.

Figure 12: Funnel plot of LABA/ICS steroid naïve for PEF AM

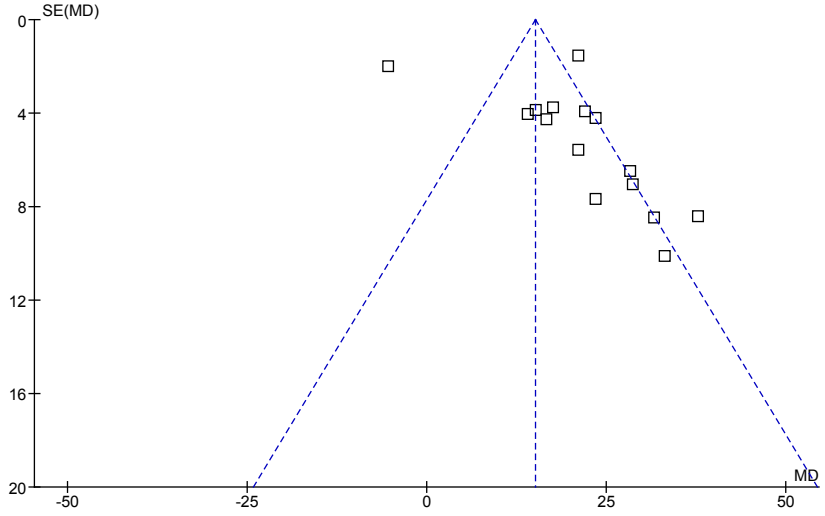


Figure 13: Funnel plot of LABA/ICS steroid naïve for PEF PM

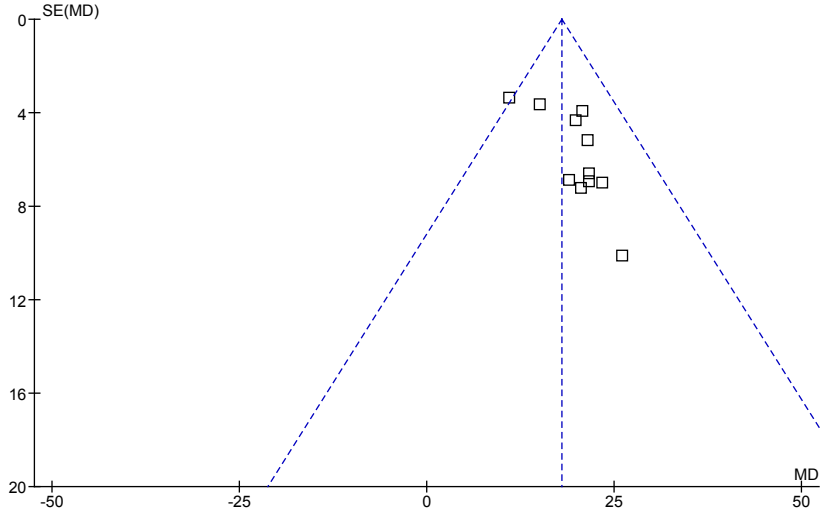
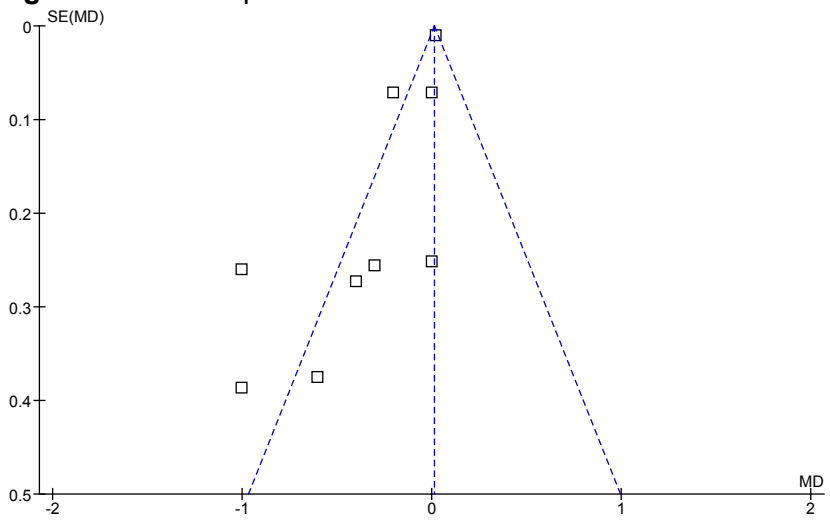


Figure 14: Funnel plot of LABA/ICS steroid naïve for SABA use



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

Thirty-seven unique RCTs[29,45,47,58,72-104] 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 ≥1 mo. prior to the treatment period. Seventeen trials[29,74-76,78,81,84,87,94,95,97-100,102-104] compared SAL/FP versus FP, ten[45,47,58,72,89,91-93,96,101] compared FORM/BUD vs BUD, three[73,82,83] compared SAL/ICS (not described or mixed) versus ICS, three[85,88,90] compared FORM/ICS versus ICS (not described or mixed), one[77] compared SAL/FP versus BDP, one[80] compared SAL/FP versus BUD, one[79] compared SAL/TAA versus TAA, and one[86] compared SAL/BDP or BUD versus BDP or BUD.

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

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

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 ≥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)

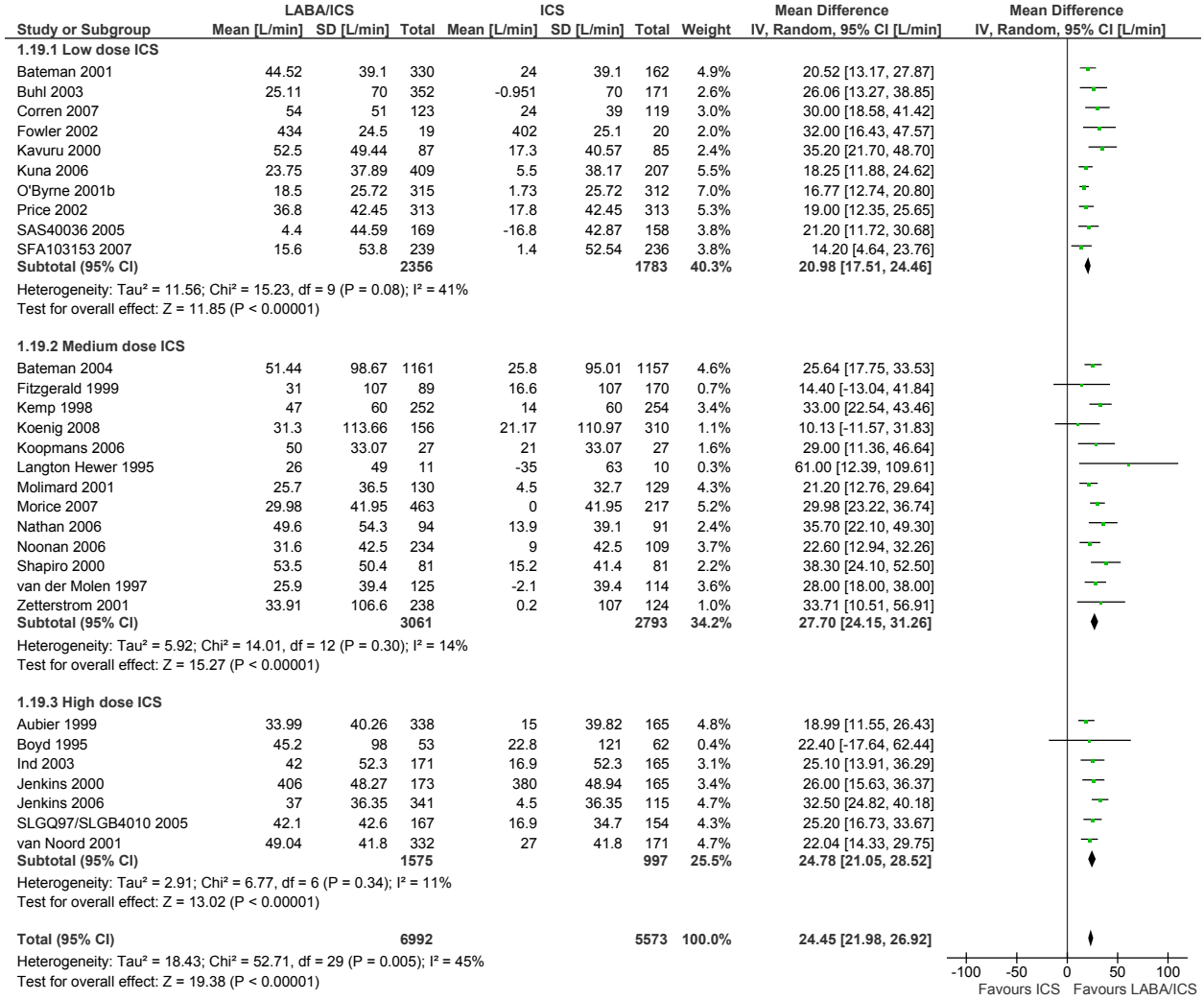
Participants in 32 trials were run-in on ICS monotherapy and all of these studies provided at least one clinical outcome for meta-analyses. Participants in five trials[74,79,84,99,101] were run-in on low-, medium- and high-dose ICS regiments or LABA/ICS combination therapy and the results were reported 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[29,45,47,58,72,73,75-78,80-83,85,87-98,100,102,104] 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.

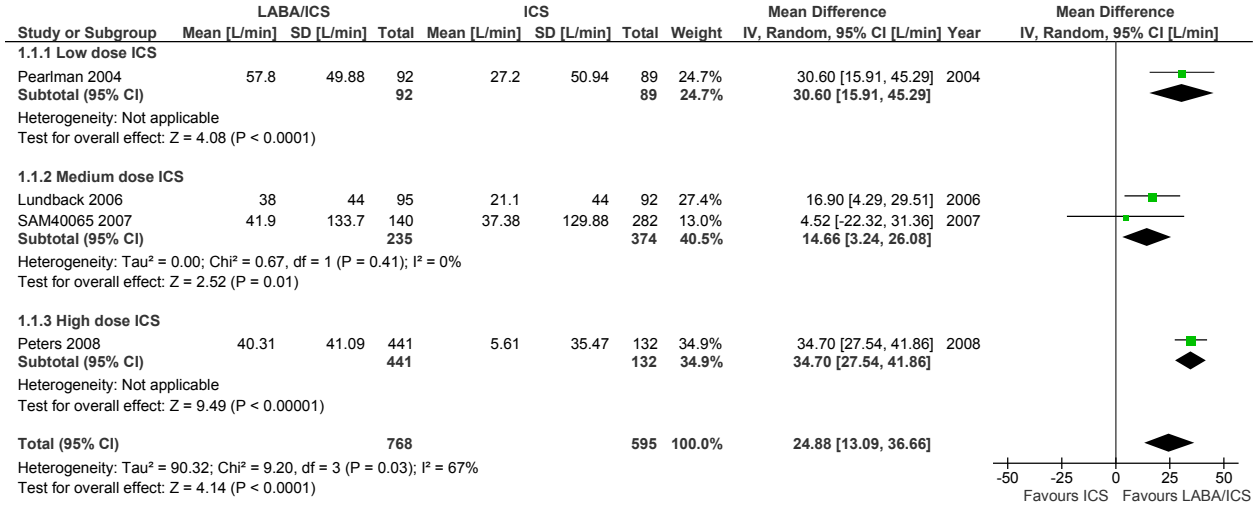
Figure 15.1: The effect of LABA/ICS versus ICS monotherapy on PEF AM (L/min)



Four trials[74,84,99,123] 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%).

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

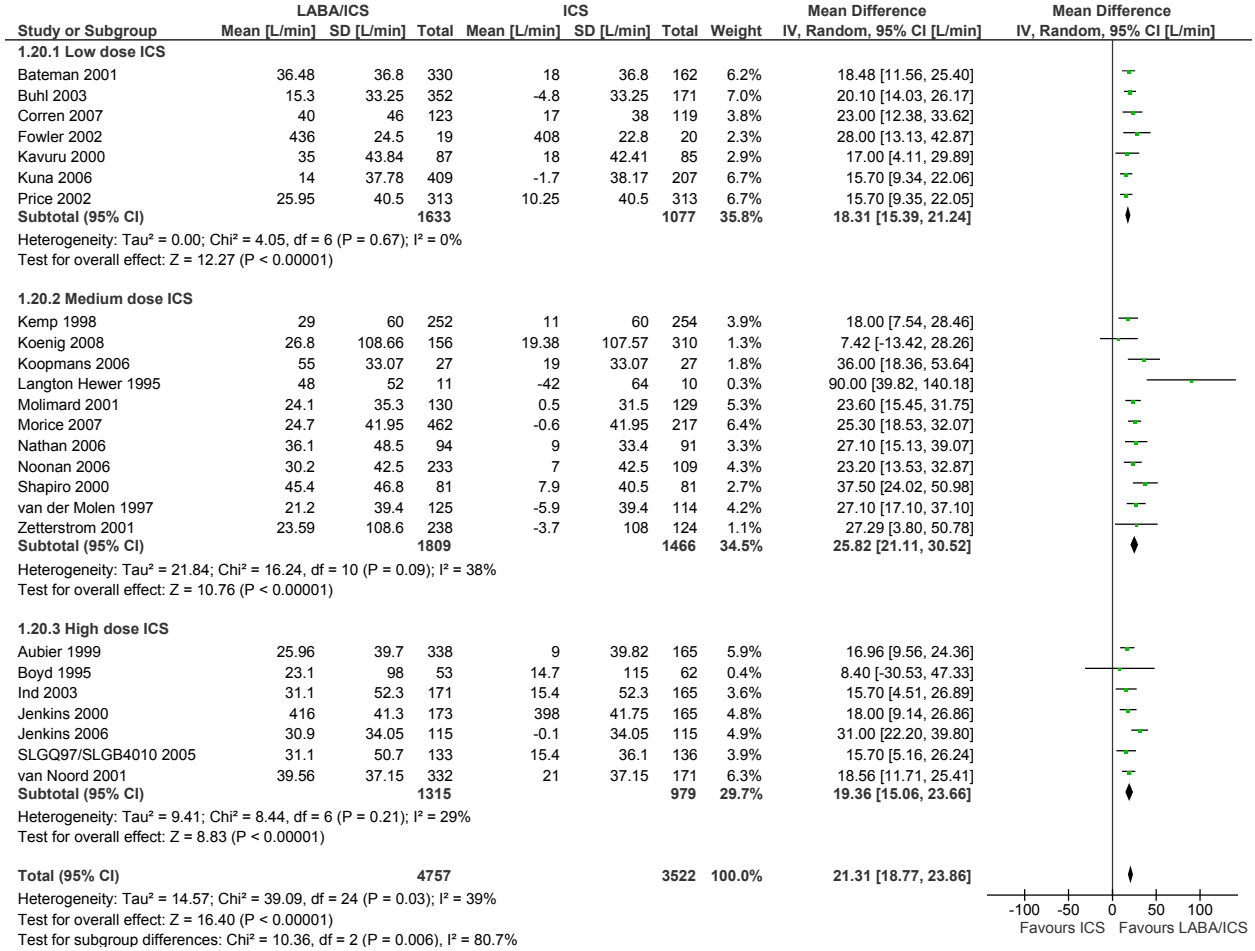


PEF PM: Twenty-five trials[45,47,72,73,75-78,80-83,85,87-89,91-98,104] involving 8,279 participants (LABA/ICS = 4,757, ICS = 3,522) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on PEF PM (L/min) (Figure 16). The pooled result indicated a statistically significant and clinically important difference favouring LABA/ICS (WMD = 21.31 L/min; 95% CI: 18.77 to 23.86; I^2 = 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[74] 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).

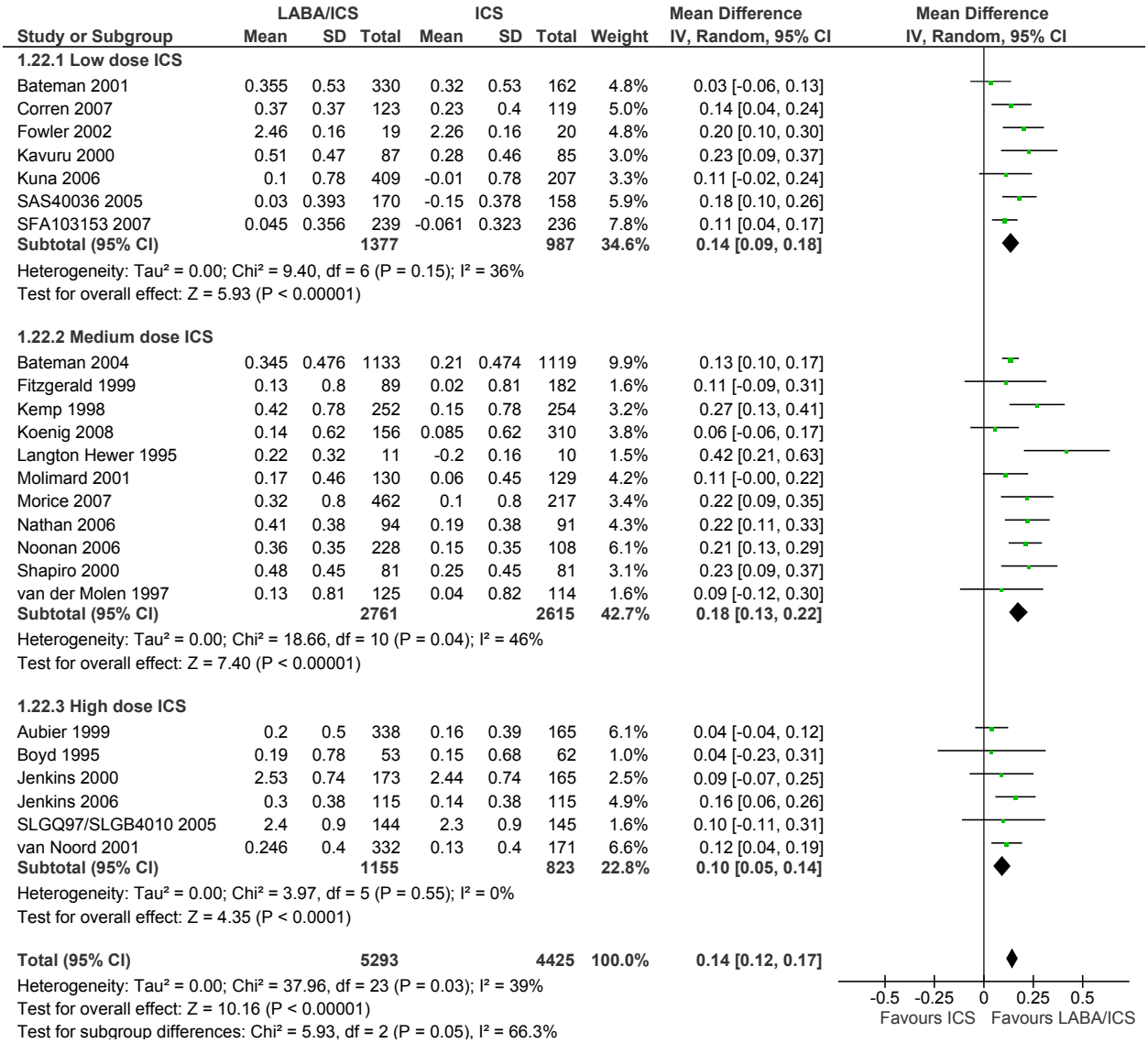
Figure 16: The effect of LABA/ICS versus ICS monotherapy on PEF PM (L/min)



FEV$_1$ absolute (L): Twenty-four trials[29,45,47,65,73,75,77,80-83,85,87,88,90,92-98,100,104] 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_1 (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^2 = 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%).

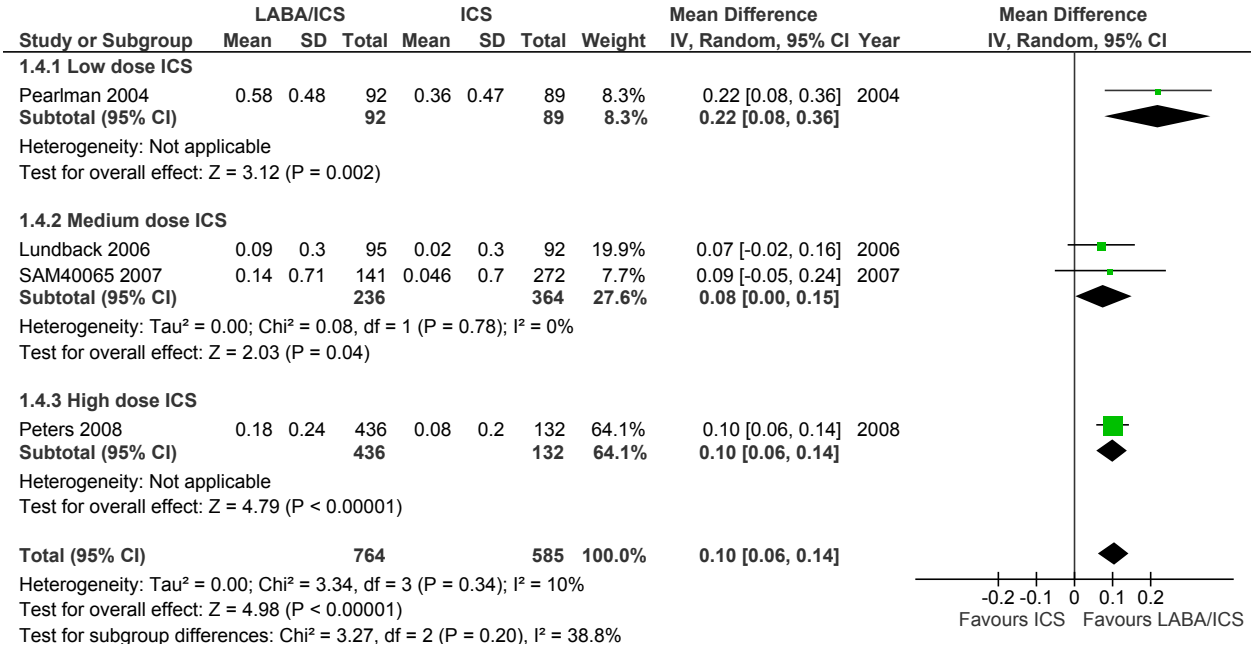
Figure 17.1: The effect of LABA/ICS versus ICS monotherapy on FEV_1 (absolute) (L)



Four trials[74,84,99,123] 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_1 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^2 = 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).

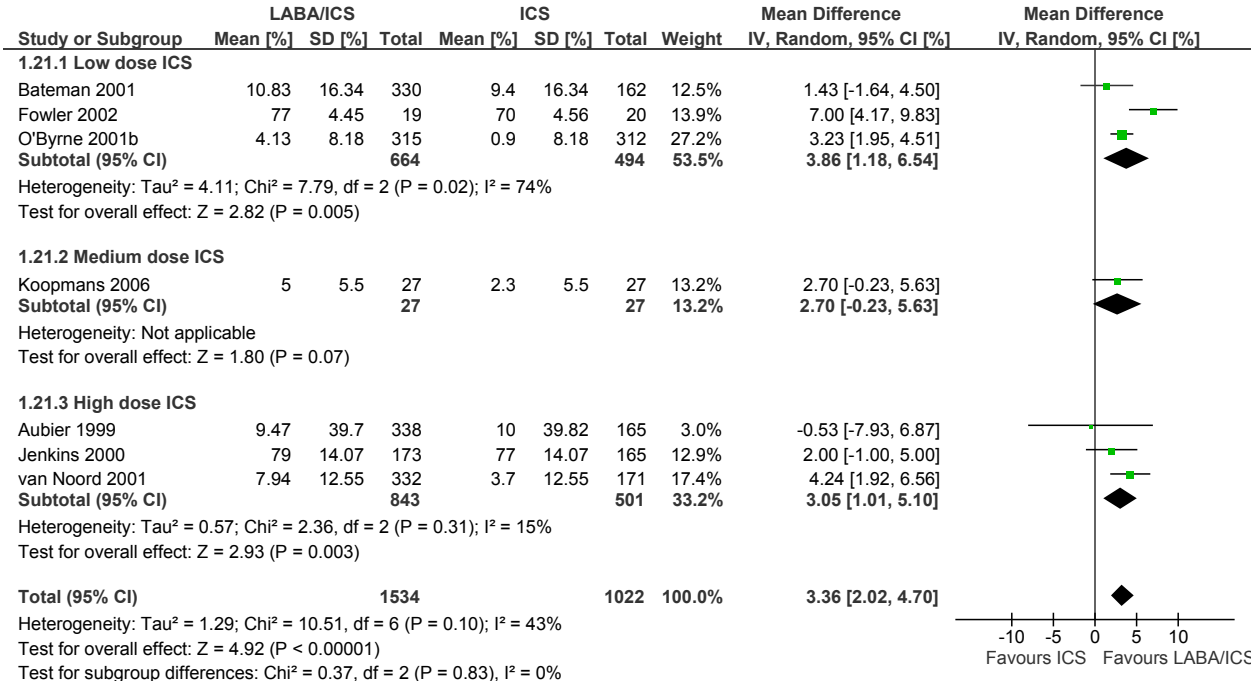
Figure 17.2: The effect of LABA/ICS versus ICS monotherapy on FEV_1 (absolute) (L) (mixed LABA/ICS use at baseline)



FEV_1 % predicted: Seven trials[58,75,77,78,80,97,98] 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_1 % predicted (Figure 18). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 3.36; 95% CI: 2.02to 4.07; I^2 = 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^2 = 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^2 = 15%) dose comparisons.

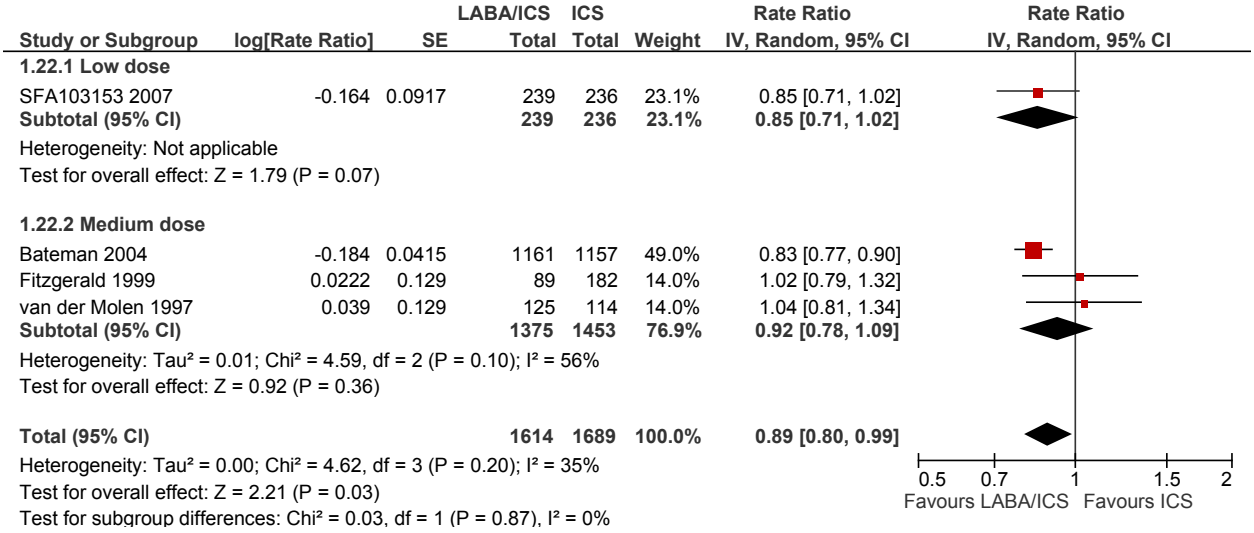
Figure 18: The effect of LABA/ICS versus ICS monotherapy on FEV_1 % predicted



Asthma control measures

Total number of exacerbations: Four trials[29,88,90,100] 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^2 = 35%).

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

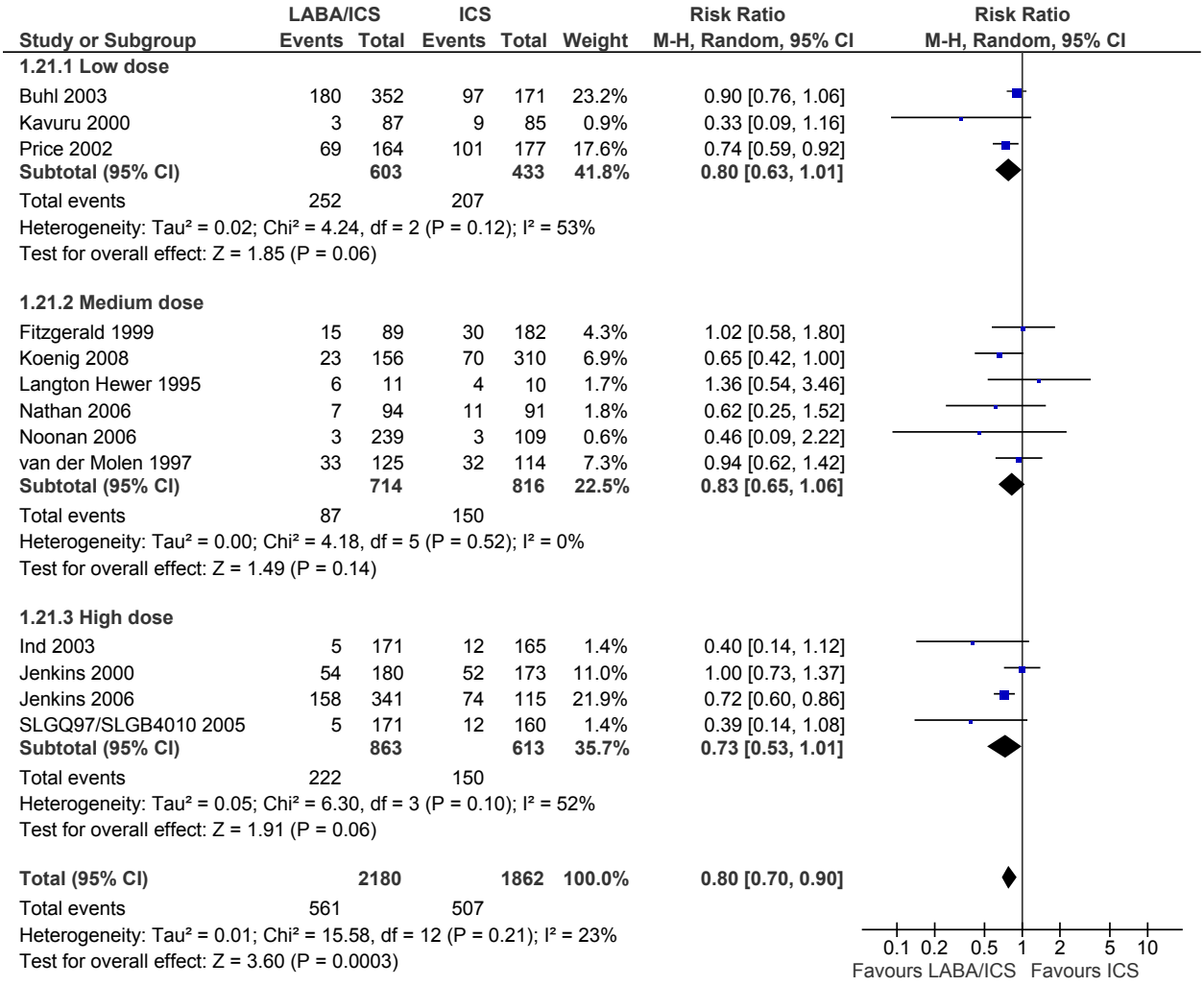


One trial[101] involving 576 participants (LABA/ICS = 443, ICS = 133) run-in on either LABA/ICS combination or ICS monotherapy provided data for a meta-analysis of the effects of

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 ≥1 exacerbation: Thirteen trials[72,76,80,81,83,88,90-95,104] 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 ≥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^2 = 23%).

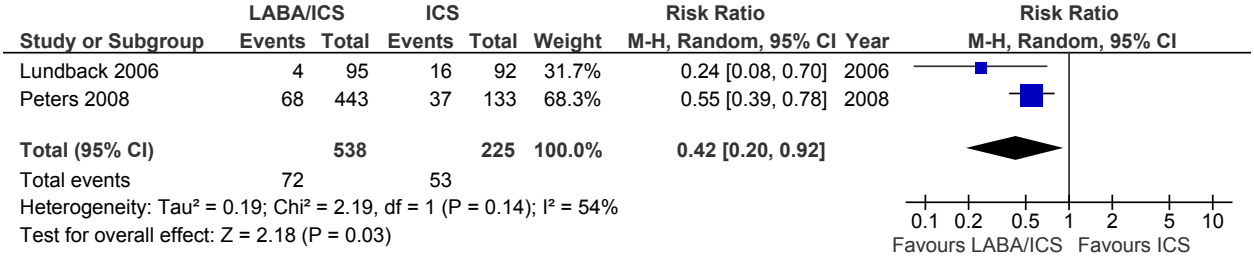
Figure 20.1: The effect of LABA/ICS versus ICS monotherapy on no. participants ≥1 exacerbation



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[84,101] 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 ≥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^2 = 54%).

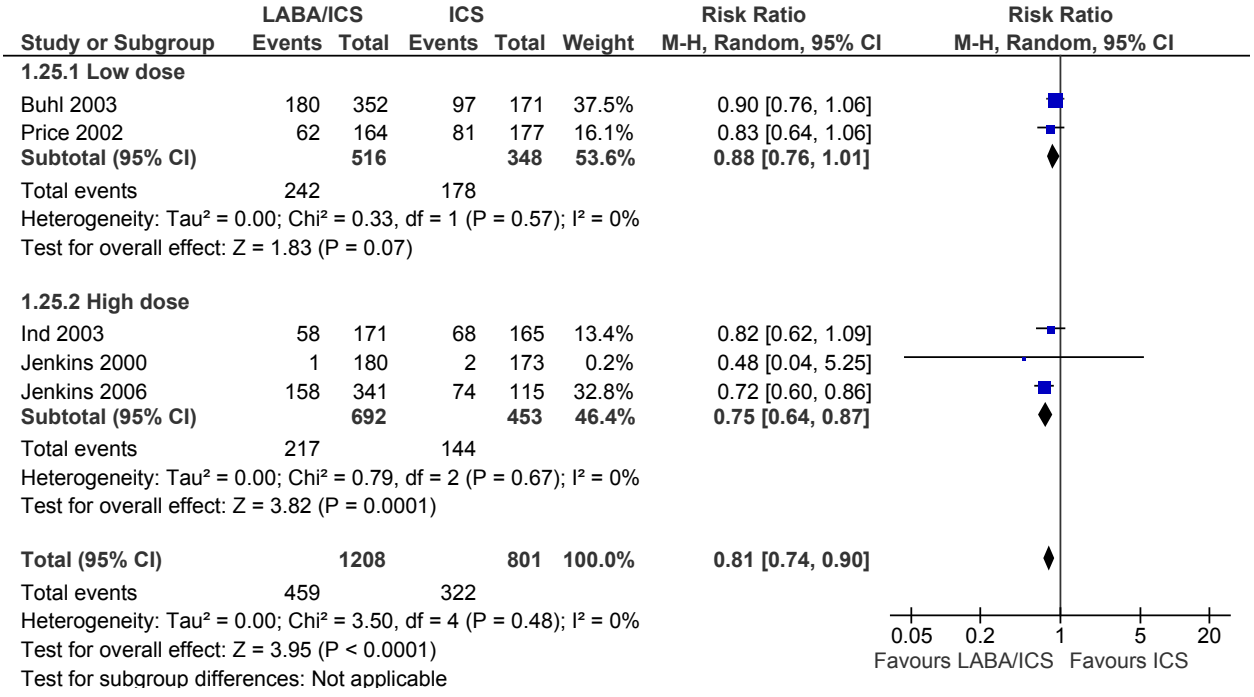
Figure 20.2: The effect of LABA/ICS versus ICS monotherapy on no. patients with ≥ 1 exacerbation (mixed LABA/ICS use at baseline)



Number of participants with ≥1 mild exacerbation: Five trials[72,76,80,91,93] 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^2 = 0%).

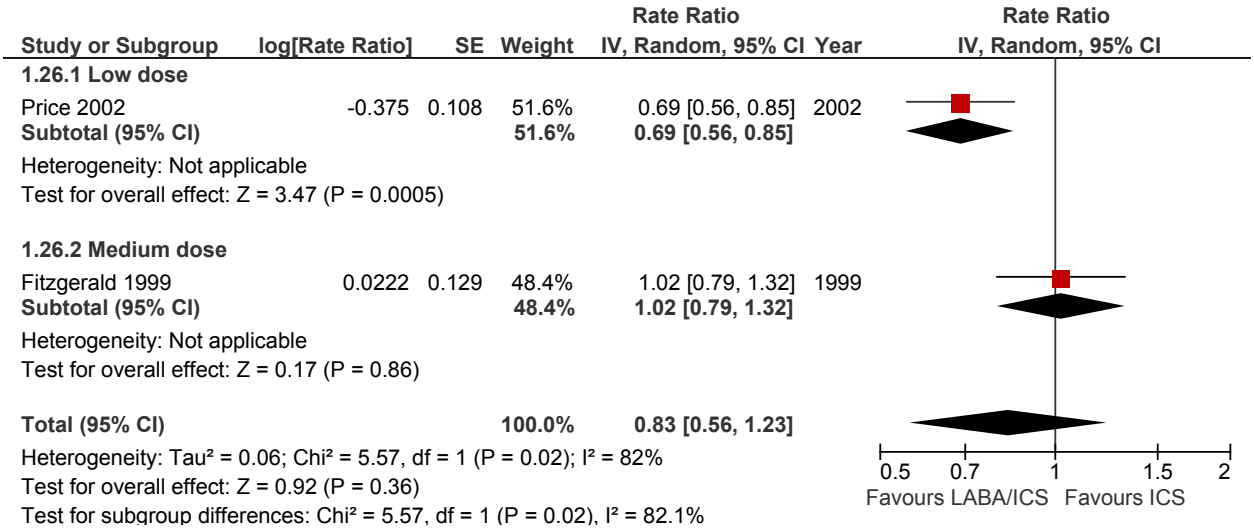
A subgroup analysis based on comparison ICS dose indicated no change in the significance of the treatment effect for the high (RR = 0.75; 95% CI: 0.64 to 0.87; I^2 = 0) dose studies. The pooled results failed to indicate a statistically significant difference between the two treatments (RR = 0.88; 95%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

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



Number of mild exacerbations: Two trials[90,91] 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%).

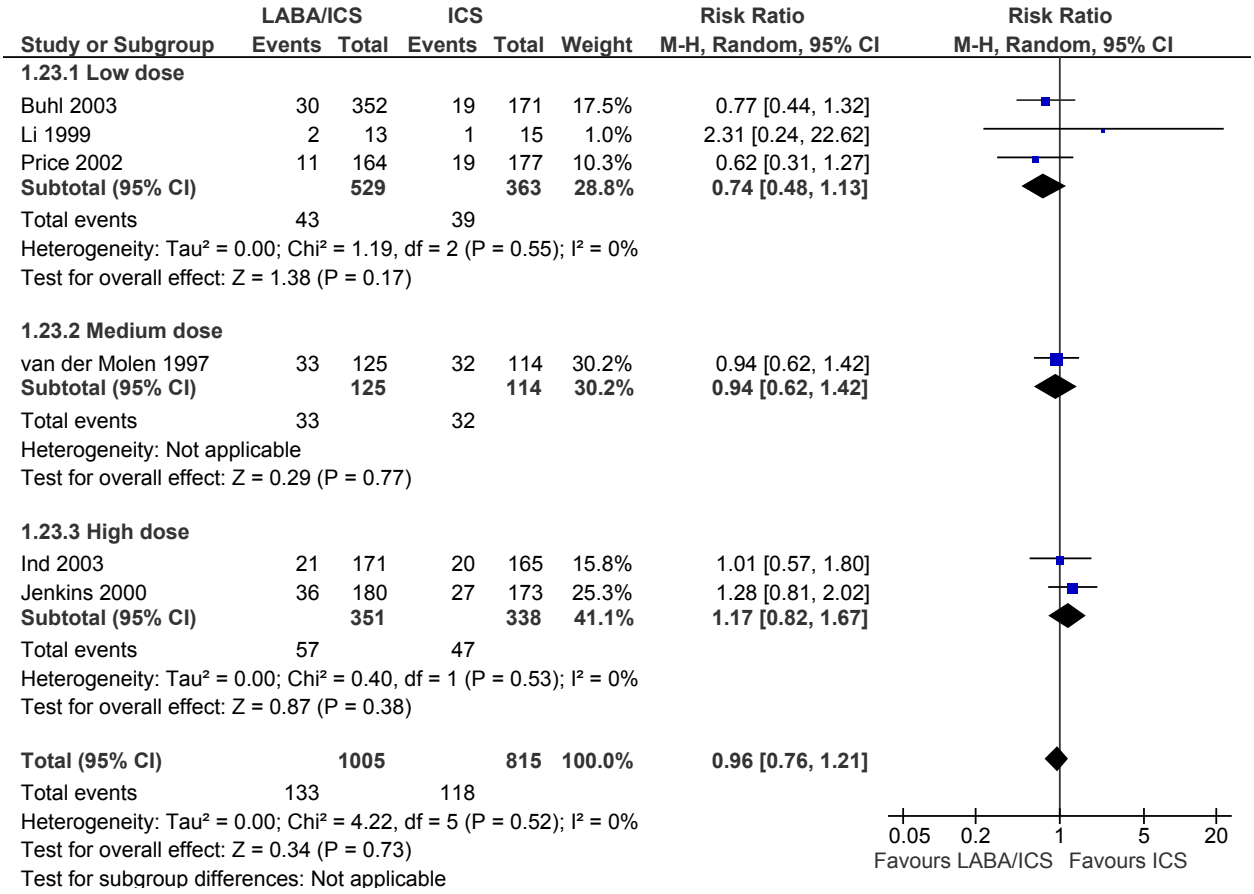
Figure 22: The effect of LABA/ICS versus ICS monotherapy on no. mild exacerbations



Number of participants with ≥1 severe exacerbation: Six trials[72,76,80,86,88,91] 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 ≥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^2 = 0%).

Figure 23: The effect of LABA/ICS versus ICS monotherapy on no. participants with ≥1 severe exacerbation

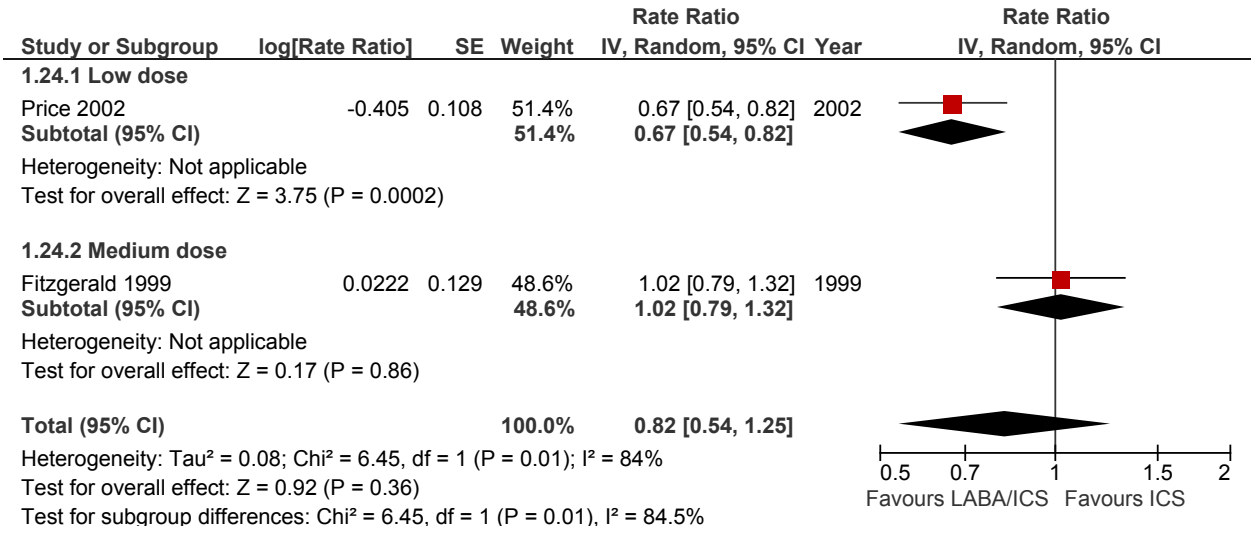


A subgroup analysis based on dose of comparison ICS failed to indicated statistically significant differences between the two treatments for low (RR = 0.74; 95% CI: 0.48 to 1.13; I^2 = 0%), medium (RR = 0.94; 95% CI: 0.62 to 1.42), and high (RR = 1.17; 95% CI: 0.82 to 1.67; I^2 = 0%) dose studies.

Number severe exacerbations:

Two trials[90,91] } 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^2 = 84%).

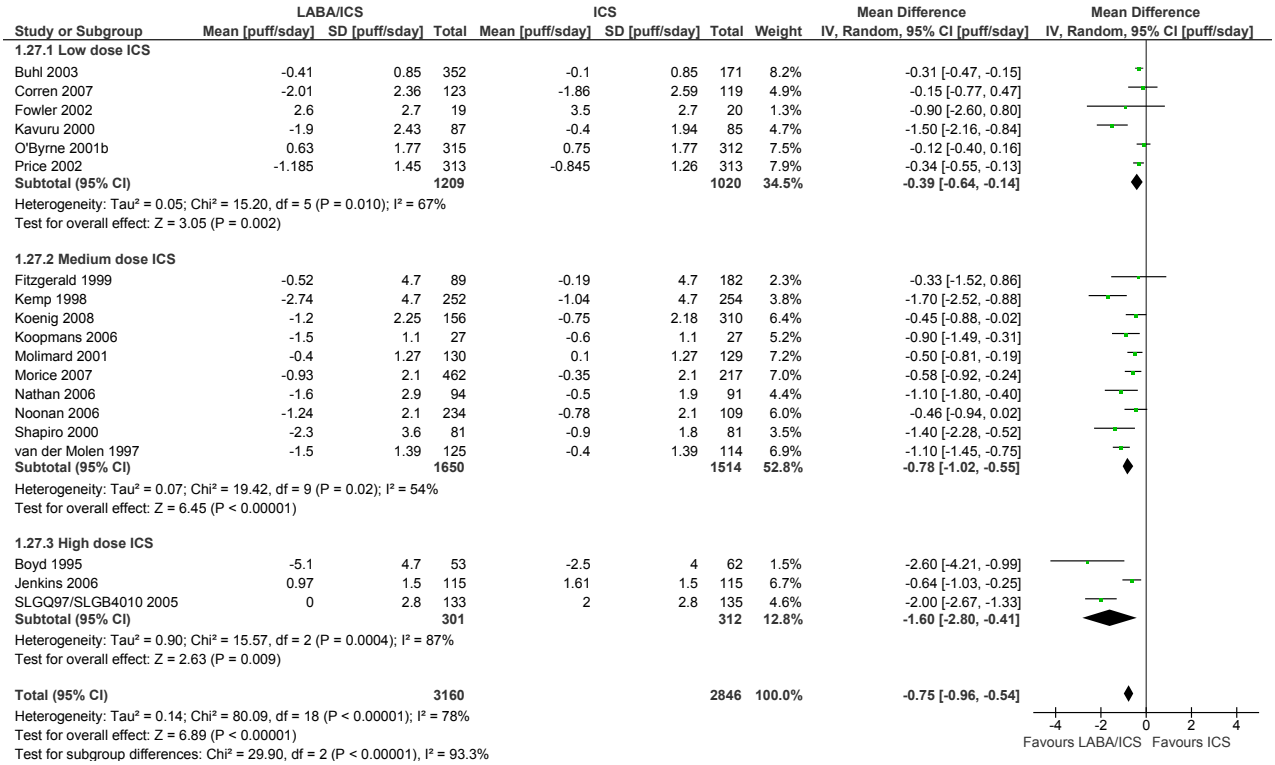
Figure 24: The effect of LABA/ICS versus ICS monotherapy on no. severe exacerbations



SABA Use (puffs/d): Nineteen trials[47,58,72,73,77,78,81,82,85,87,88,90-96,104] 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^2 = 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^2 = 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%).

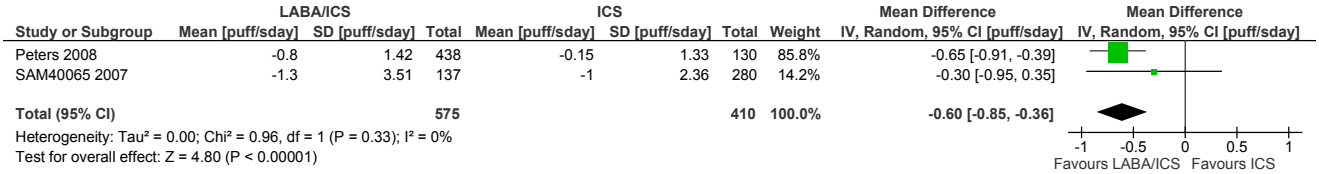
Figure 25.1: The effect of LABA/ICS versus ICS monotherapy on SABA use (puffs/d)



Two trials[99,101] 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[101] (WMD = -0.65; 95% CI: -0.91 to -0.39) dose comparison. The result for the low dose[99] comparison failed to indicate a statistically significant difference between the two treatments[101] (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)



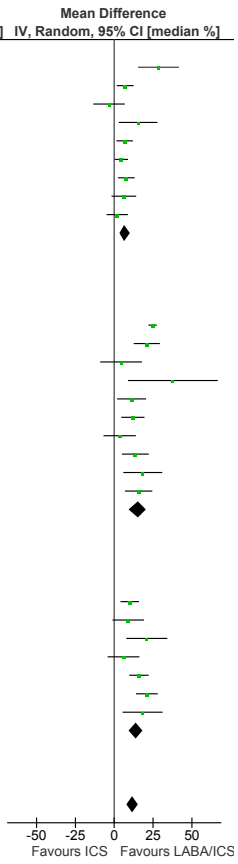
Symptom-free days (SFD): Twenty-six trials[29,45,47,58,72,73,75,76,80-83,85,87,89,91-98,100,102,104] involving 11,796 participants (LABA/ICS = 6,579, ICS = 5,217) provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on SFD (Figure

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%).

Figure 26.1: The effect of LABA/ICS versus ICS monotherapy on no. SFD

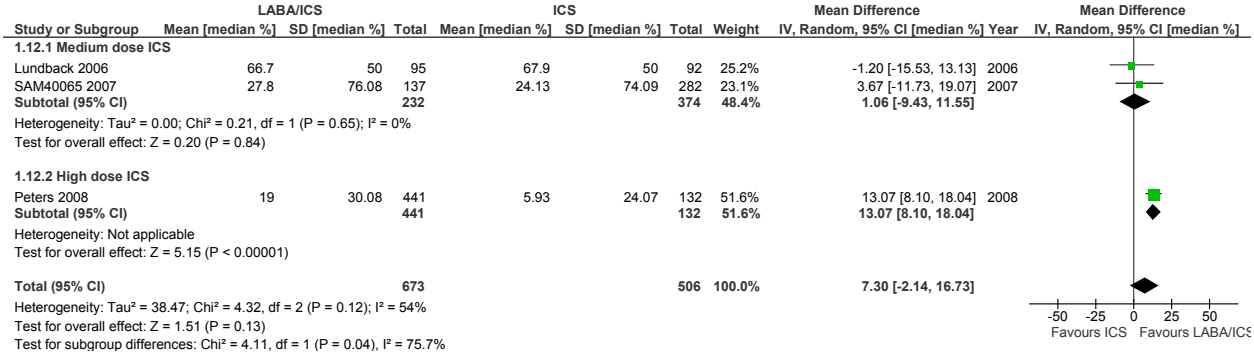
Study or Subgroup	LABA/ICS Mean [median %]	LABA/ICS SD [median %]	LABA/ICS Total	ICS Mean [median %]	ICS SD [median %]	ICS Total	Weight	Mean Difference IV, Random, 95% CI [median %]
1.28.1 Low dose ICS								
Bateman 2001	53.48	68	330	25	68	162	3.1%	28.48 [15.69, 41.27]
Buhl 2003	58.4	27.55	352	51.3	27.55	171	4.6%	7.10 [2.07, 12.13]
Corren 2007	26.47	39.46	123	29.77	38.19	119	3.7%	-3.30 [-13.08, 6.48]
Kavuru 2000	22.6	42.81	87	7.2	37.71	85	3.3%	15.40 [3.35, 27.45]
Kuna 2006	50.15	29.15	409	43.4	29.36	207	4.6%	6.75 [1.85, 11.65]
O'Byrne 2001b	74.9	25.2	315	70.3	25.2	312	4.7%	4.60 [0.65, 8.55]
Price 2002	34.6	32.3	313	26.8	32.3	313	4.6%	7.80 [2.74, 12.86]
SAS40036 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]
Subtotal (95% CI)			**2335**			**1759**	**36.9%**	**6.87 [3.41, 10.34]**
Heterogeneity: Tau² = 15.44; Chi² = 20.40, df = 8 (P = 0.009); I² = 61%								
Test for overall effect: Z = 3.89 (P = 0.0001)								
1.28.2 Medium dose ICS								
Bateman 2004	65.12	28	1161	40.44	28	1157	4.9%	24.68 [22.40, 26.96]
Kemp 1998	42	46	252	21	46	254	4.0%	21.00 [12.98, 29.02]
Koenig 2008	19.9	68.45	156	15.5	67.13	310	3.1%	4.40 [-8.69, 17.49]
Langton Hewer 1995	27.7	33.3	11	-10.1	33.3	10	1.3%	37.80 [9.28, 66.32]
Molimard 2001	17.8	36.7	130	6.6	37.1	129	3.9%	11.20 [2.21, 20.19]
Morice 2007	31.07	44	462	19.1	44	217	4.2%	11.97 [4.87, 19.07]
Nathan 2006	18.5	37.8	94	15	31.5	91	3.7%	3.50 [-6.51, 13.51]
Noonan 2006	23.14	31.95	121	9.5	31.95	109	4.0%	13.64 [5.37, 21.91]
Shapiro 2000	33.8	41.4	81	15.4	37.8	81	3.2%	18.40 [6.19, 30.61]
Zetterstrom 2001	23.7	37.04	238	8	40	124	4.0%	15.70 [7.23, 24.17]
Subtotal (95% CI)			**2706**			**2482**	**36.2%**	**15.20 [9.52, 20.87]**
Heterogeneity: Tau² = 57.70; Chi² = 44.74, df = 9 (P < 0.00001); I² = 80%								
Test for overall effect: Z = 5.25 (P < 0.00001)								
1.28.3 High dose ICS								
Aubier 1999	37	30	338	27	30	165	4.5%	10.00 [4.42, 15.58]
Boyd 1995	22	30	53	13	22	62	3.7%	9.00 [-0.76, 18.76]
Ind 2003	21	60	171	0	60	165	3.1%	21.00 [8.17, 33.83]
Jenkins 2000	60	45.95	173	54	45.95	165	3.7%	6.00 [-3.80, 15.80]
Jenkins 2006	31.5	27.85	341	15.6	27.85	115	4.4%	15.90 [10.01, 21.79]
SLGQ97/SLGB4010 2005	21	27.8	130	0	27.2	133	4.3%	21.00 [14.35, 27.65]
van Noord 2001	32.25	68	332	14	68	171	3.2%	18.25 [5.70, 30.80]
Subtotal (95% CI)			**1538**			**976**	**26.9%**	**14.20 [9.83, 18.57]**
Heterogeneity: Tau² = 15.97; Chi² = 11.77, df = 6 (P = 0.07); I² = 49%								
Test for overall effect: Z = 6.37 (P < 0.00001)								
Total (95% CI)			**6579**			**5217**	**100.0%**	**12.15 [8.43, 15.87]**
Heterogeneity: Tau² = 72.56; Chi² = 186.96, df = 25 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 6.40 (P < 0.00001)								
Test for subgroup differences: Chi² = 110.05, df = 2 (P < 0.00001), I² = 98.2%								



Three trials[84,99,101] 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[101] (WMD = 13.07; 95% CI: 8.10 to 18.04) dose comparison. The result for the medium[84,99] dose comparison failed to indicate a statistically significant difference between the two treatments (WMD = 1.06; 95% CI: -9.43 to 11.55).

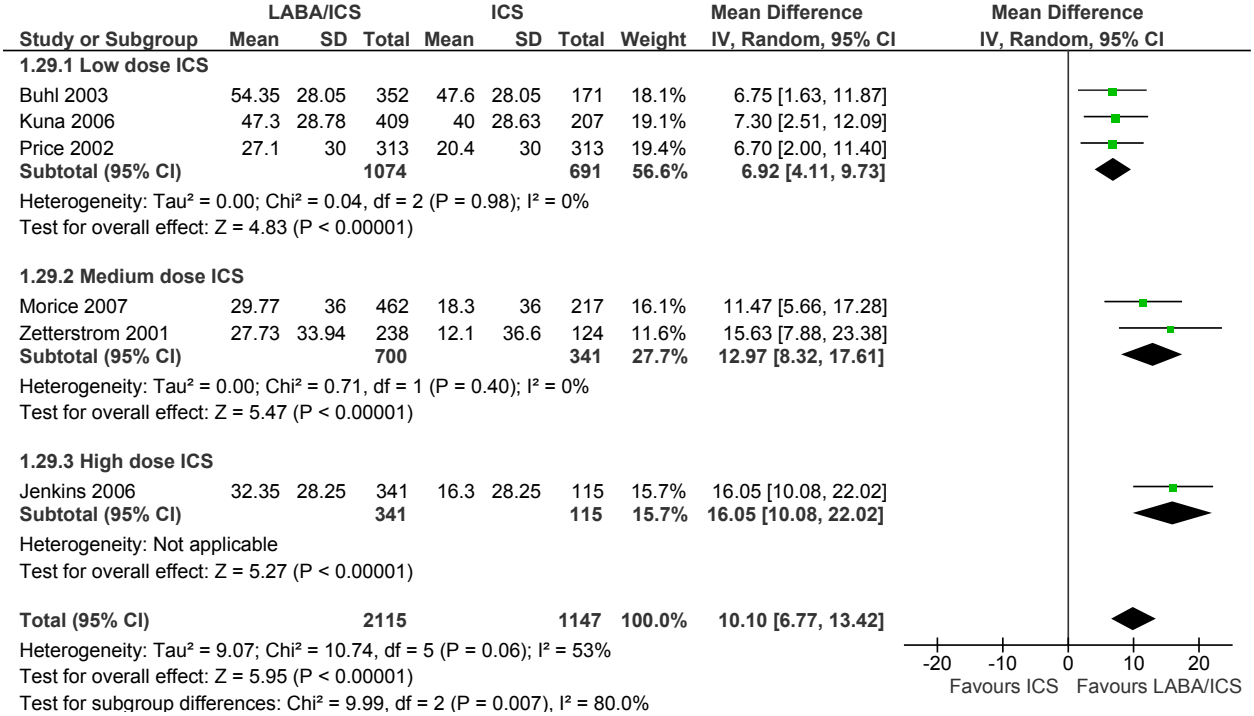
Figure 26.2: The effect of LABA/ICS versus ICS monotherapy on no. SFD (mixed LABA/ICS use at baseline)



Days with optimal control: Six trials[45,72,89,91,93,96] 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; $I^2 = 53\%$).

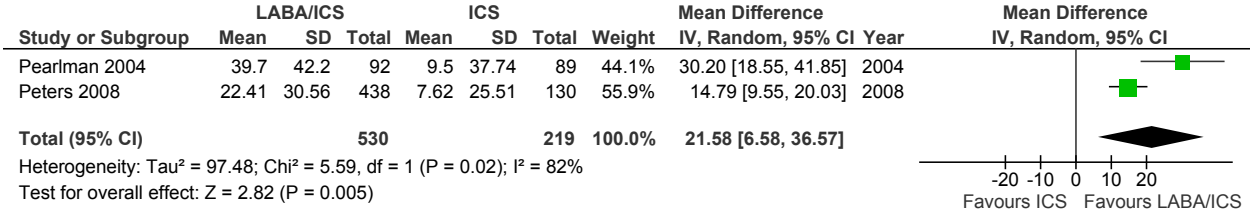
A subgroup analysis based on comparison ICS dose indicated greater treatment differences for the medium[89,96] (WMD = 12.97; 95% CI: 8.32 to 17.61; $I^2 = 0\%$), and high[93] (WMD = 16.05; 95% CI: 10.08 to 22.02) dose comparisons than for the low (WMD = 6.92; 95% CI: 4.11 to 9.73; $I^2 = 0\%$) comparisons. 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 $I^2 = 80.0\%$).

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



Two trials[74,101] 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[74] (WMD = 30.20; 95% CI: 18.55 to 41.85) and high[101] (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)

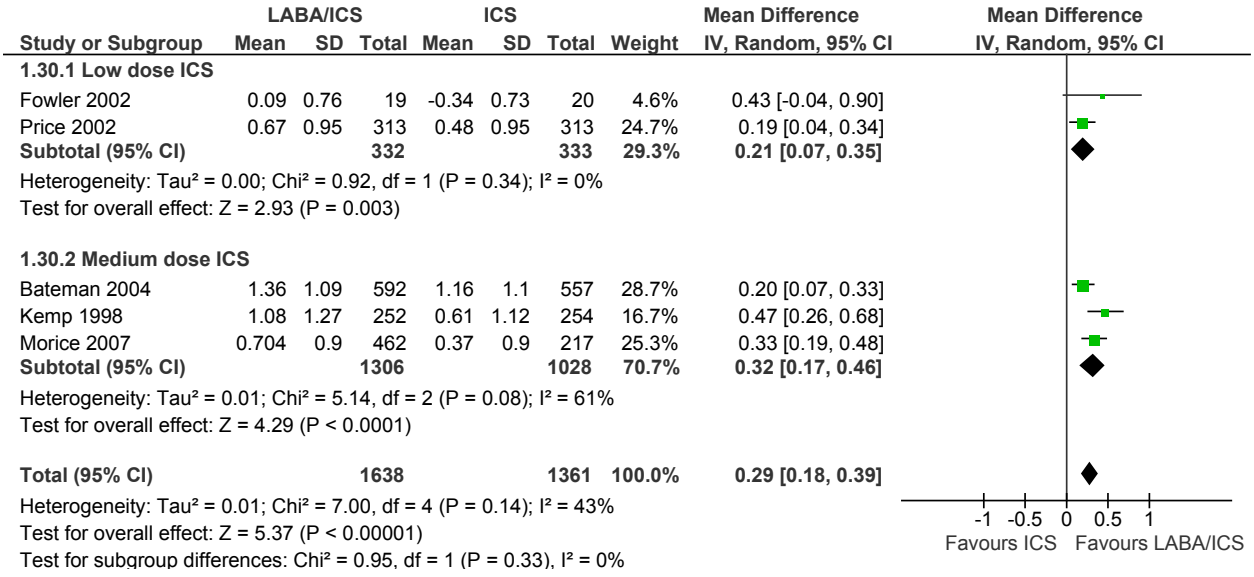


Health-related quality of life measures

Asthma quality of life questionnaire (AQLQ): Five trials[29,77,82,91,96] 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.

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 ≥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 ≥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

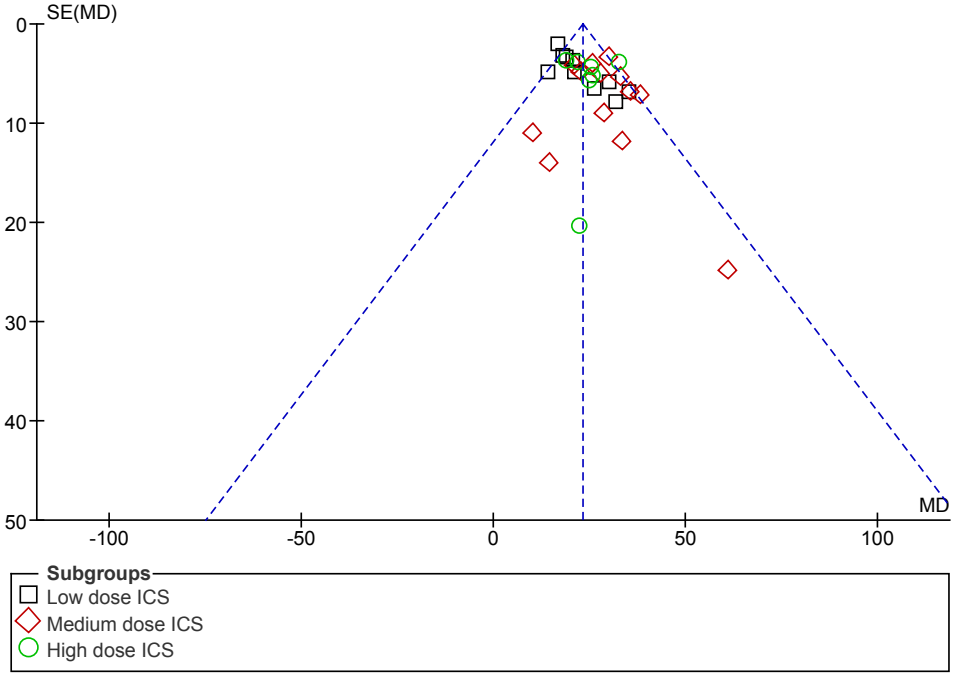


Figure 29.2: Funnel plot of LABA/ICS vs. similar dose ICS for PEF PM

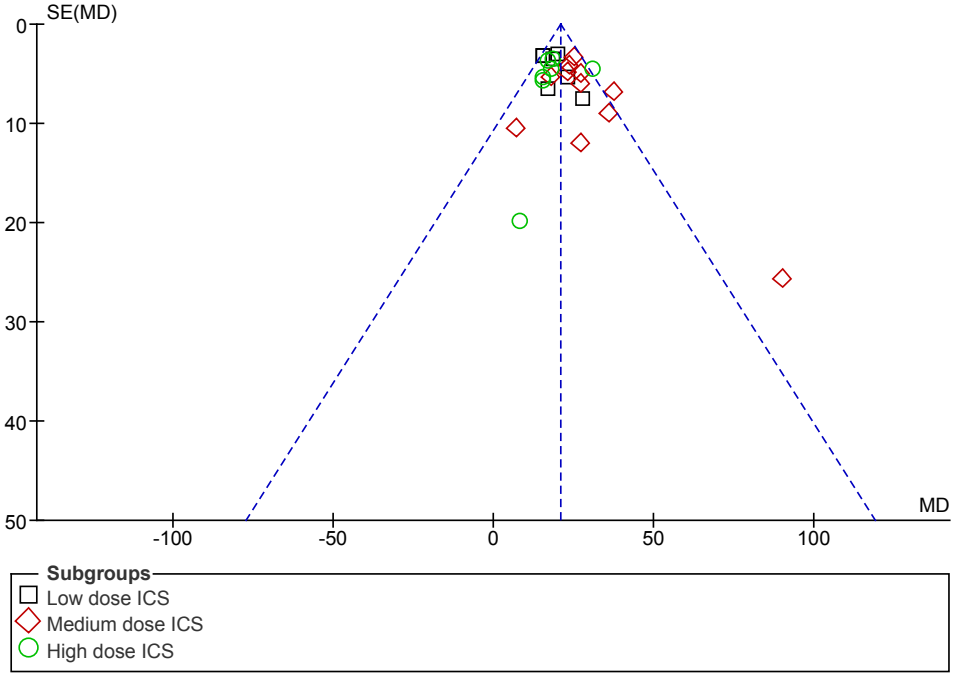


Figure 29.3: Funnel plot of LABA/ICS vs. similar dose ICS for no. participants with ≥1 exacerbation

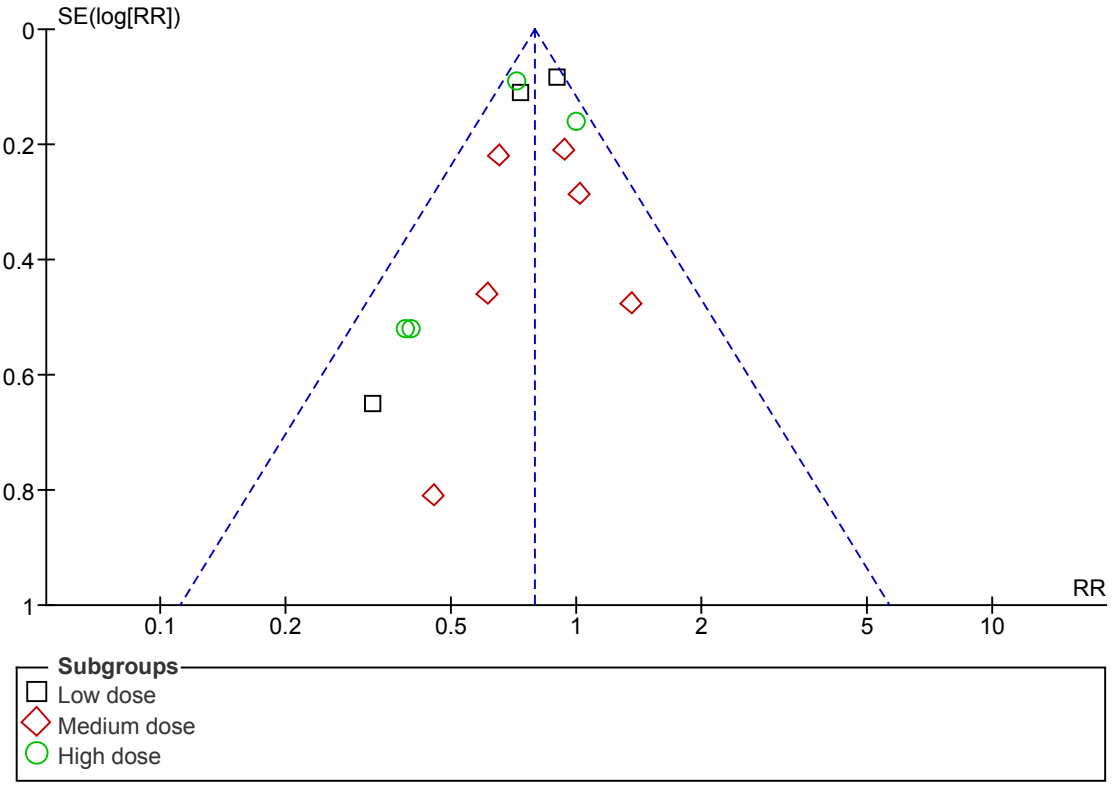


Figure 29.4: Funnel plot of LABA/ICS vs. similar dose ICS for SABA use

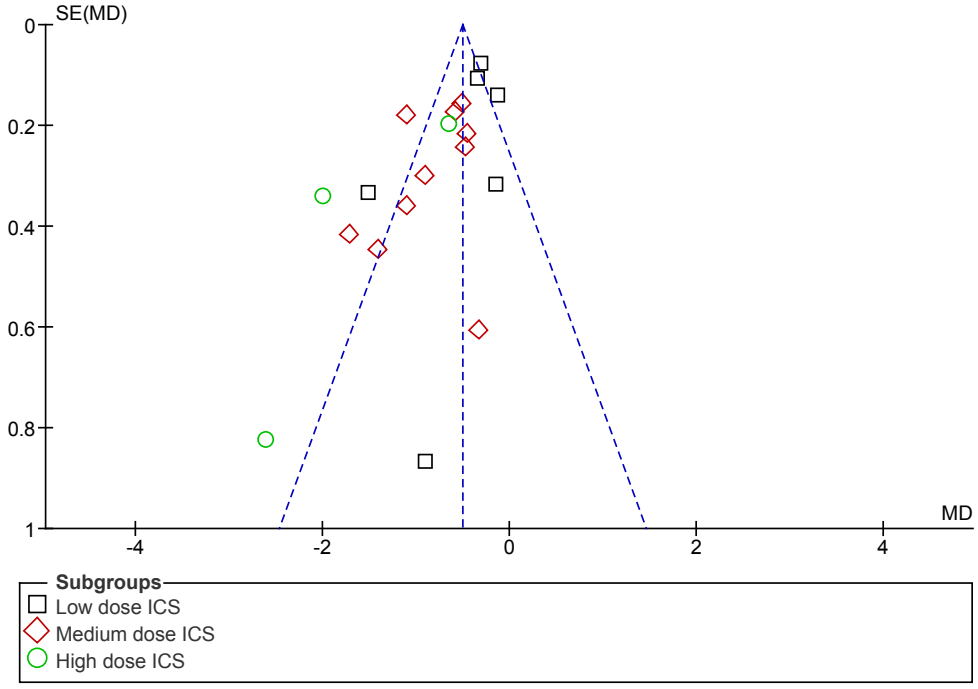
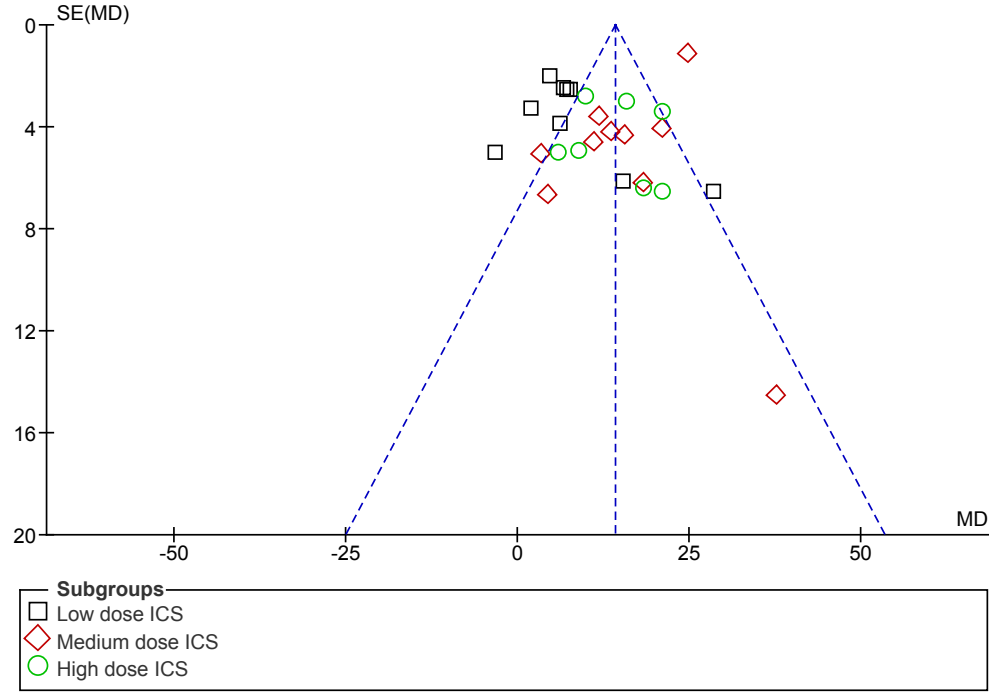


Figure 29.5: Funnel plot of LABA/ICS vs. similar dose ICS for SFD



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

Thirty-one unique RCTs[53,58,65,66,76,79,101,103-126] 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[53,66,76,103,104,108-110,116,120,123,125,126] compared SAL/FP versus FP, six compared FORM/BUD versus BUD,[58,101,105,113,119,122] five compared SAL/BDP versus BDP,[111,114,117,118,121] three compared SAL/FP versus BUD,[65,112,124] two compared FORM/BDP versus BDP,[107,115] one compared FORM/BUD versus FP,[106] and one compared SAL/TAA versus TAA.[79] One study that compared SAL/FP versus FP also compared SAL/FP versus TAA.[109] Two trials compared variable dose LABA/ICS with a fixed dose ICS monotherapy.[105,119] 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 ≥18 years in 12 (38.7%) studies.[53,66,106,108,111,113-115,117,118,120,121] In terms of asthma severity, three trials[79,121,123] included only participants with mild asthma, and four[106,108,114,124] included only participants with moderate asthma. The remaining trials examined participants covering a range of asthma severity: intermittent to mild (1 trial),[58] intermittent to moderate (2 trials),[103,113] intermittent to severe (5 trials),[76,105,111,115,125] mild to moderate (5 trials),[65,112,120,122,126] mild to severe (4 trials),[53,66,104,107] and moderate to severe (7 trials).[101,109,110,116-119] Treatment duration also varied among studies: 12 wk (15 trials),[53,65,66,106-109,112,113,115,116,120,121,124,126] 16 wk (1 trial),[123] 24 wk (8 trials),[76,79,104,110,114,117,118,125] 26 wk (1 trial),[111] 36 wk (1 trial),[103] 48 wk (1 trial),[105] 52 wk (3 trials),[58,101,119] and 72 wk (1 trial).[122] The median duration of treatment was 16 weeks (IQR: 12, 24).

Methodological quality

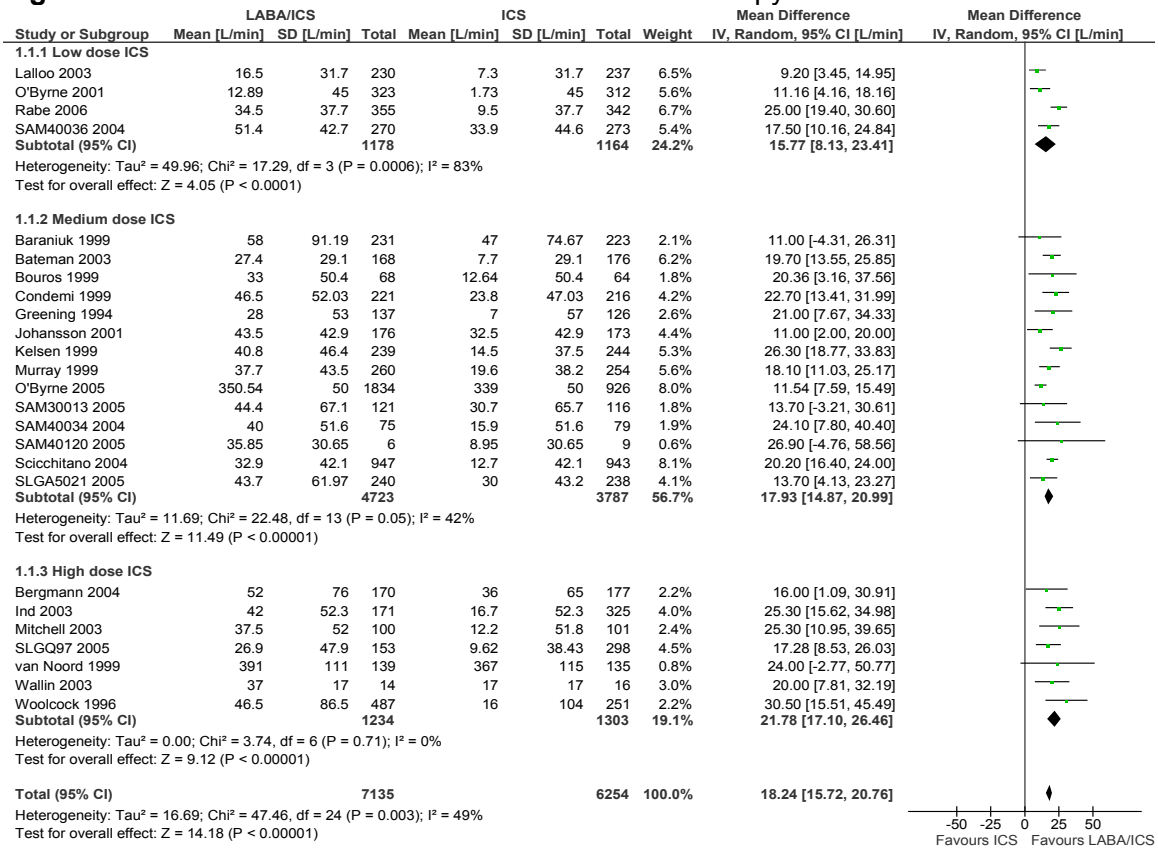
Overall, the methodological quality of included higher dose maintenance ICS studies (N = 31) was moderate (Table 5). Jadad scores ranged from 2-5 with a median score of 4 (IQR, 3 to 4.5). Allocation concealment was considered adequate in 4 (12.9%) studies and unclear in 27 (87.1%). All studies were randomized 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 ≥3) of almost all studies, no sensitivity analyses were conducted based on quality.

Table 5: Methodological quality of maintenance ICS studies: higher 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[53,58,65,66,76,104-120,122,125,126] 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

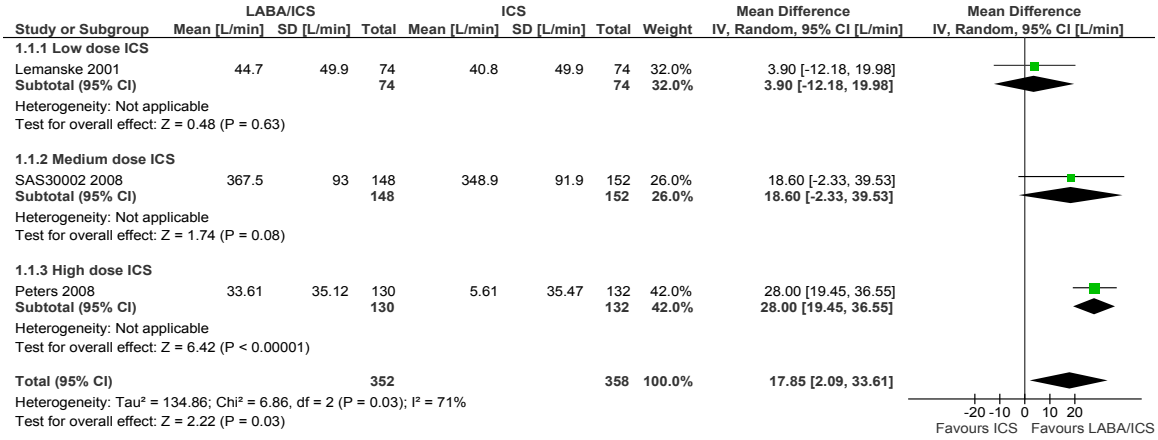


A subgroup analysis based on comparison ICS indicated a clinically important difference for the high dose comparison (WMD = 21.79; 95% CI: 17.10, 26.46). The low and medium dose comparisons did not indicate clinically important differences between treatments.

Three trials[79,101,124] 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 meta-analysis 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.

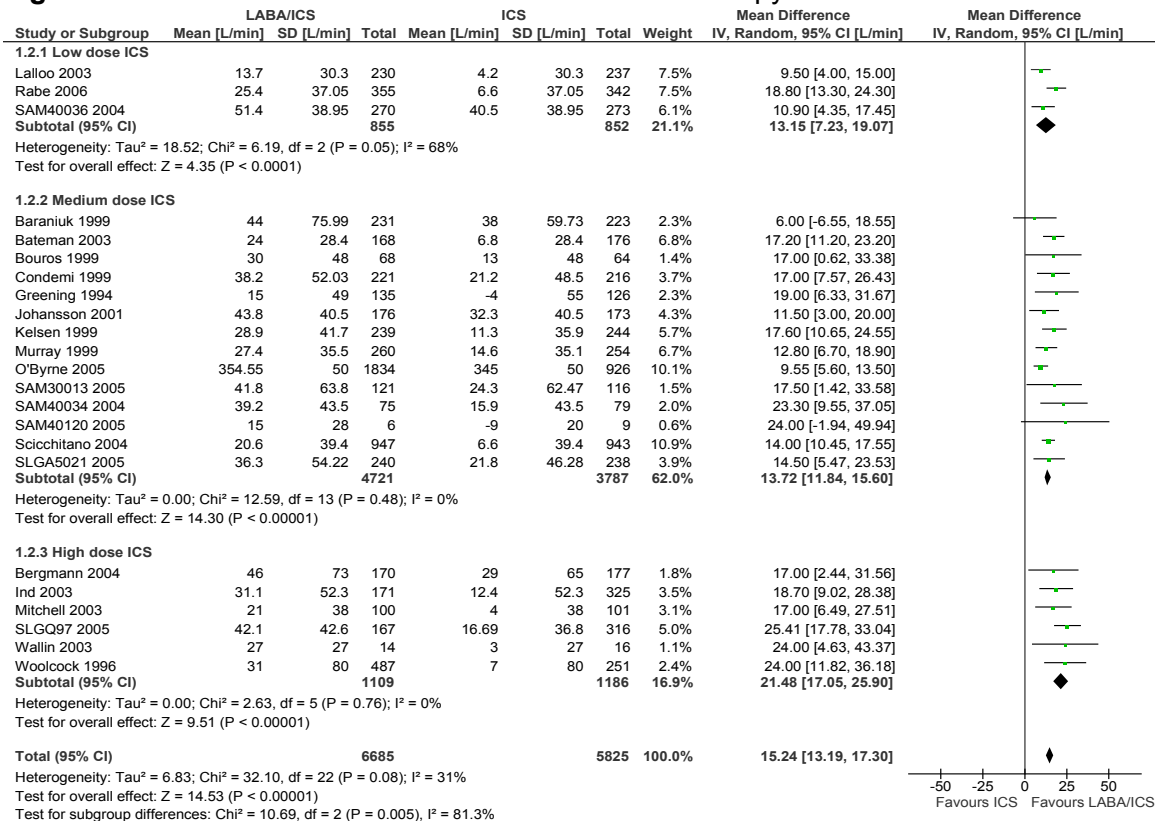
A subgroup analysis based on comparison ICS dose failed to indicate a statistically significant difference between treatments for the low (WMD = 3.90; 95% CI: -12.18 to 19.98) and medium (WMD = 18.60; 95% CI: -2.33 to 39.53) dose comparisons. In addition the precision of the confidence intervals suggests 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).

Figure 31: The effect of LABA/ICS versus ICS monotherapy on PEF AM (mixed LABA/ICS use at baseline)



PEF PM: Twenty three trials[53,65,66,76,104-119,122,125,126] 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^2 = 31%). The precision of the confidence interval, however, suggests that the two treatments are clinically equivalent (MCID = ±18.79 L/min).

Figure 32: The effect of LABA/ICS versus ICS monotherapy on PEF PM

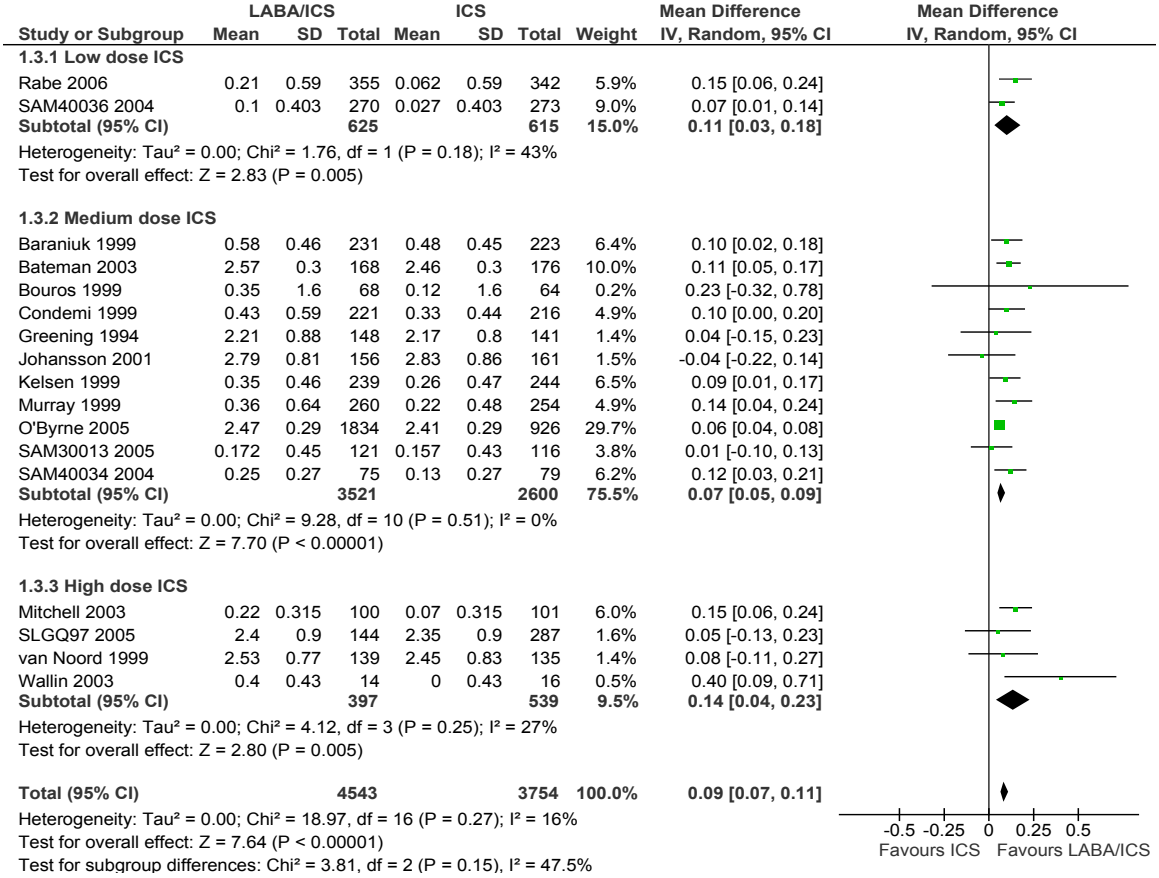


A subgroup analysis based on comparison ICS dose failed to demonstrate a clinically important difference among the low (WMD = 13.15; 95% CI: 7.23 to 19.07; I^2 = 68%) and medium (WMD = 13.72; 95% CI: 11.84 to 15.60; I^2 = 0%) dose comparisons. There was a statistically significant difference favouring 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[124] 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_1 (absolute): Seventeen trials[65,66,104-107,109-112,114,115,115,116,120,122,126] 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_1 (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^2 = 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_1 (absolute)

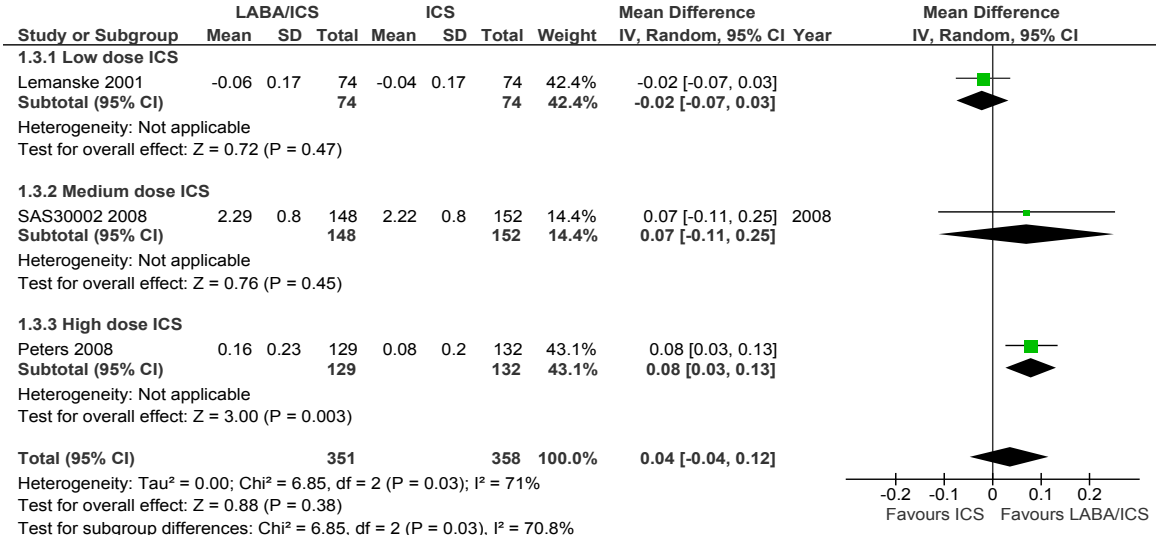


A subgroup analysis based on comparison ICS dose failed to demonstrate a difference among the low (WMD = 0.11; 95% CI: 0.03 to 0.18; I^2 = 43%), medium (WMD = 0.07; 95% CI: 0.05 to 0.09; I^2 = 0%) and high (WMD = 0.14; 95% CI: 0.04 to 0.23; I^2 = 27%) dose comparisons. The precision of the confidence intervals suggests that the two treatments are clinically equivalent (MCID = ±0.23 L/min) for all three subgroups.

Three trials[79,101,124] 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_1 (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^2 = 71%); %); however, the lack of precision of the estimates prevents conclusions regarding the equivalence of the two treatments (MCID = ±0.23 L/min).

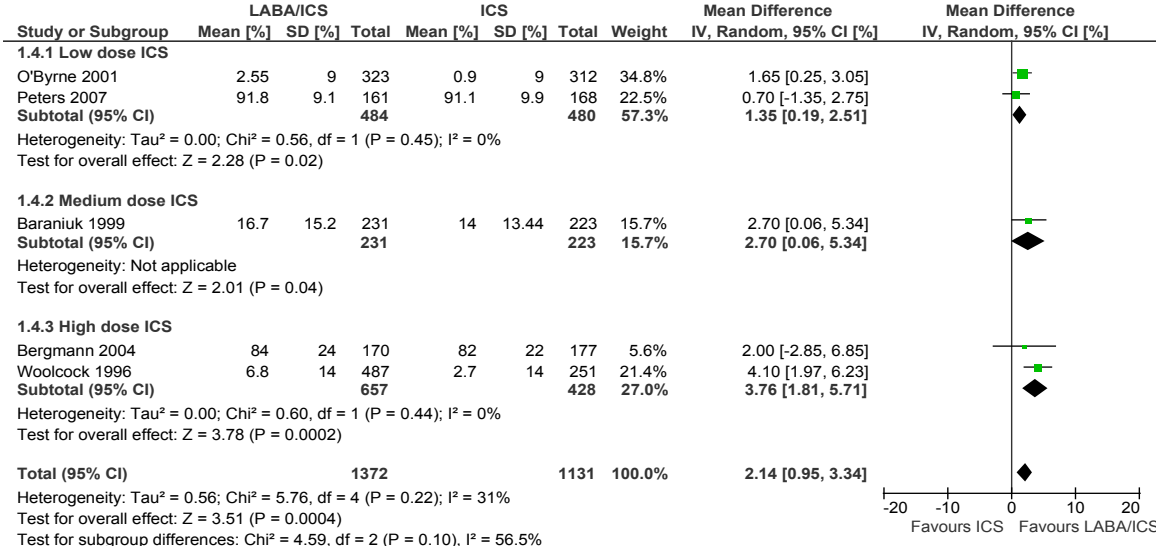
A subgroup analysis based on comparison ICS dose failed to demonstrate a difference among the low (WMD = -0.02; 95% CI: -0.07 to 0.03) and medium (WMD = 0.07; 95% CI: -0.11 to 0.25) dose comparisons. There was an increase in the magnitude and precision of the treatment effect for the high (WMD = 0.08; 95% CI: 0.03 to 0.13) dose comparison. The precision of the confidence intervals suggests that the two treatments are clinically equivalent (MCID = ±0.23 L/min) for all three subgroups.

Figure 34: The effect of LABA/ICS versus ICS monotherapy on FEV_1 (absolute) (mixed LABA/ICS use at baseline)



FEV_1 (% predicted): Five trials[58,108,109,118,123] 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_1 (Figure 35). The pooled result indicated a statistically significant difference favouring LABA/ICS (WMD = 2.14; 95% CI: 0.95 to 3.34; I^2 = 31%). The precision of the confidence interval suggests that the two treatments are clinically equivalent (MCID = ±12%).

Figure 35: The effect of LABA/ICS versus ICS monotherapy on FEV_1 (% predicted)



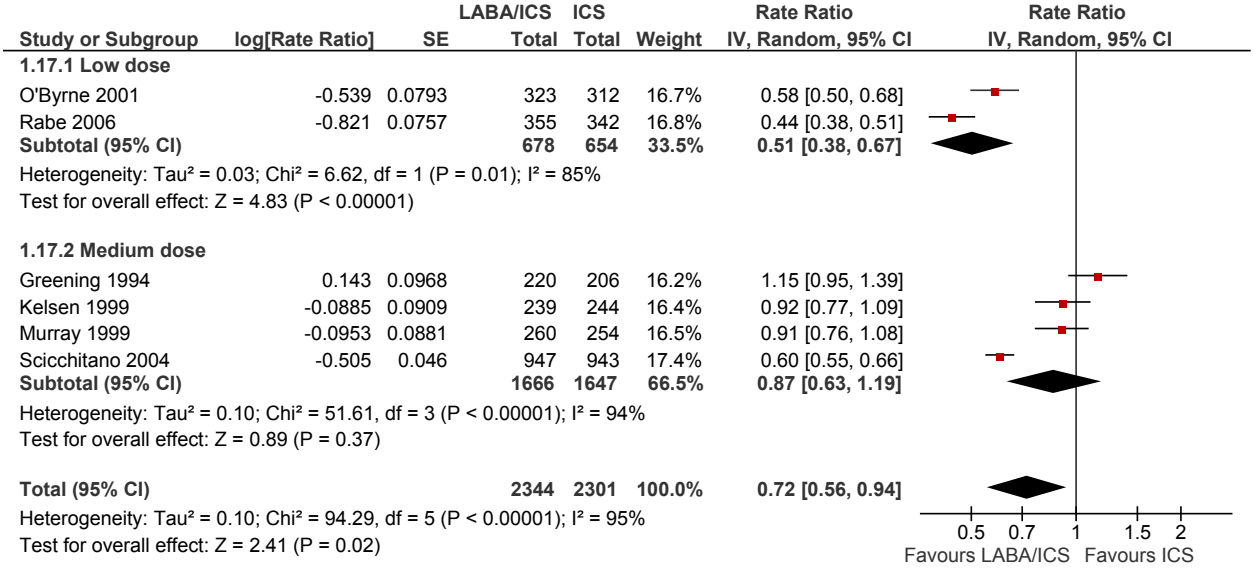
A subgroup analysis based on comparison ICS dose failed to demonstrate a difference among the low (WMD = 1.35; 95% CI: 0.19 to 2.51; I^2 = 0%), medium (WMD = 2.70; 95% CI: 0.06 to 5.34) and high (WMD = 3.76; 95% CI: 1.81 to 5.71; I^2 = 0%) dose comparisons. Moreover, the precision of the 95% CIs for all differences suggest that the two treatments are clinically equivalent (MCID = ±12%) for all three subgroups.

One trial[124] 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_1 (% 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 = ±12%).

Asthma control measures

Total number of exacerbations: Six trials[58,111,114,117,119,122] 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^2 = 95%). The low dose ICS trials[58,122] compared FORM/BUD with BUD; however, the trial that most favoured LABA/ICS[58] (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,[58] intermittent to severe,[111] mild to moderate,[122] moderate,[114] and moderate to severe[117,119].

Figure 36: The effect of LABA/ICS versus ICS monotherapy on total number of exacerbations

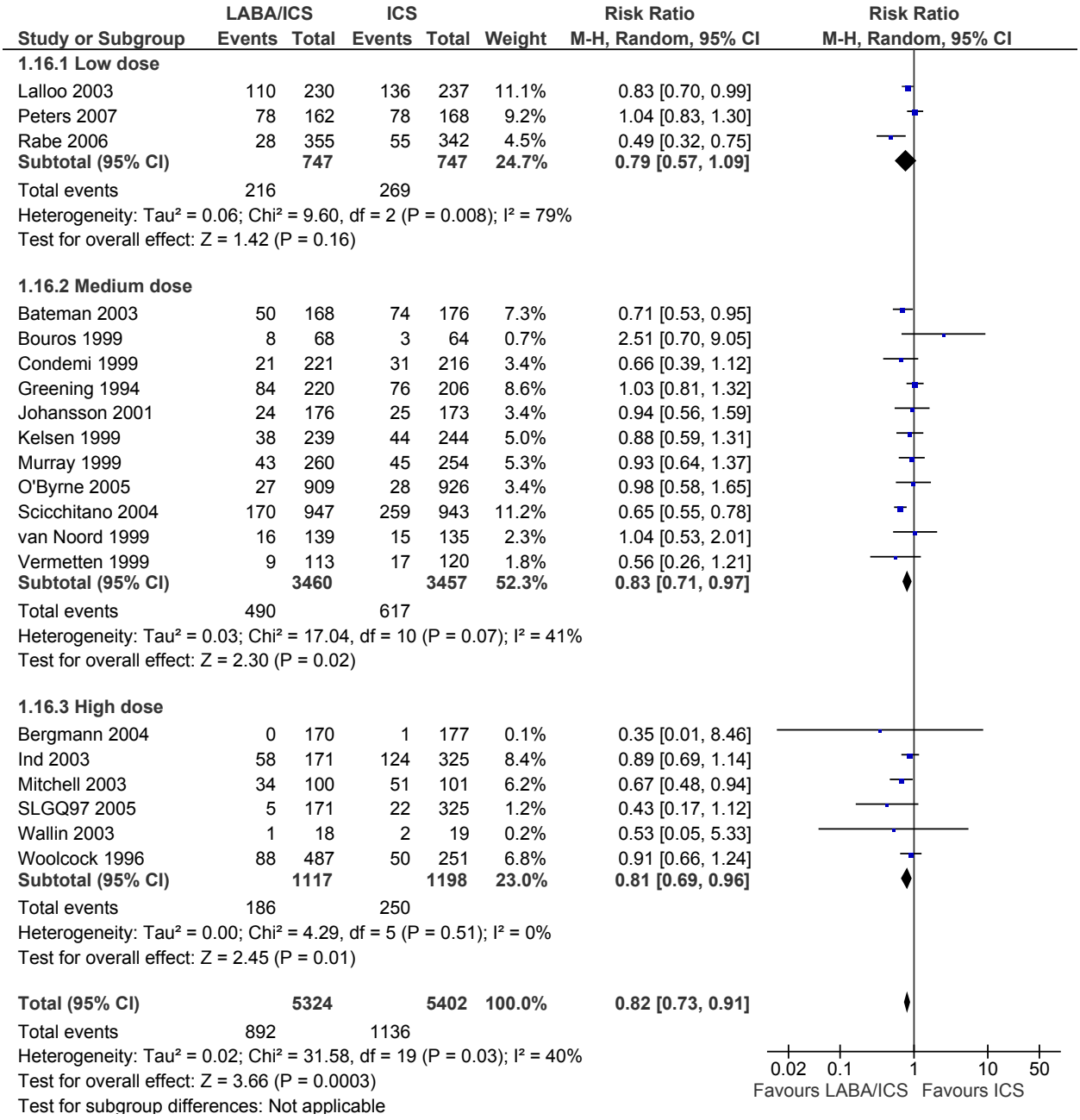


A subgroup analysis based on comparison ICS dose indicated a statistically significant difference favouring LABA/ICS for the low (Rate ration = 0.51; 95% CI: 0.38 to 0.67; I^2 = 85%) dose comparison, but not for the medium (Rate ratio = 0.87; 95% CI: 0.63 to 1.19; I^2 = 94%) dose comparison.

One trial[101] 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 ≥1 exacerbations: Twenty trials[76,104,106,110-113,115-118] involving 10,726 participants (LABA/ICS = 5,324, ICS = 5,402) provided data for a meta-analysis 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^2 = 40%).

Figure 37: The effect of LABA/ICS versus higher dose ICS on % participants experiencing ≥1 exacerbations

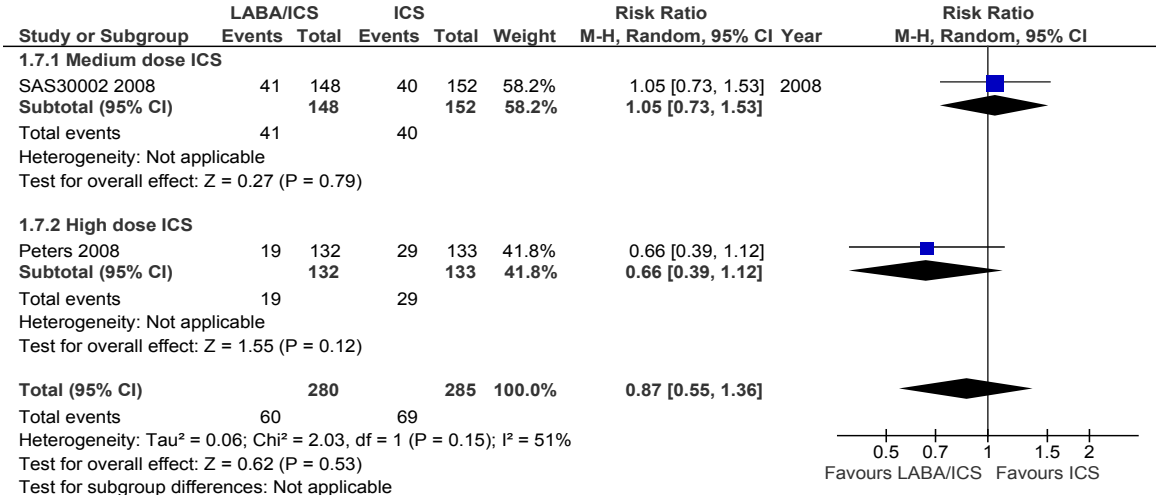


A subgroup analysis based on comparison ICS dose failed to indicate a different between the treatments for the low (RR = 0.79; 95% CI: 0.57 to 1.09; I^2 = 79%) dose comparison. However,

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[101,124] 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 ≥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^2 = 51%).

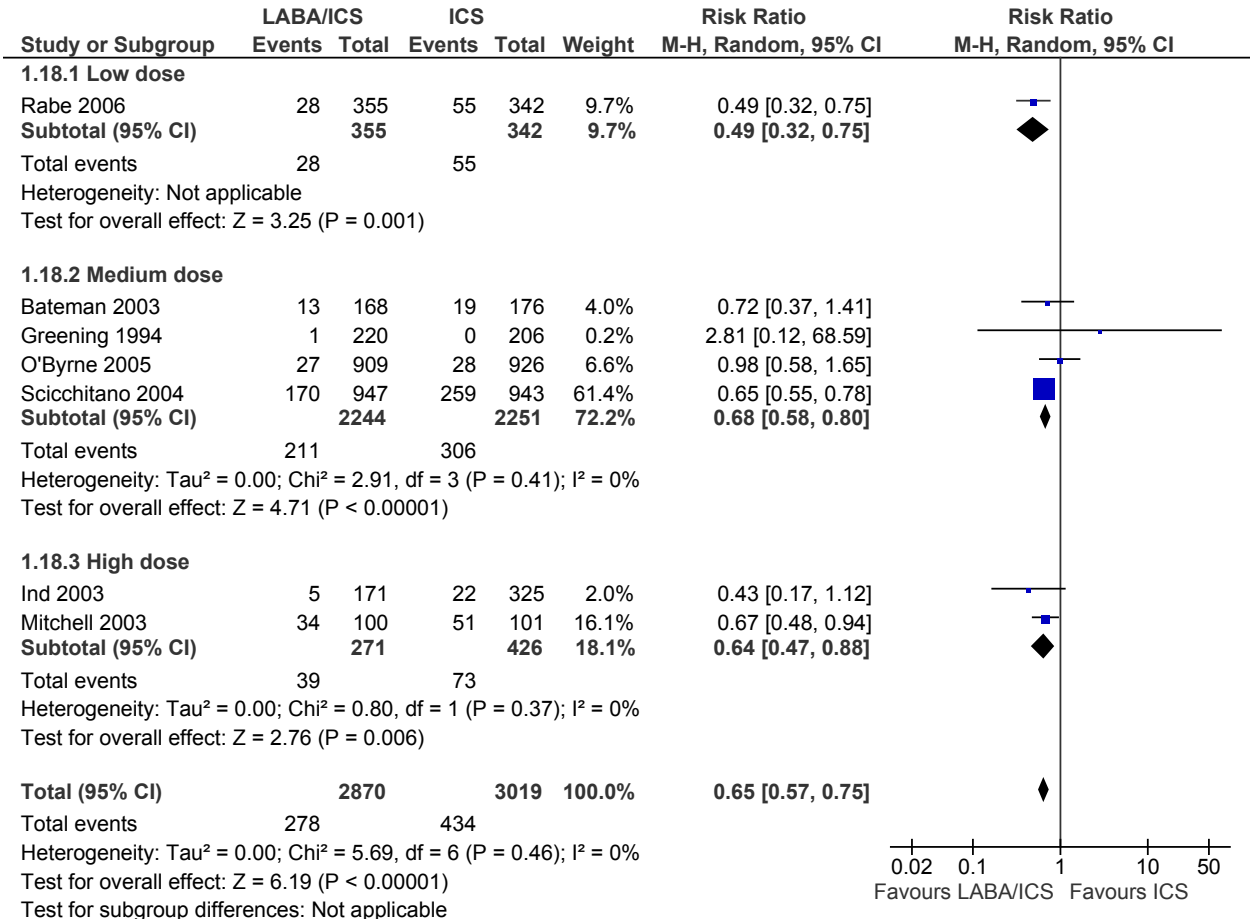
Figure 38: The effect of LABA/ICS versus higher dose ICS on % participants experiencing ≥1 exacerbations (mixed LABA/ICS use at baseline)



A subgroup analysis based on comparison ICS dose failed to indicate a statistically significant difference between the two treatments for the medium[124] (RR = 1.05; 95% CI: 0.73 to 1.53) and high [101] (RR = 0.66; 95% CI: 0.39 to 1.12) dose comparisons.

Number of patients with severe exacerbations: Seven trials[76,105,106,111,115,119,122] 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%).

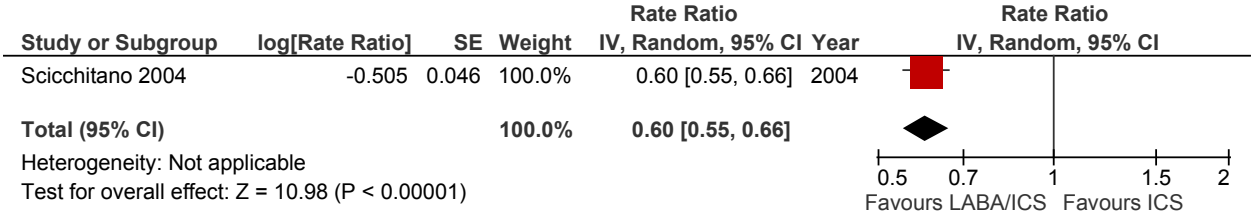
Figure 39: The effect of LABA/ICS versus ICS monotherapy on the number of patients with severe exacerbations



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.

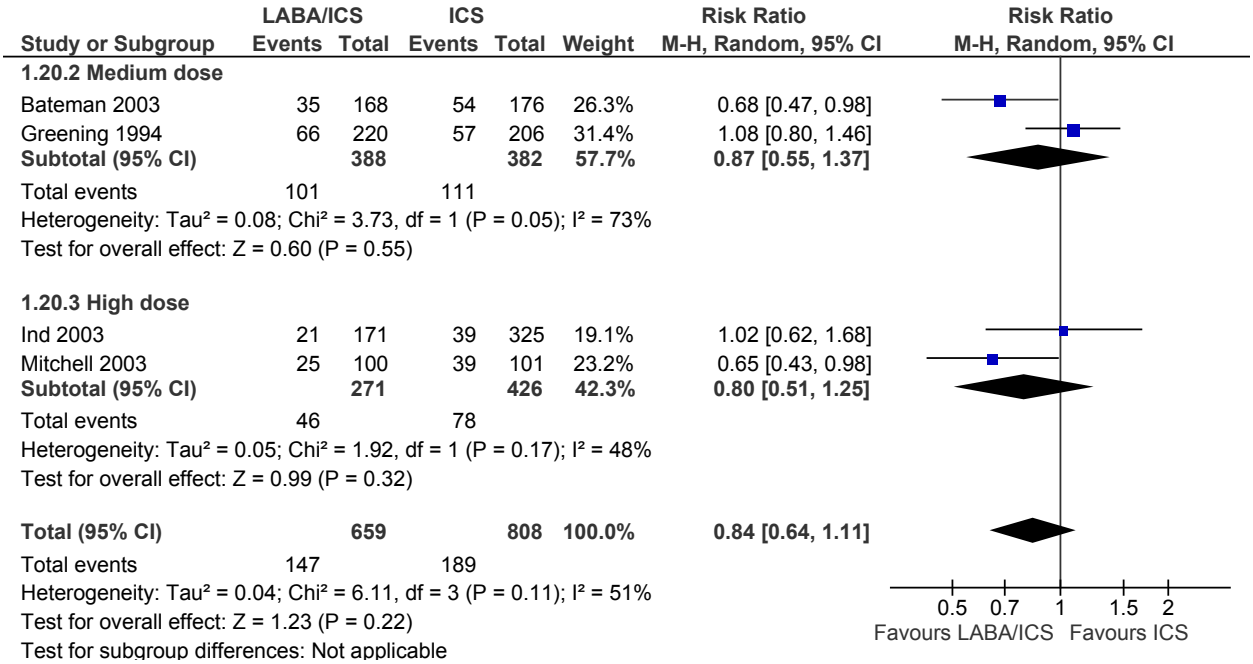
Number of severe exacerbations: One trial[119] involving 2,760 participants (LABA/ICS = 1,834, ICS = 926) provided data for an analysis of the effects of LABA/ICS combination therapy compared with higher-dose ICS monotherapy on the number of severe exacerbations (Figure 40). The result indicated a statistically 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[76,106,111,115] 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^2 = 51%).

Figure 41: The effect of LABA/ICS versus ICS monotherapy on number of patients with mild exacerbations

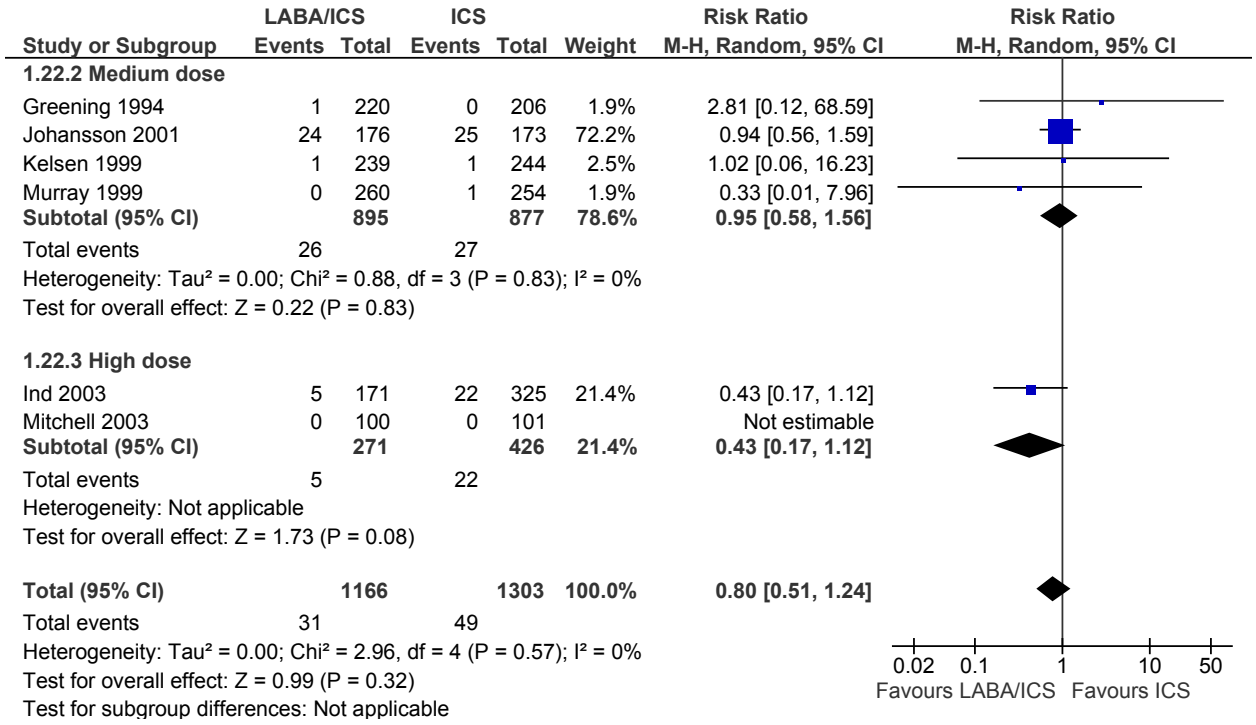


A subgroup analysis based on comparison ICS dose failed to identify a difference between the medium (RR = 0.87; 95% CI: 0.55 to 1.37; I^2 = 73%) and high (RR = 0.80; 95% CI: 0.51 to 1.25; I^2 = 48%) dose comparisons. Heterogeneity among the medium dose comparisons may be explained by variations in patient disease severity. One study[106] included only participants with moderate disease severity, while the other study[111] 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[76] compared SAL/FP versus FP, while the other study[115] compared FORM/BDP to BDP.

Number of mild exacerbations: One trial[111] 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[76,111,112,114,115,117] 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%).

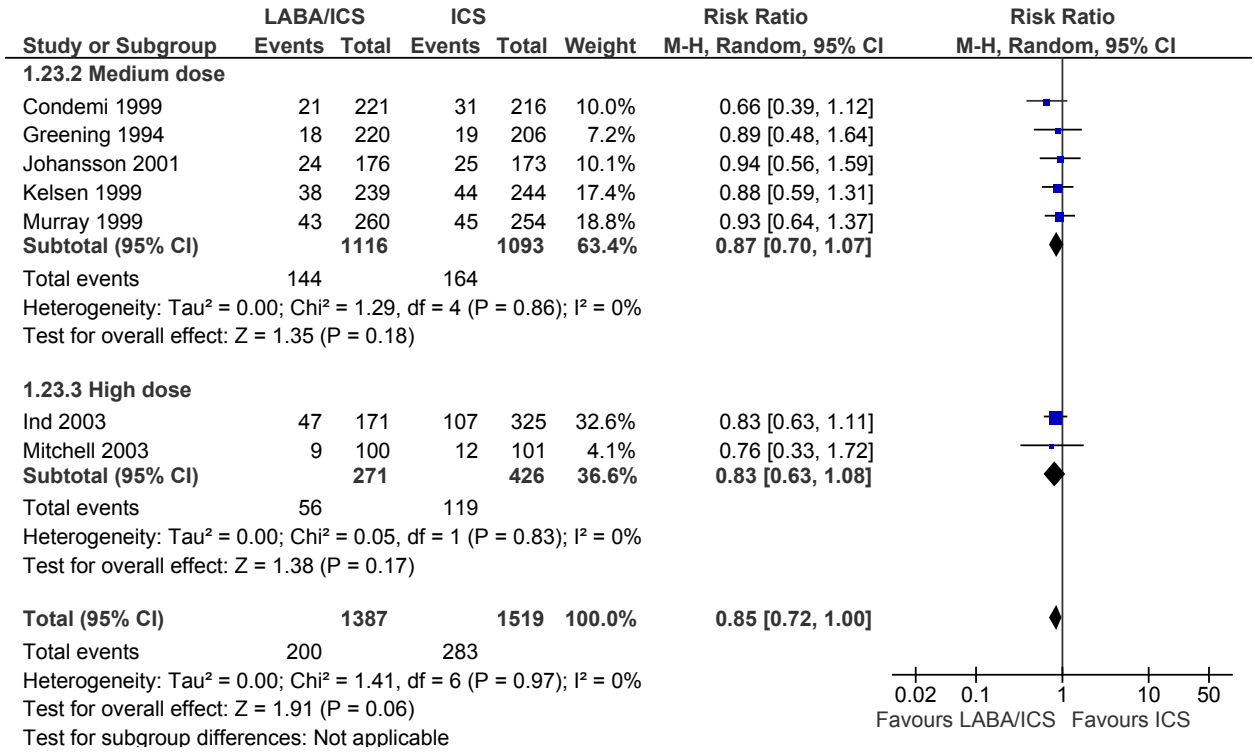
Figure 42: The effect of LABA/ICS versus ICS monotherapy on no. exacerbations requiring hospitalization



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[76,110-112,114,115,117] 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; $I^2 = 0\%$)

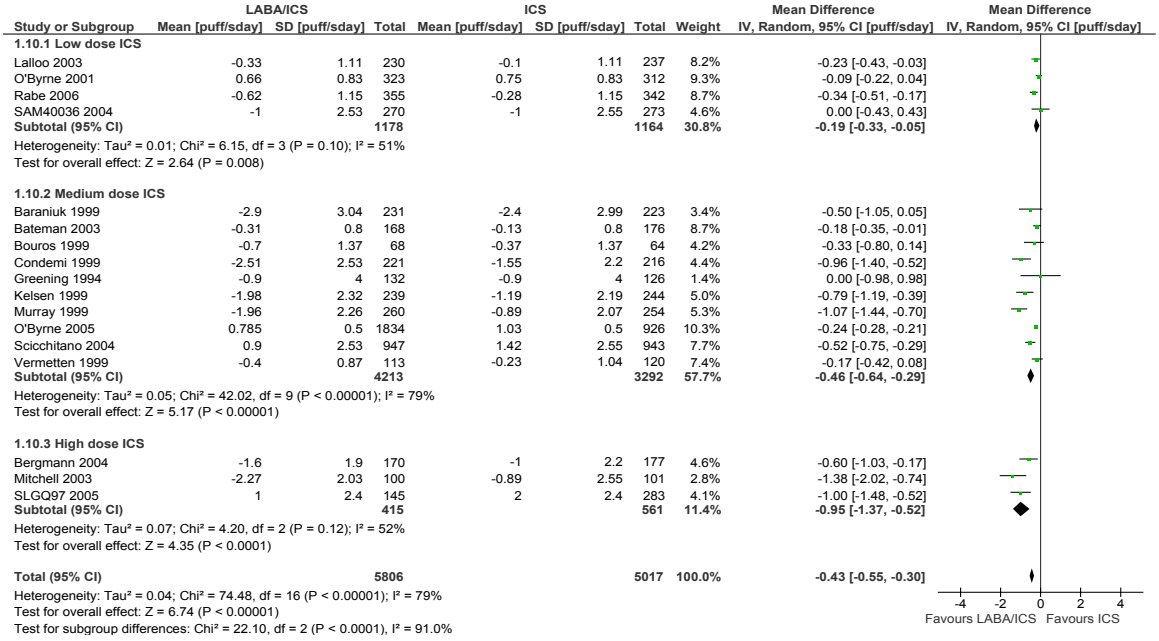
Figure 43: The effect of LABA/ICS versus ICS monotherapy on no. exacerbations requiring OCS



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$_2$-agonist (SABA) use: Seventeen trials[58,65,104-111,113-115,117,119,121,122] 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; $I^2 = 79\%$). 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.

Figure 44: The effect of LABA/ICS versus ICS monotherapy on SABA use

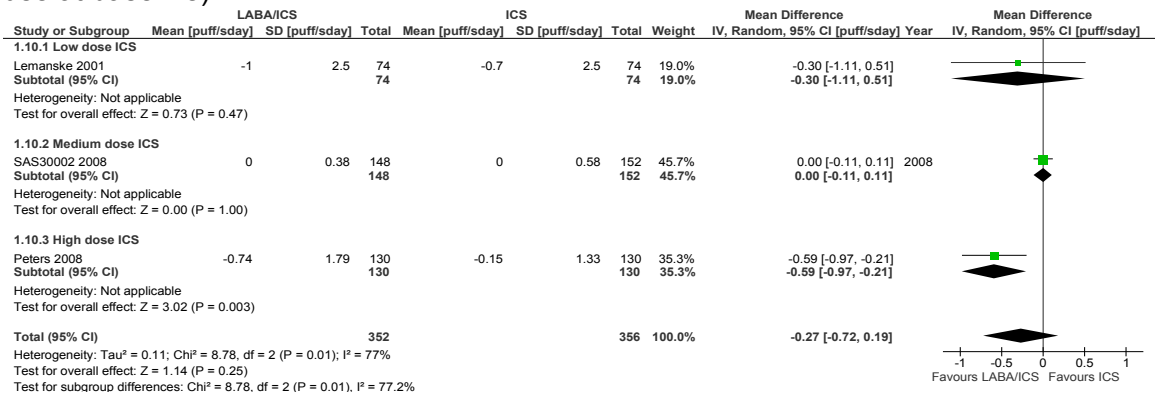


A subgroup analysis based on comparison ICS dose failed to identify a difference between the low (WMD = -0.19; 95% CI: -0.33 to -0.05; I^2 = 51%), medium (WMD = -0.46; 95% CI: -0.64 to -0.29; I^2 = 79%) and high (WMD = -0.95; 95% CI: -1.37 to -0.52; I^2 = 52%) dose comparisons. Moreover, the precision of the 95% CIs for all differences suggest that the three treatments are clinically equivalent (MCID = ±0.81).

Three trials[79,101,124] 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).

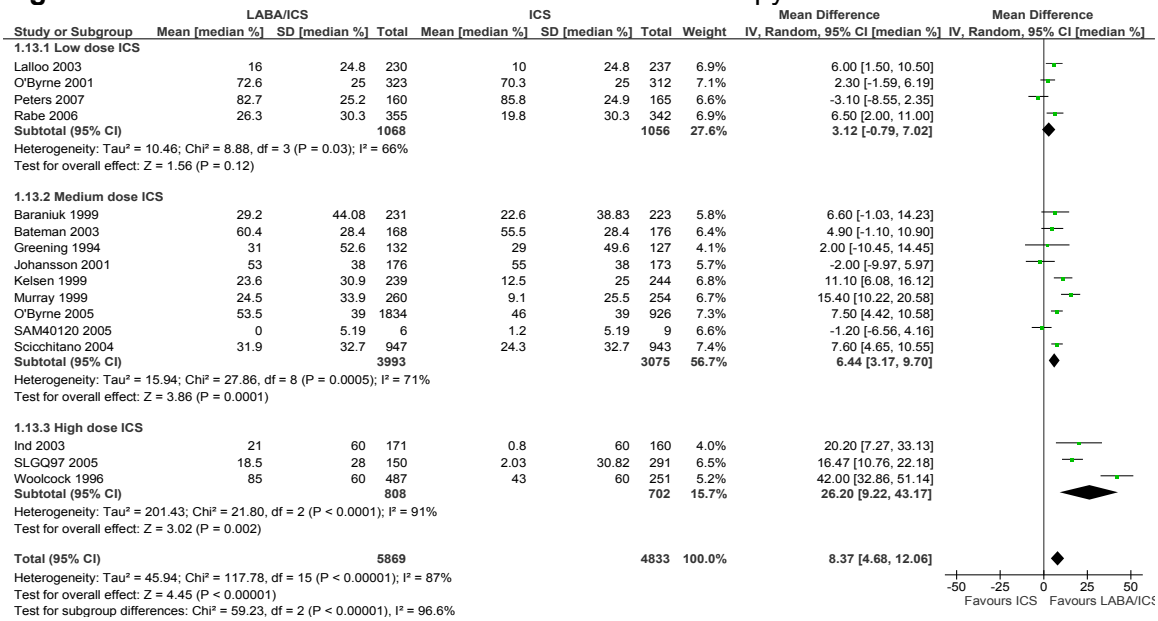
A subgroup analysis based on comparison ICS dose failed to indicate a statistically significant difference for the low (WMD = -0.30; 95% CI: -1.11 to 0.51) and medium (WMD = 0.00; 95% CI: -0.11 to 0.11) dose comparisons. The result for the high dose comparison indicated statistically significant difference 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)



Symptom free days (SFD): Sixteen trials[53,58,76,104-106,109,111-114,117-119,122,123] 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.

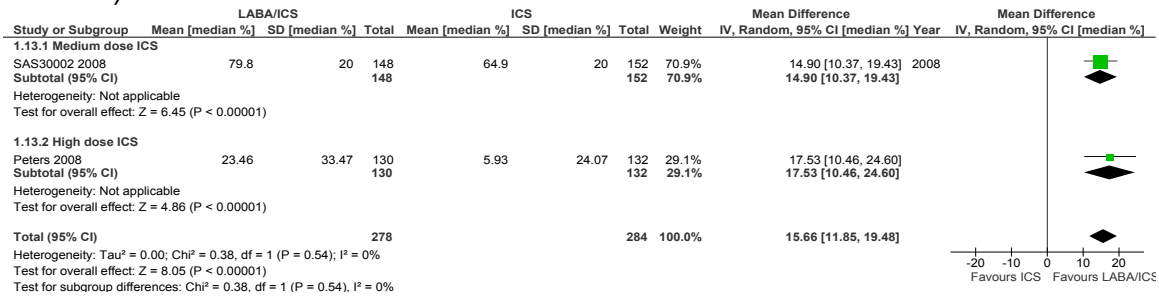
Figure 46: The effect of LABA/ICS versus ICS monotherapy on SFD



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^2 = 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^2= 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^2= 91%) comparisons.

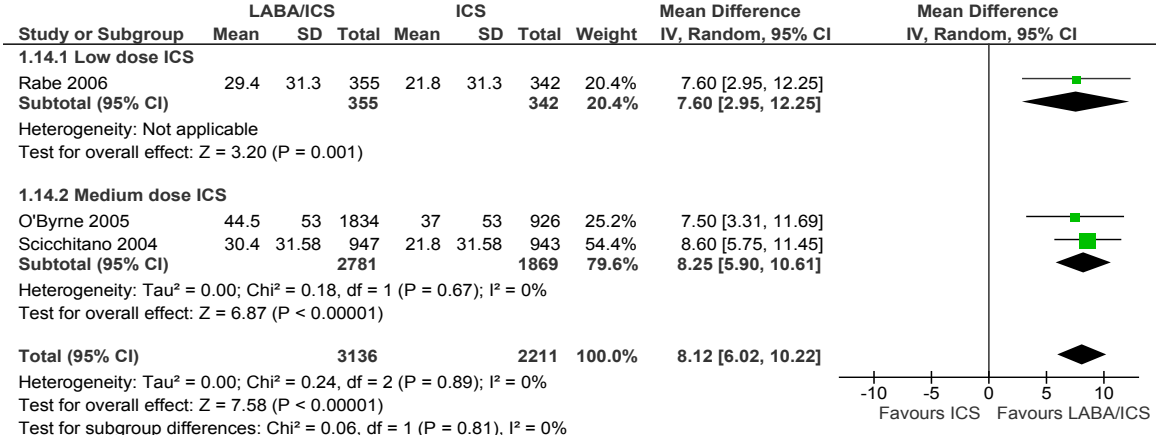
Two trials[101,124] involving 562 participants (LABA/ICS = 278, ICS = 284) receiving either LABA/ICS combination or higher-dose ICS monotherapy at run-in provided data for a meta-analysis of the effects of LABA/ICS combination therapy compared with ICS monotherapy on SFD (Figure 47). The pooled result 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)



Days with optimal control (OC): Three trials[105,119,122] 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.

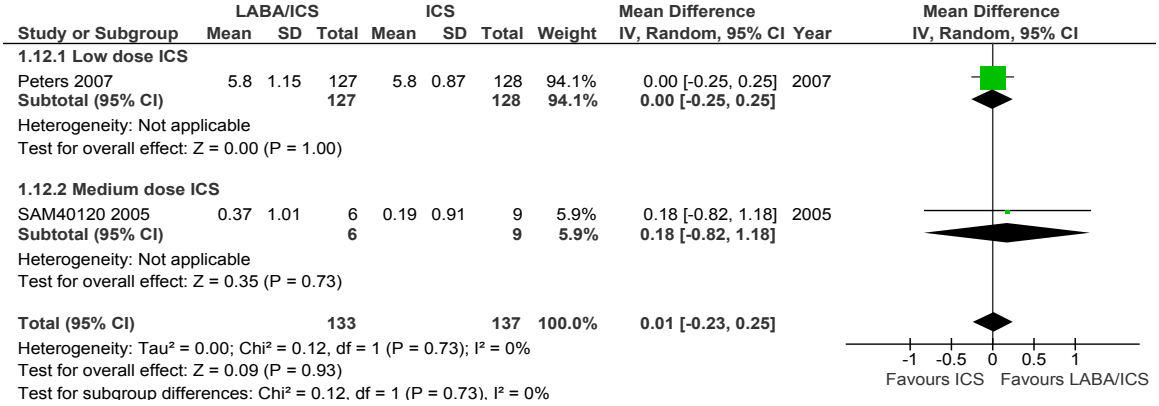
Mean ICS dose: One trial[119] involving 1,890 participants (LABA/ICS = 947, ICS = 943) provided data on the effects of LABA/ICS combination therapy compared with higher ICS monotherapy on mean ICS dose (Figure X). The result indicated a statistically significant decrease in ICS dose favouring LABA/ICS (SMD = -0.20; 95% CI: -0.30 to -0.11).

Change in ICS dose: One trial[105] 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[53,123] 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[79] 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_1, 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_1, % participants with ≥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 50.1: Funnel plot for PEF AM

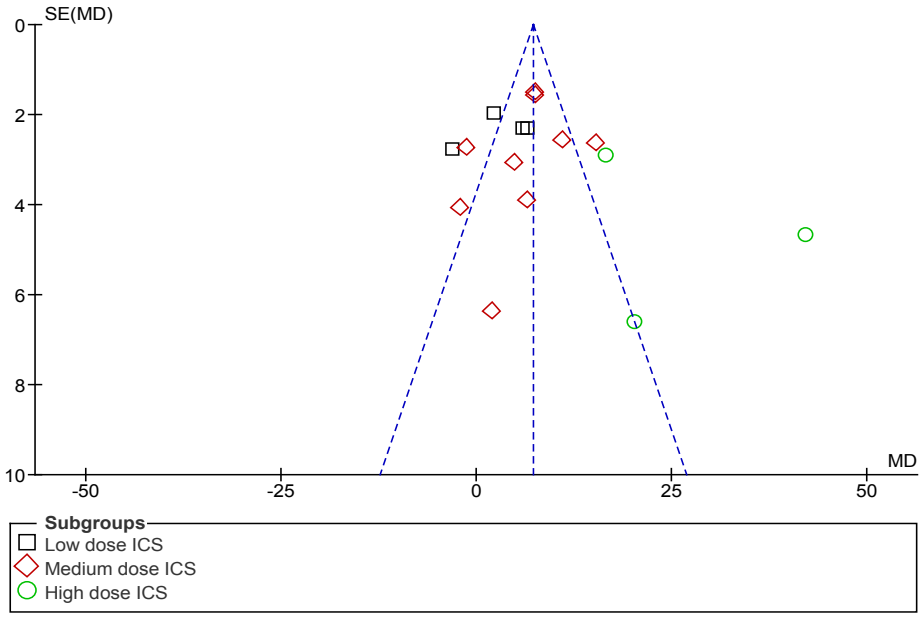


Figure 50.2: Funnel plot for PEF PM

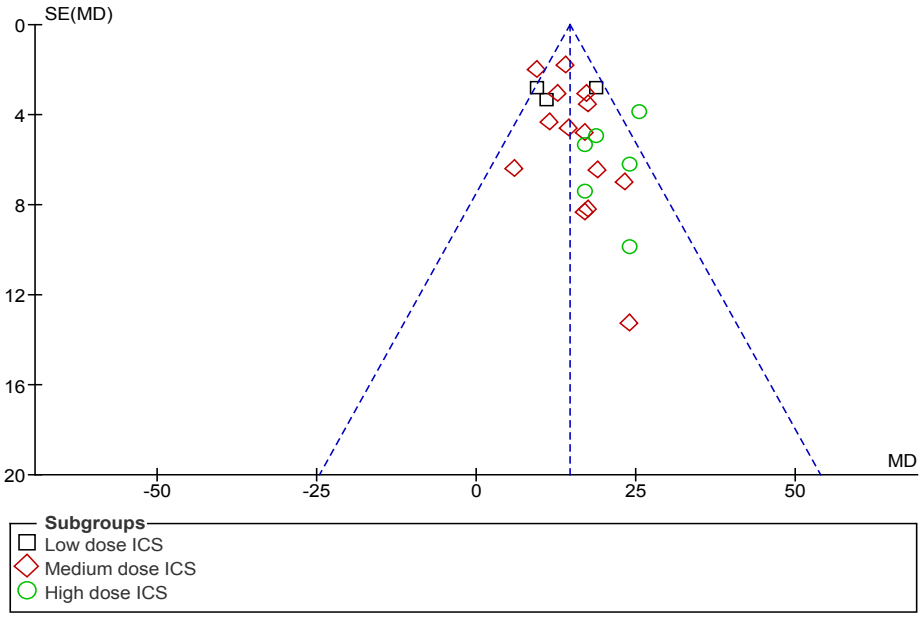


Figure 50.3: Funnel plot for FEV_1 (absolute)

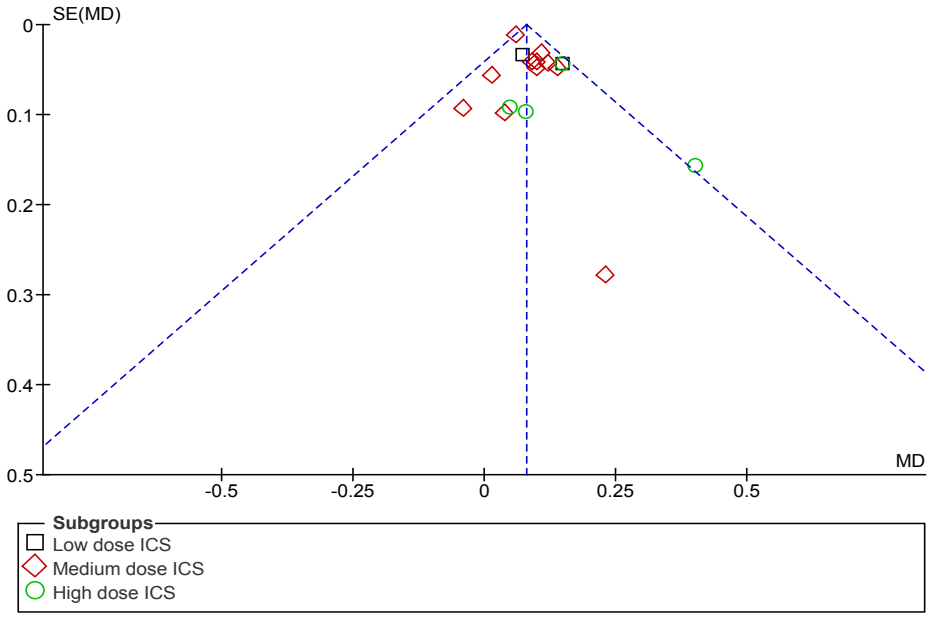


Figure 50.4: Funnel plot for percent participants experiencing one or more exacerbations

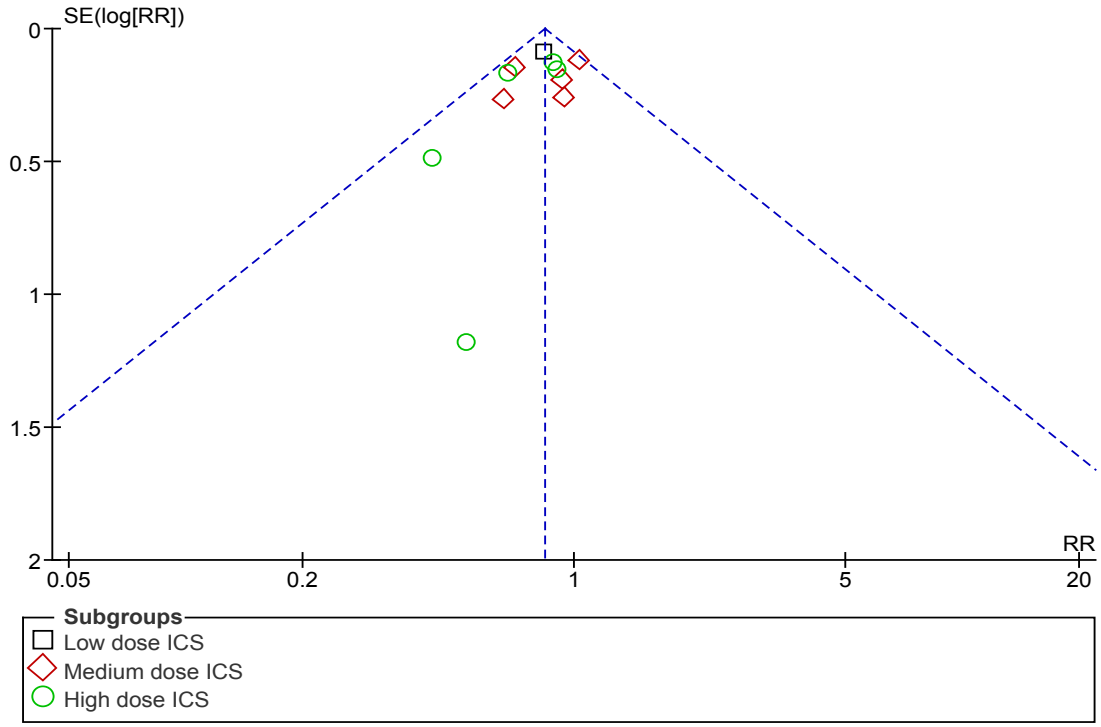


Figure 50.5: Funnel plot for SABA use

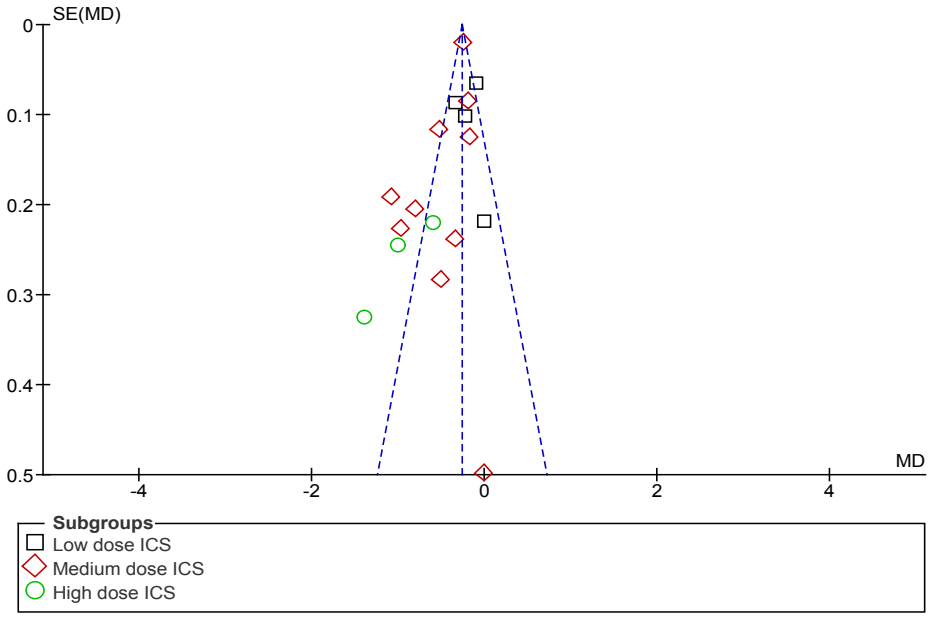
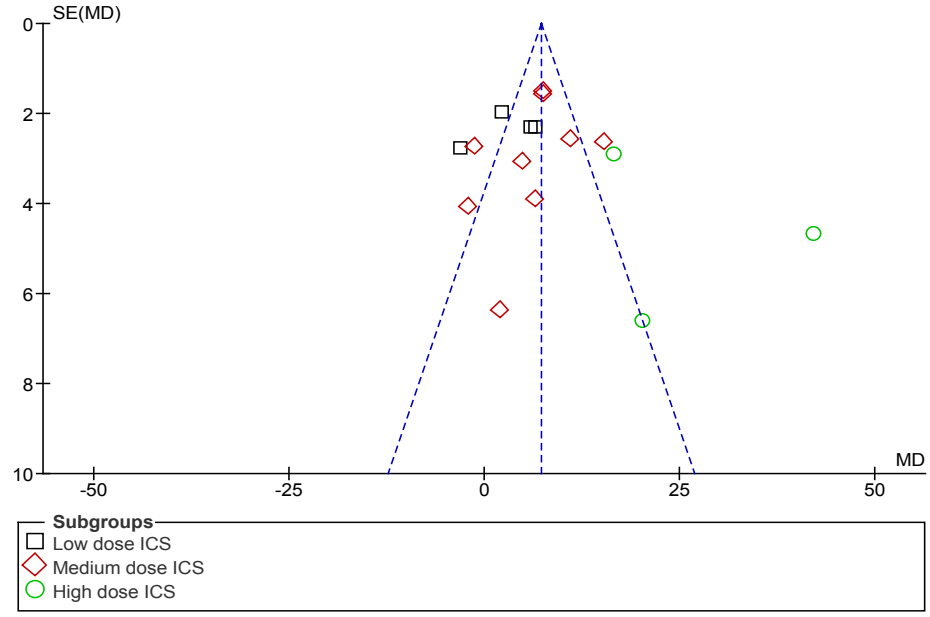


Figure 50.6: Funnel plot for SFD



Effectiveness of LABA/ICS therapy versus a different LABA/ICS therapy in adults

Twelve unique RCTs[10,11,127-136] were identified that assessed the comparative efficacy of LABA/ICS combination therapies for adult persistent asthma against one another. Nine trials[10,11,127-131,133,136] compared FORM/BUD vs SAL/FP, two compared FORM/BDP vs SAL/FP,[134,135] and one compared FORM/BUD vs FORM/BDP.[132] Eight trials[10,128-130,132,134-136] compared fixed dose vs fixed dose. Three trials[127,131,133] compared variable dose vs fixed dose. One trial[131] compared variable dose vs variable dose . LABA/ICS vs a similar dose of LABA/ICS was examined in 8 trials,[11,127-129,131,133,134,136] and the remaining four trials[10,130,132,135]

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 ≥18 years in 4 (33.3%) studies.[11,128,132,135] In terms of asthma severity, two trials[128,135] included only participants with moderate asthma. The remaining trials examine participants covering a range of asthma severity: intermittent-moderate (2 trials),[11,129] intermittent-severe (2 trials),[131,133] mild-severe (2 trials),[127,136] and moderate-severe (4 trials).[10,130,132,134] The duration of the trials varied: 12 wk (6 trials),[127,130,132,134-136] 24 wk (2 trials),[128,133] 26 wk,[10,129] and 52 wk (2 trials).[11,131] The median treatment duration was 18 wk (IQR: 12, 26).

An additional seven RCTs[105,186-191] 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[133] 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 ≥ 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

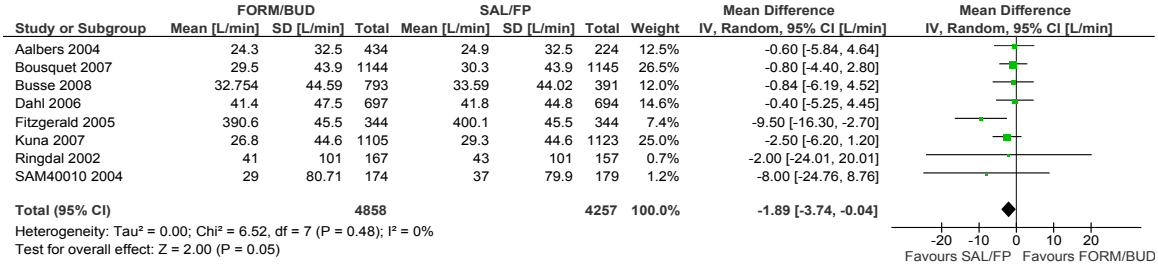
Quality Components	No. Yes (%)
Randomization	12 (100)
Double-blinding	10 (83.3)
Description of withdrawals/dropouts	12 (100)
Appropriate method of randomization	9 (75.0)
Appropriate method of double-blinding	10 (83.3)
Inappropriate method of randomization	0 (0)
Inappropriate method of double-blinding	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[10,11,127-130,133,136] 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^2 =

0%); however, the result did not meet our a priori criteria for clinical importance (MCID = 18.79 L/min).

Figure 51: The effect of FORM/BUD versus SAL/FP on PEF AM (L/min)

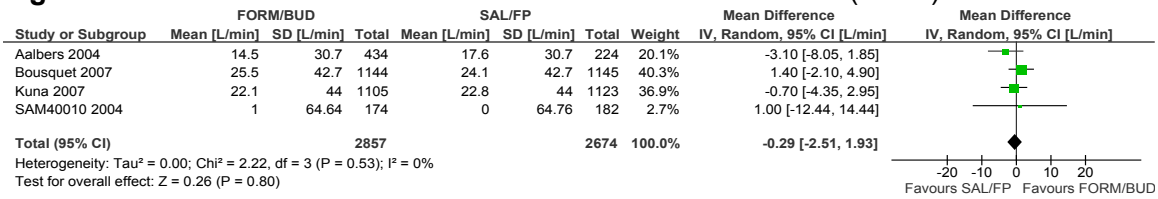


Two trials[134,135] involving 469 participants (FORM/BDP = 240, SAL/FP = 229) provided data for a meta-analysis of the effects of FORM/BDP compared with SAL/FP on PEF AM (L/min). The combined result indicated a difference favouring SAL/FP (WMD=-8.11 L/min; 95% CI: -20.24 to 4.02; I^2 = 0%); however, the result was neither statistically nor clinically important (MCID = 18.79 L/min).

One trial[132] 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[10,127,129,136] 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).

Figure 52: The effect of FORM/BUD versus SAL/FP on PEF PM (L/min)

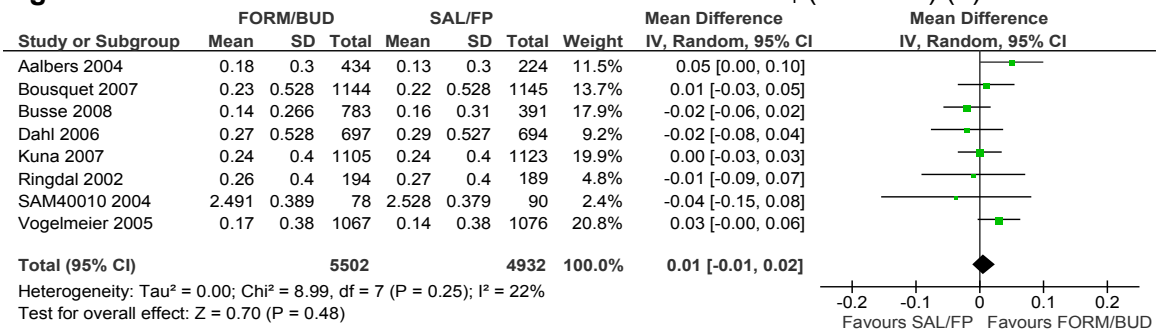


Two trials[134,135] involving 469 participants (FORM/BDP = 240, SAL/FP = 229) provided data for a meta-analysis of the effects of FORM/BDP compared with SAL/FP on PEF PM (L/min). The pooled result failed to identify a statistically significant difference between the treatments (WMD=-6.01; 95% CI: -19.89 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[132] 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_1 (absolute): Eight trials[10,127-131,133,136] 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_1 (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^2 = 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).

Figure 53: The effect of FORM/BUD versus SAL/FP on FEV_1 (absolute) (L)



Two trials[134,135] 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_1 (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).

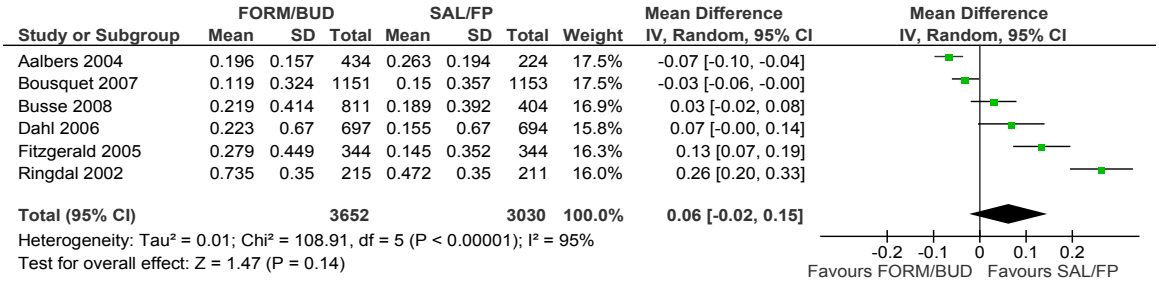
One trial[132] involving 216 participants (FORM/BUD = 109, FORM/BDP = 107) provided data for an analysis on the effects of FORM/BDP compared with FORM/BUD on FEV_1 (L). This study did not identify a statistically significant difference between the treatments (WMD = 0.05; 95% CI: -0.07 to 0.17). In addition, 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_1 % predicted: One trial[135] 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_1 % 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

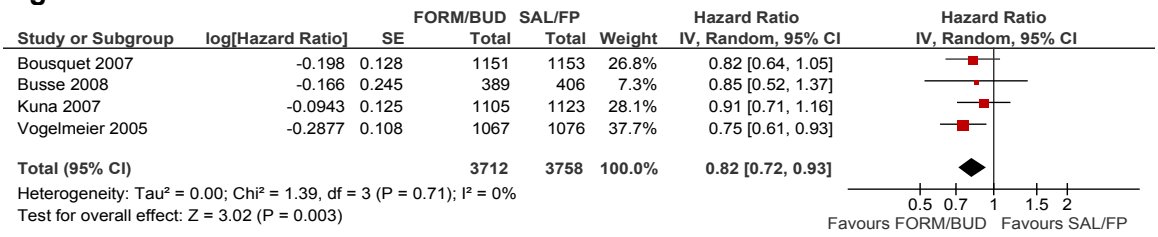
Total number of exacerbations: Six trials[10,11,127,128,130,133] involving 6,682 participants (FORM/BUD = 3,652, SAL/FP = 3,030) provided data for a meta-analysis on the effects of FORM/BUD compared with SAL/FP on the total number of exacerbations during the study period (Figure 54). The study periods 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^2 = 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



Time to first exacerbation: Four trials[10,129,131,133] 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



One trial[134] 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.

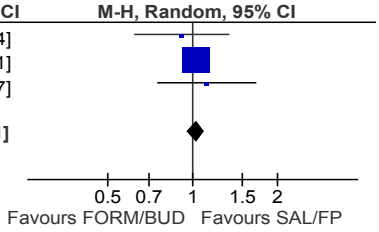
One trial[132] involving 216 participants (FORM/BUD = 109, FORM/BDP = 107) provided data on the effects of FORM/BDP compared with FORM/BUD on time to first exacerbation. This study did not identify a statistically significant difference between the treatments (Hazard Ratio=0.83; 95% CI: 0.56 to 1.23). 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 ≥1 or more exacerbations: Three trials[128,133,136] 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 ≥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; $I^2 = 0\%$); 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

Study or Subgroup	FORM/BUD Events	FORM/BUD Total	SAL/FP Events	SAL/FP Total	Weight	Risk Ratio M-H, Random, 95% CI
Busse 2008	68	811	37	404	4.0%	0.92 [0.62, 1.34]
Dahl 2006	451	697	436	694	92.4%	1.03 [0.95, 1.11]
SAM40010 2004	40	183	37	190	3.7%	1.12 [0.75, 1.67]
Total (95% CI)		**1691**		**1288**	**100.0%**	**1.03 [0.95, 1.11]**
Total events	559		510			

Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)



One trial[134] 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 ≥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.

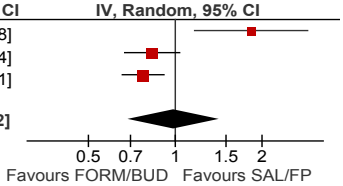
One trial[132] involving 216 participants (FORM/BUD = 109, FORM/BDP = 107) provided data on the effects of FORM/BDP compared with FORM/BUD on the percentage of participants with ≥1 exacerbations. This study did not identify a statistically significant difference between the treatments (RR=0.69; 95% CI: 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[128,129,131] 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^2=84%); however, the 95% CIs of the pooled estimate include possible values that would meet our a priori criteria for clinical importance. Dahl 2006[128] only included participants with moderate asthma, while the other two studies[129,131] included participants with intermittent-moderate asthma[129]and intermittent-severe asthma[131].

Figure 57: The effect of FORM/BUD versus SAL/FP on number of severe exacerbations

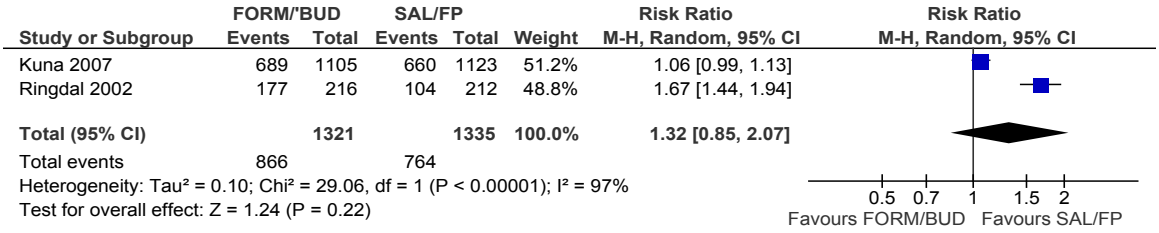
Study or Subgroup	log[Rate Ratio]	SE	FORM/BUD Total	SAL/FP Total	Weight	Rate Ratio IV, Random, 95% CI
Dahl 2006	0.606	0.23	697	694	25.3%	1.83 [1.17, 2.88]
Kuna 2007	-0.184	0.112	1105	1123	36.2%	0.83 [0.67, 1.04]
Vogelmeier 2005	-0.2559	0.085	1067	1076	38.4%	0.77 [0.66, 0.91]
Total (95% CI)			**2869**	**2893**	**100.0%**	**0.99 [0.69, 1.42]**

Heterogeneity: Tau² = 0.08; Chi² = 12.41, df = 2 (P = 0.002); I² = 84%
Test for overall effect: Z = 0.06 (P = 0.95)



Number of mild exacerbations: Two trials[129,130] 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[129] included participants with intermittent-moderately severe asthma, while Ringdal 2002[130] included participants with moderate-severe asthma.

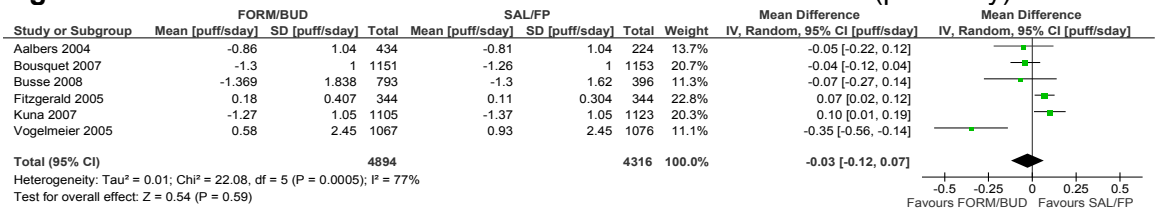
Figure 58: The effect of FORM/BUD versus SAL/FP on number of mild exacerbations



One trial[132] 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[10,11,127,129,131,133] 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[131] 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)

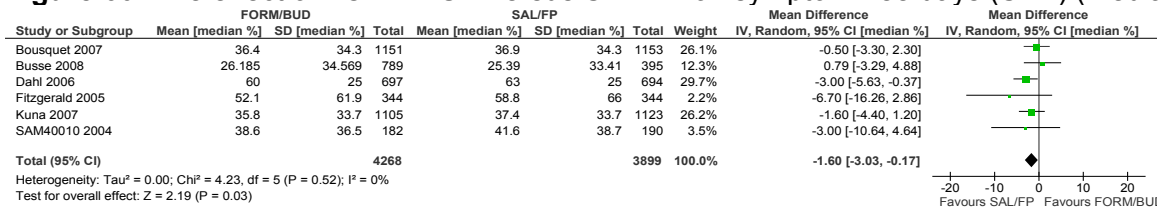


One trial[134] involving 228 participants (FORM/BDP = 115, SAL/FP = 113) provided data on the effects of FORM/BDP compared with SAL/FP on SABA use (puffs/day). The combined results failed to demonstrate a statistically significant difference between the two groups (WMD = -0.19; 95% CI: -0.04 to 0.42). 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[132] 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[10,11,128,129,133,136] 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 %)

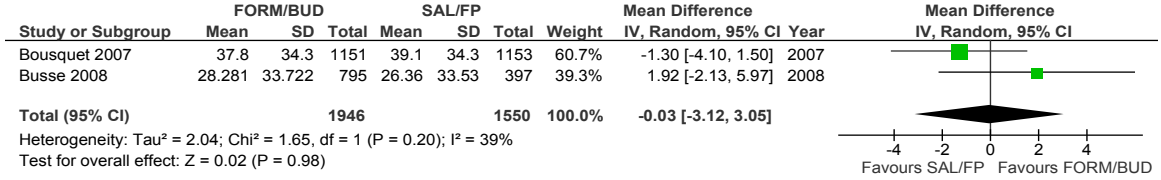


Two trials[134,135] involving 469 participants (FORM/BDP = 240, SAL/FP = 229) provided data for a meta-analysis of the effects of FORM/BDP compared with SAL/FP on median % SFD. The combined result failed to demonstrate a statistically significant difference between the two groups (WMD = -1.07; 95% CI: -6.22 to 8.35; I^2 = 0%).

One trial[132] 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[10,133] 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 (OC)



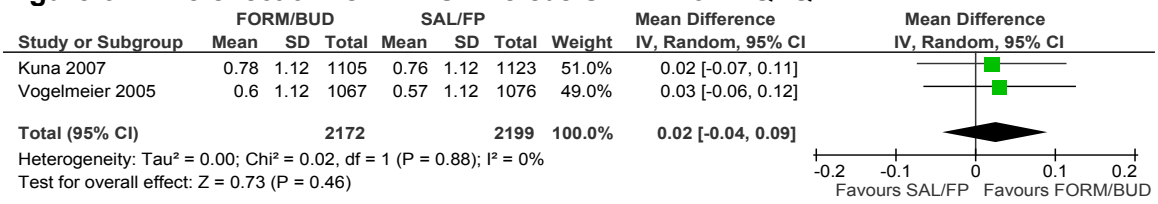
% participants stepping down their dose: One trial[131] involving 2143 participants (FORM/BUD = 1067, SAL/FP = 1076) provided data for an analysis on the effects of FORM/BUD therapy compared with SAL/FP on the % of participants stepping down their dose. The result favoured

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[127] 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[129,131] 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; $I^2 = 0\%$). In addition, the precision of the confidence intervals suggest that any differences would not meet our a priori criteria for clinical importance (MCID = 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[49,137-147] were identified that assessed the potential steroid sparing effects of LABA/ICS combination therapy versus ICS monotherapy. Seven trials[49,137,138,140,141,144,147]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[142] used the abrupt dose-reduction design with patients symptomatic on ICS monotherapy. Four trials[139,143,145,147]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[49,137,142,144-146] compared SAL/FP vs FP alone, three[138,140,141] compared FORM/BUD vs BUD alone, one[147] compared SAL/BDP vs BDP alone, one[139] compared SAL/BUD vs BUD alone, and one[143] 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 ≥18 years in 8 (66.7%) studies.[138-141,143,145-147] In terms of asthma severity, three trials[49,137,146] included only participants with moderate asthma and one[145] included only participants with severe asthma. The remaining trials examined participants covering a range of asthma severity:

intermittent to mild (1 trial),[147] intermittent to severe (3 trials),[138,140,141] mild to moderate (1 trial),[139], mild to severe (1 trial),[144] and moderate to severe (1 trial).[143] One trial[142] did not report the baseline severity of the study participants. Treatment duration also varied across studies: 12 wk (3 trials),[49,142,144] 20 wk (1 trial),[141] 24 wk (3 trials),[137,145,146] 26 wk (1 trial),[147] 48 wk (1 trial),[143] and 52 wk (2 trials).[138,140] The treatment duration in one trial[139] 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 ≥3) of almost all studies, no sensitivity analyses were conducted.

Table 7: **Methodological quality of steroid sparing studies (N = 12)**

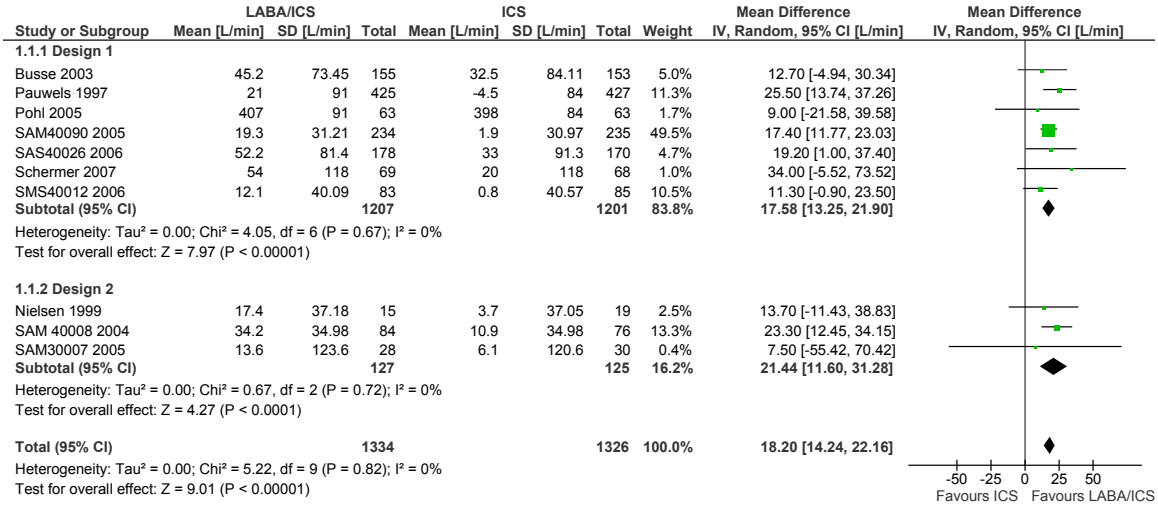
Quality Components	No. Yes (%)
Randomization	12 (100)
Double-blinding	12 (100)
Description of withdrawals/dropouts	10 (83.3)
Appropriate method of randomization	2 (16.7)
Appropriate method of double-blinding	3 (25.0)
Inappropriate method of randomization	0 (0)
Inappropriate method of double-blinding	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[49,137,139-142,144-147] 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; $I^2 = 0\%$). The lack of precision of the estimates prevents conclusions regarding the equivalence of the two treatments (MCID = ±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).

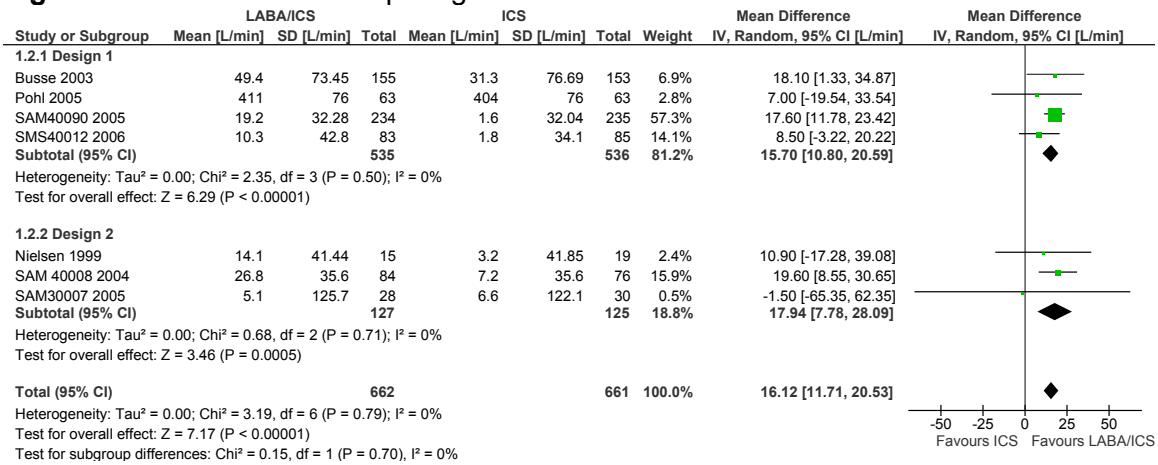
Figure 63: Potential steroid-sparing effect of LABA/ICS vs ICS on PEF AM



PEF PM: Seven trials[137,139,141,144-147] 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%).

Figure 64: Potential steroid-sparing effect of LABA/ICS vs ICS on PEF PM

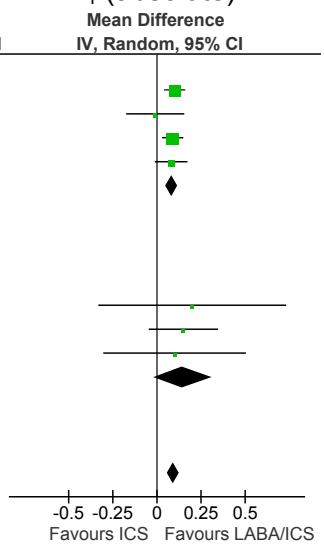


FEV_1 (absolute): Seven trials[49,137,139,141,142,145,146] involving 1,171 participants (LABA/ICS = 592, ICS = 579) provided data for a meta-analysis of the potential steroid sparing effects of LABA/ICS combination therapy compared with ICS monotherapy on absolute FEV_1 (Figure 65). The pooled result 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_1 (absolute)

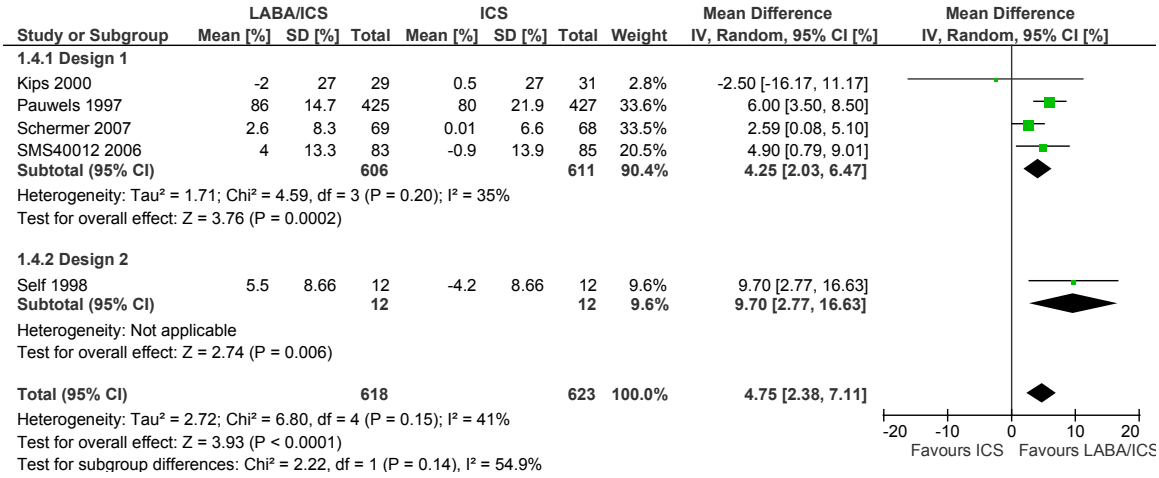
Study or Subgroup	LABA/ICS Mean	LABA/ICS SD	LABA/ICS Total	ICS Mean	ICS SD	ICS Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 Design 1								
Busse 2003	0.1	0.25	155	0	0.25	153	37.9%	0.10 [0.04, 0.16]
Pohl 2005	0.36	0.46	63	0.37	0.46	63	4.6%	-0.01 [-0.17, 0.15]
SAS40026 2006	0.08	0.27	178	-0.01	0.26	170	38.1%	0.09 [0.03, 0.15]
Schermer 2007	0.0758	0.308	69	-0.0045	0.211	68	15.1%	0.08 [-0.01, 0.17]
Subtotal (95% CI)			**465**			**454**	**95.6%**	**0.09 [0.05, 0.12]**
Heterogeneity: Tau² = 0.00; Chi² = 1.64, df = 3 (P = 0.65); I² = 0%								
Test for overall effect: Z = 4.89 (P < 0.00001)								
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: Tau² = 0.00; Chi² = 0.09, df = 2 (P = 0.95); I² = 0%								
Test for overall effect: Z = 1.74 (P = 0.08)								
Total (95% CI)			**592**			**579**	**100.0%**	**0.09 [0.06, 0.12]**
Heterogeneity: Tau² = 0.00; Chi² = 2.20, df = 6 (P = 0.90); I² = 0%								
Test for overall effect: Z = 5.15 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.47, df = 1 (P = 0.49), I² = 0%								



FEV_1 % predicted: Five trials[138,140,142,143,147] 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^2 = 41%); the precision of the 95% CI suggests that the two treatments are clinically equivalent (MCID = ±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%).

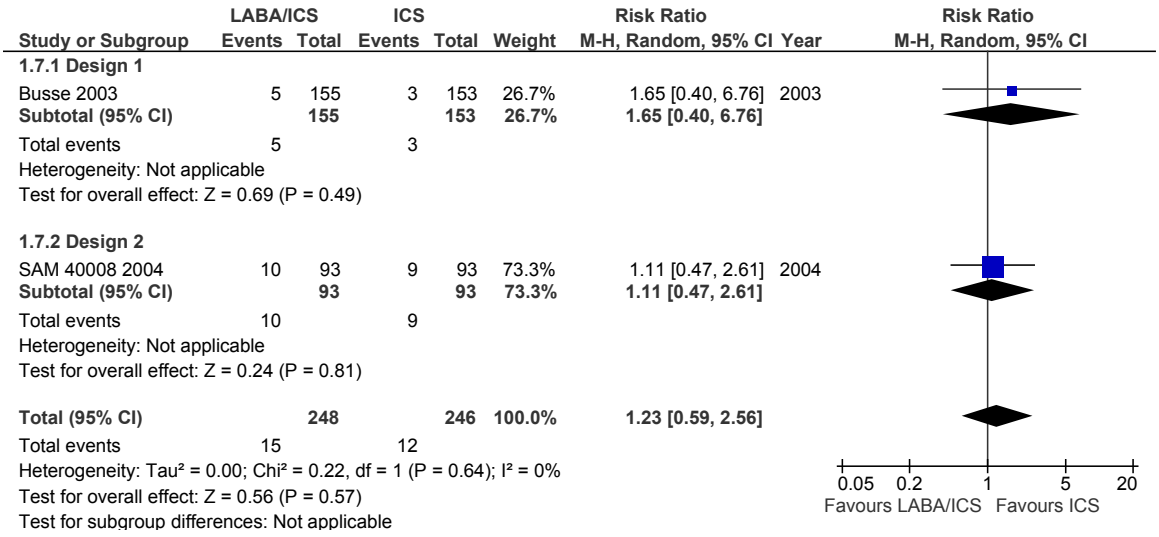
Figure 66: Potential steroid-sparing effect of LABA/ICS vs ICS on FEV_1 % predicted



Asthma control measures

No. participants with ≥1 exacerbations: Two trials[137,145] 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 ≥ 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^2 = 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).

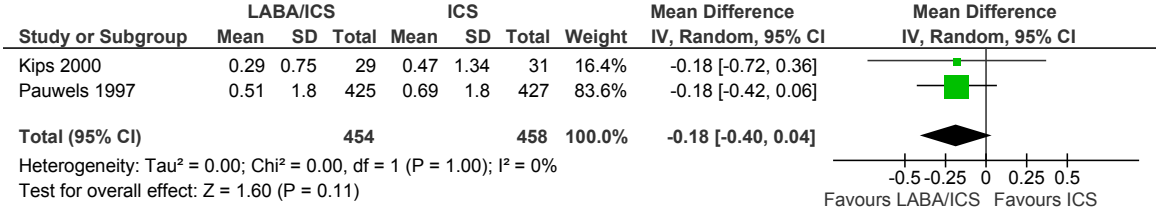
Figure 67: Potential steroid-sparing effect of LABA/ICS vs ICS on no. participants with ≥1 exacerbation



No. severe exacerbations: Two trials[138,140] 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

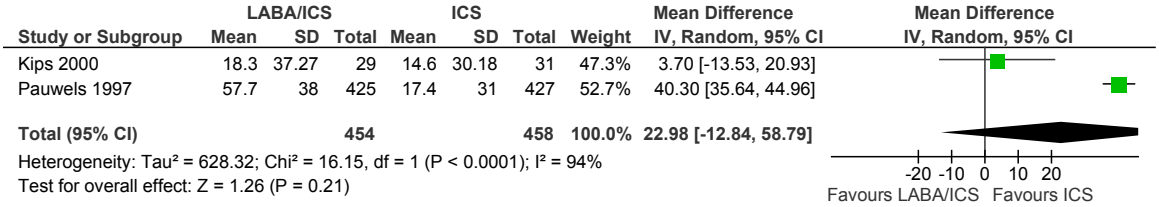
pooled result failed to identify a statistically significant difference between treatments (WMD = -0.18; 95% CI: -0.40 to 0.04; I^2 = 0%).

Figure 68: Potential steroid-sparing effect of LABA/ICS vs ICS on no. severe exacerbations



No. mild exacerbations: Two trials[138,140] 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%).

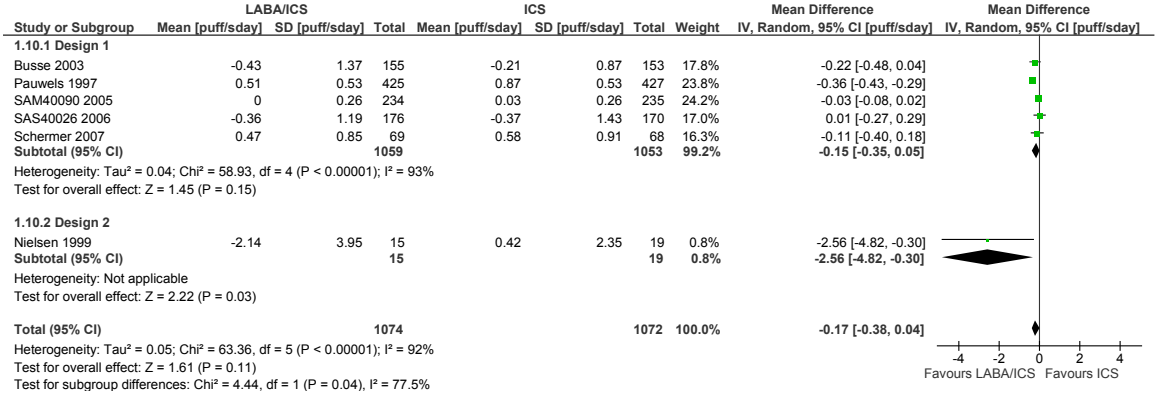
Figure 69: Potential steroid-sparing effect of LABA/ICS vs ICS on no. mild exacerbations



SABA use (puffs/day): Six trials[49,137,139,140,142,144] 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^2 = 92%); however, the precision of the 95% CI suggests that LABA/ICS is clinically equivalent to ICS monotherapy (MCID = ±0.81).

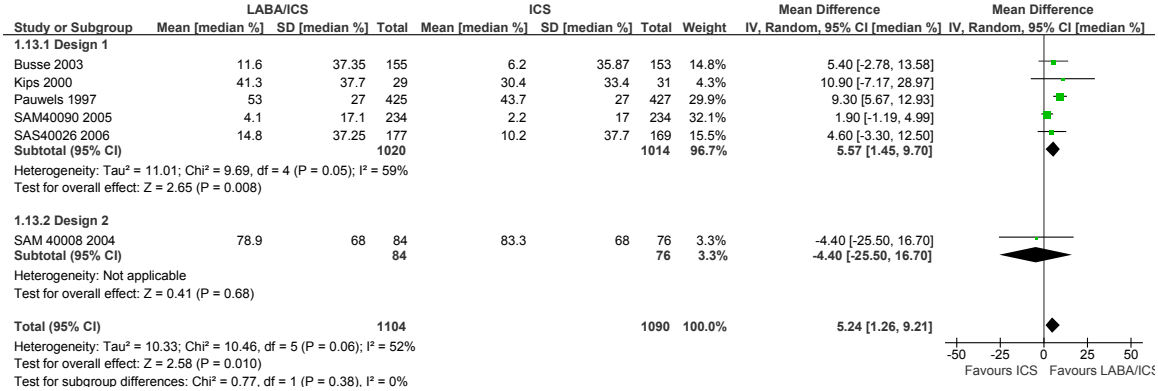
A subgroup analysis based on design indicated a potential clinical equivalence between treatments for studies that employed Design 1 (WMD = -0.15; 95% CI: -0.35 to 0.05; I^2 = 93%; MCID = ±0.81). The result for the study that employed Design 2 indicated a statistically significant difference favouring 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)



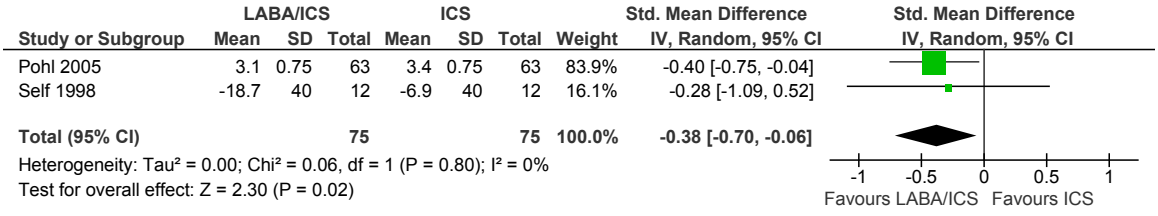
Symptom-free days (SFD): Six trials[49,137,138,140,144,145] involving 2,194 participants (LABA/ICS =1,104, ICS = 1,090) provided data for a meta-analysis of the potential steroid sparing effects of LABA/ICS combination therapy compared with ICS monotherapy on SFD (Figure 71). The pooled result indicated 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)



Mean ICS dose: Two trials[141,143] 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 µg; 95% CI: -0.70 to -0.06; I^2 = 0%).

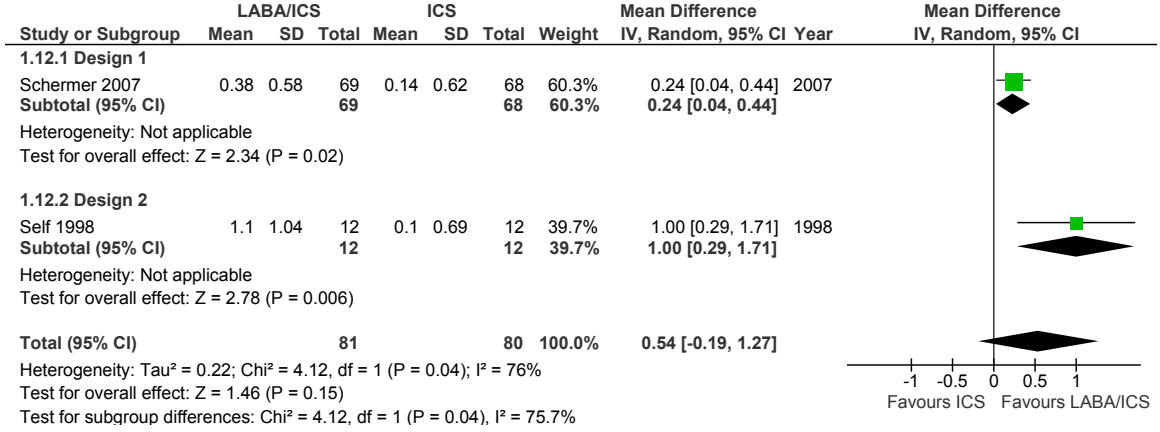
Figure 72: Potential steroid-sparing effect of LABA/ICS vs ICS on mean ICS dose (µg)



Health-related quality of life measures

AQLQ: Two trials[142,143] 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 to 1.27; I^2 = 76%). Moreover, the lack of precision of the estimates prevents conclusions regarding the equivalence of the two treatments (MCID = ±0.5).

Figure 73: Potential steroid-sparing effect of LABA/ICS vs ICS on AQLQ score

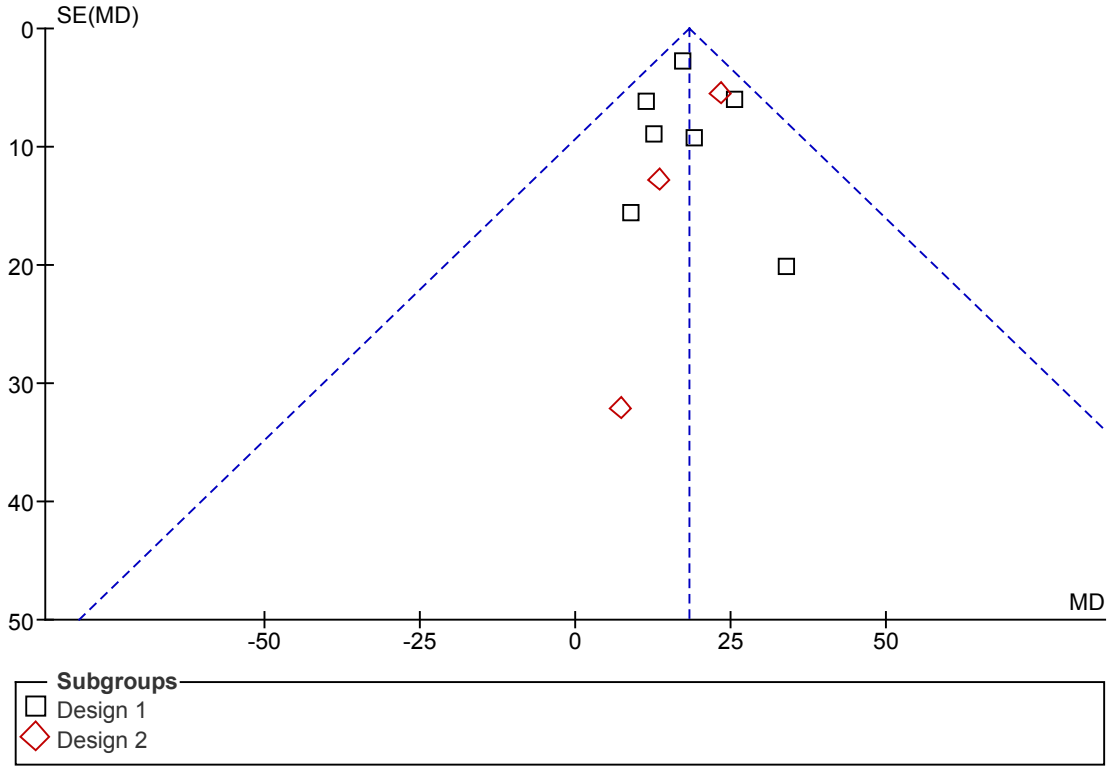


The results of the clinical analysis are summarized in Table X. It was not considered appropriate to conduct subgroup analyses based on asthma severity as only a small proportion of studies (< 20% of available studies for any single outcome) reported results for populations restricted to a single asthma 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).

Figure 74: Funnel plot of PEF AM



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 ≥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).

Figure 75: The effect of LABA/ICS versus ICS monotherapy on no. participants experiencing ≥ 1 AE

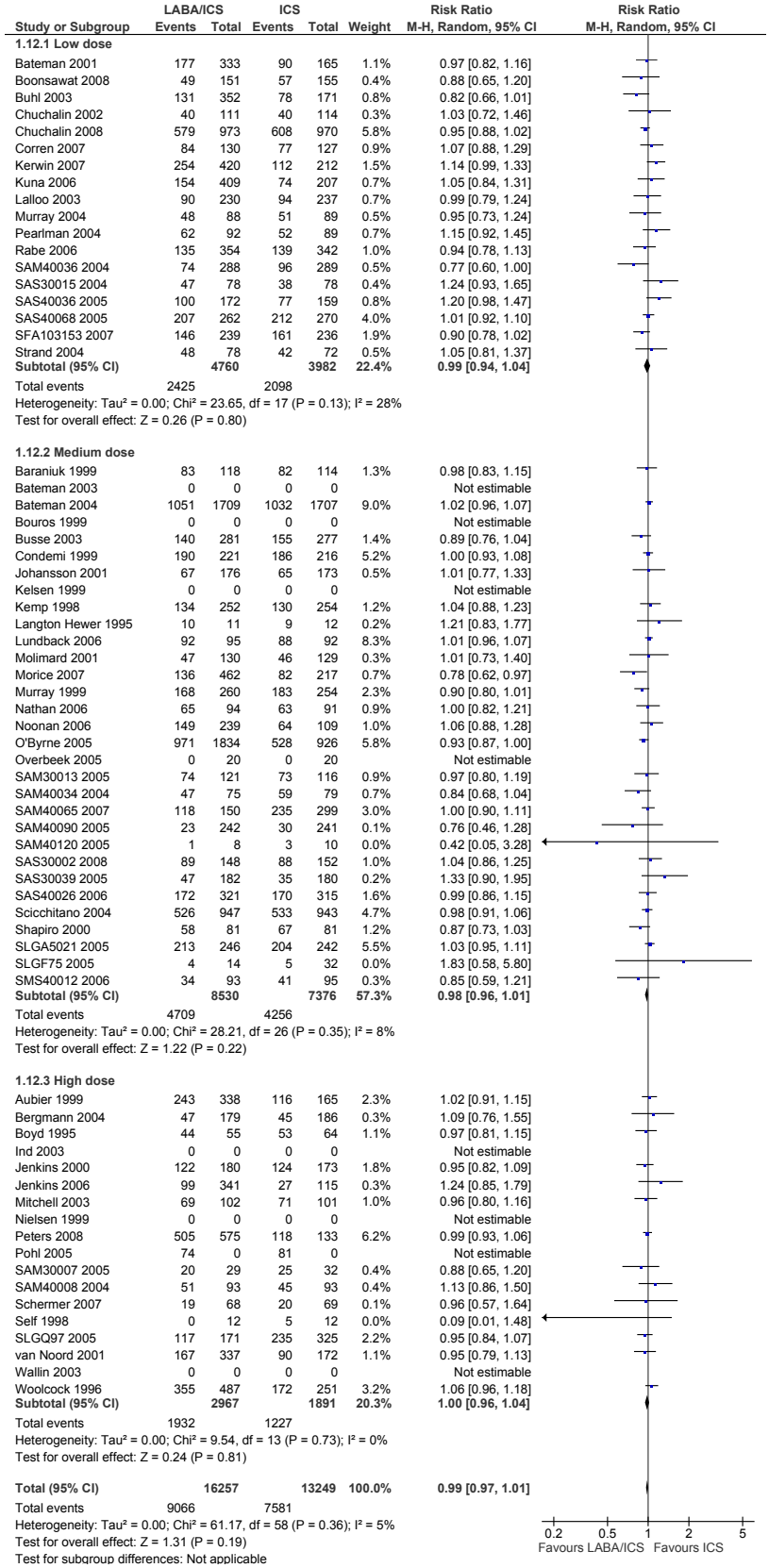


Figure 76: The effect of LABA/ICS versus ICS monotherapy on total SAEs

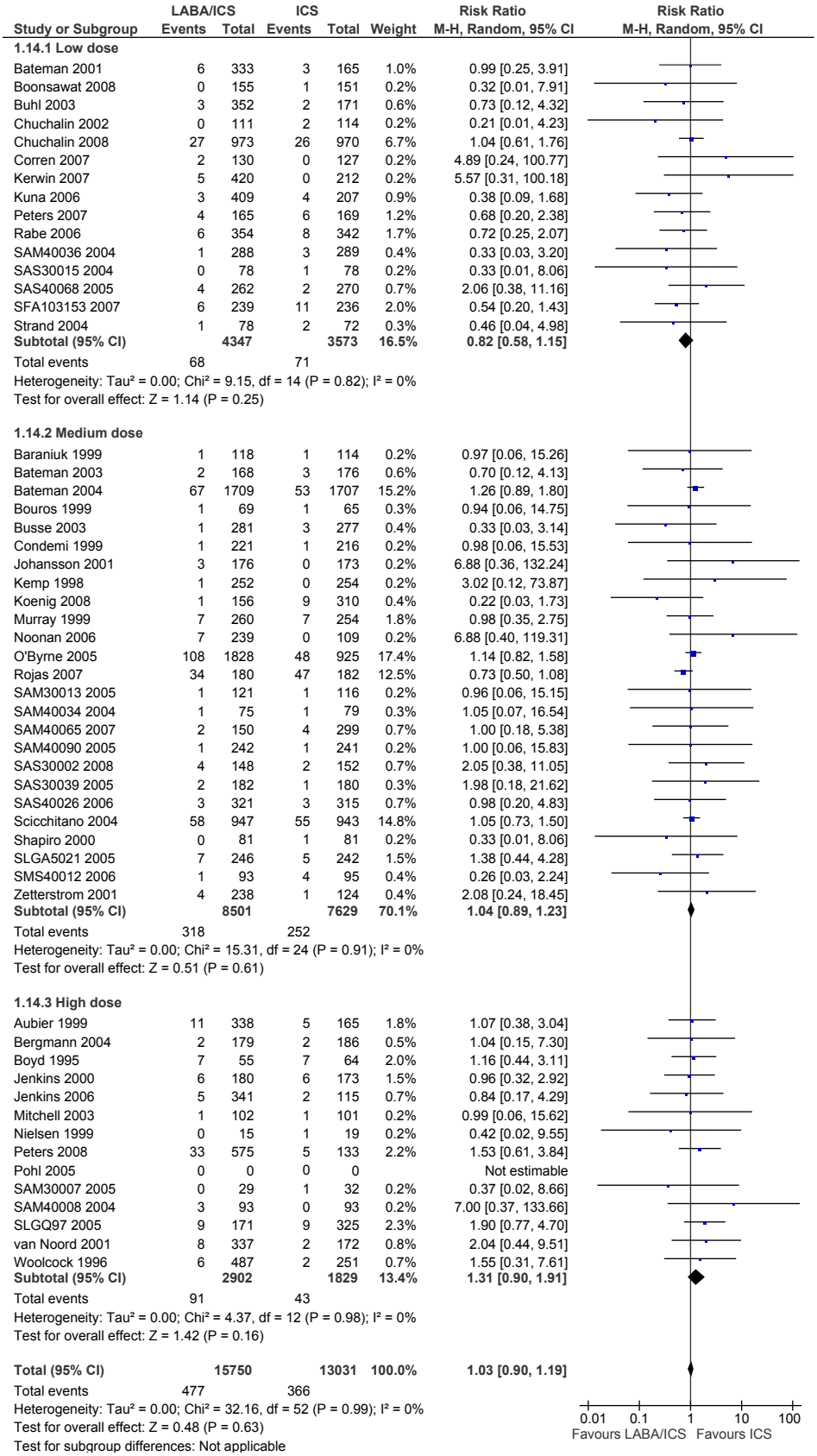


Figure 77: The effect of LABA/ICS versus ICS monotherapy on headache

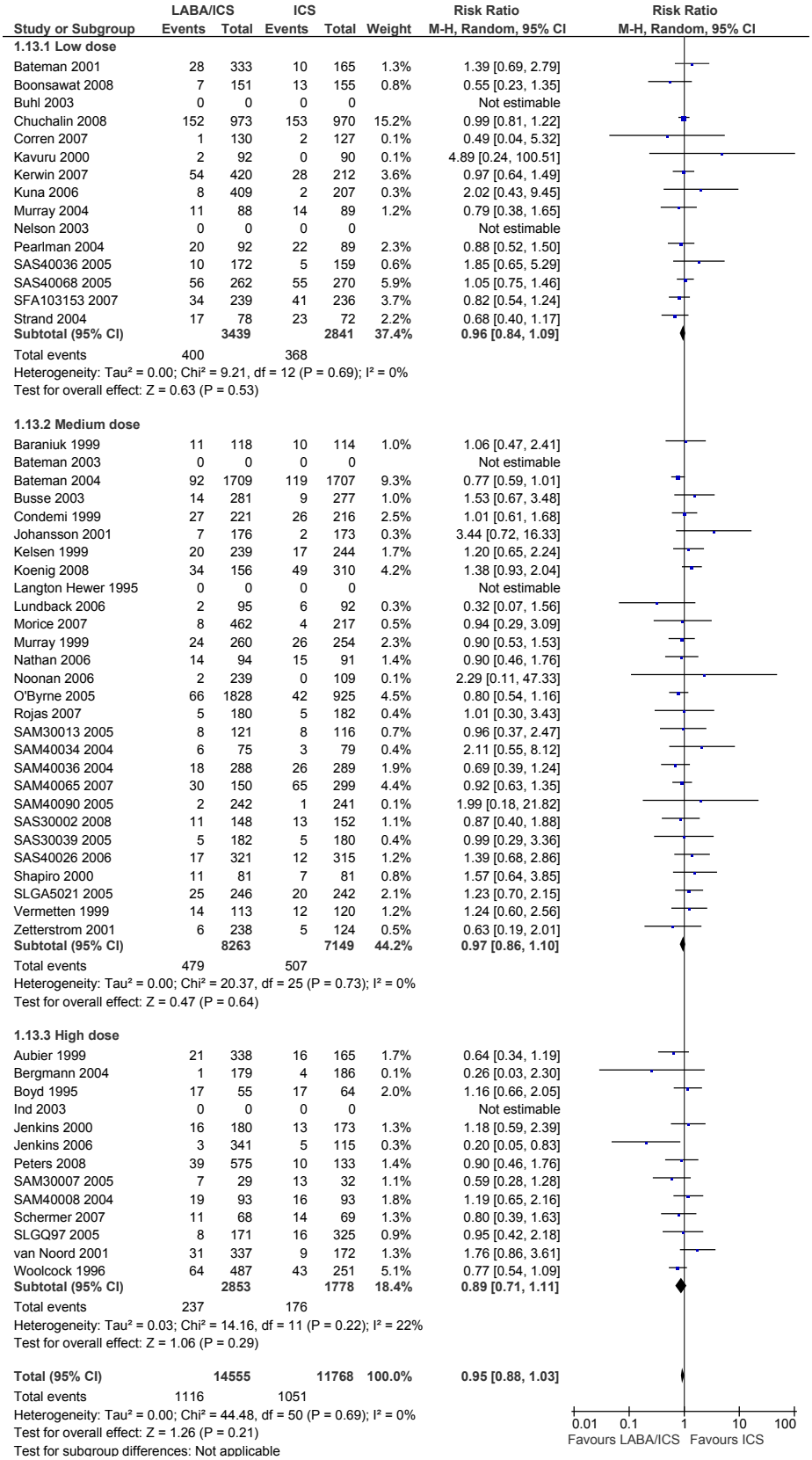


Figure 78: The effect of LABA/ICS versus ICS monotherapy on withdrawal due to AE

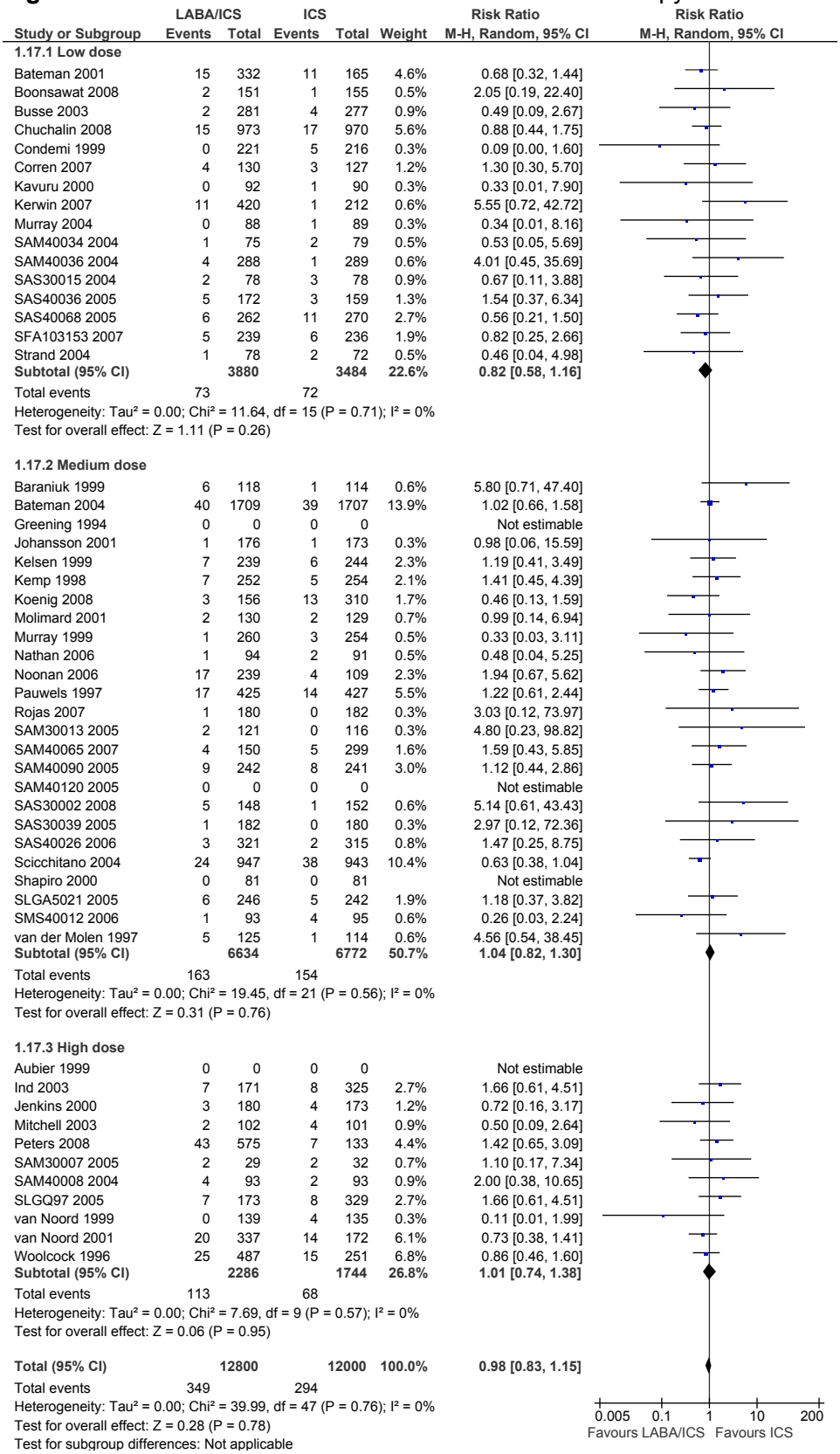


Figure 79: The effect of LABA/ICS versus ICS monotherapy on upper respiratory tract infection

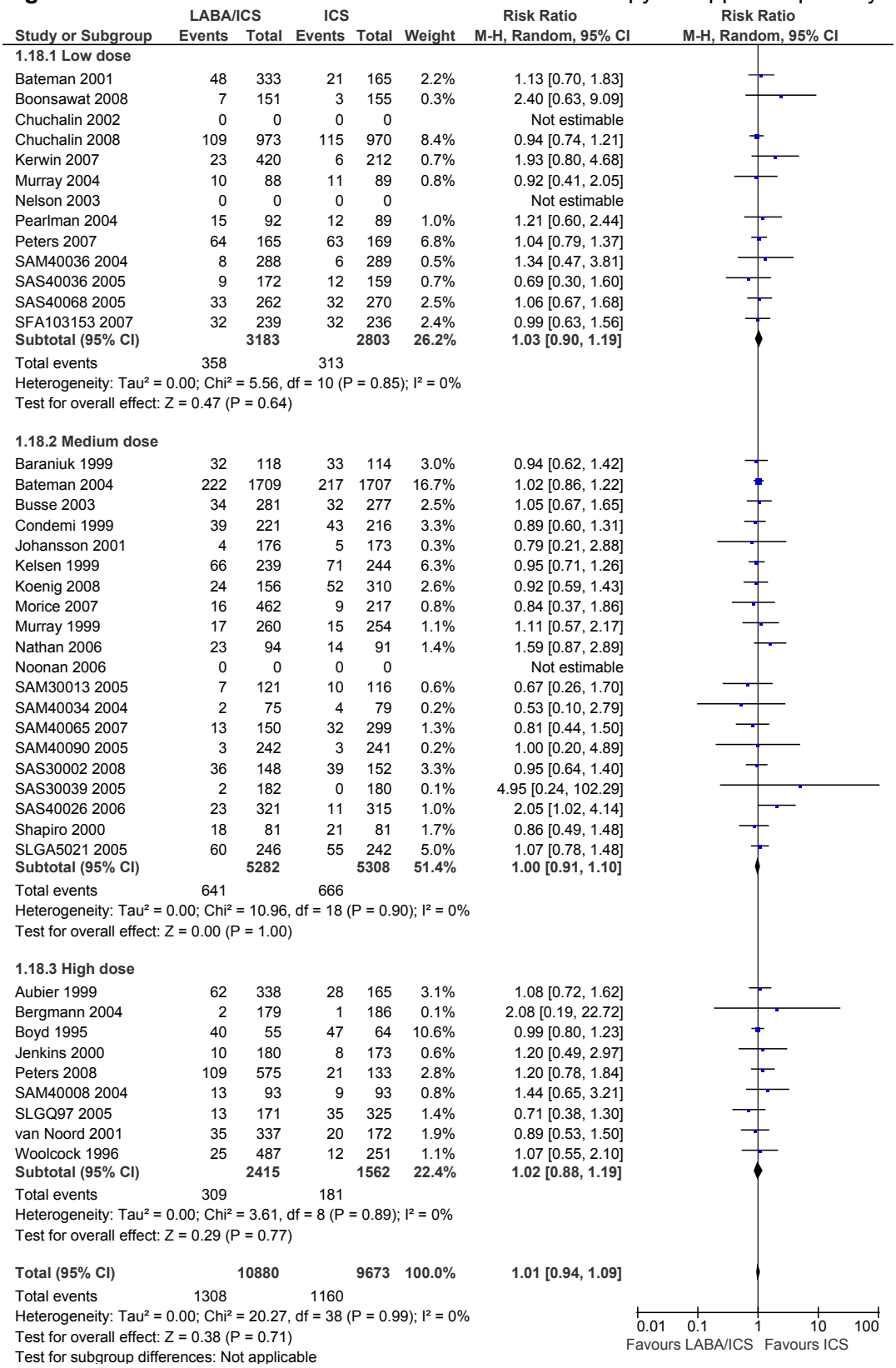


Figure 80: The effect of LABA/ICS versus ICS monotherapy on candidiasis

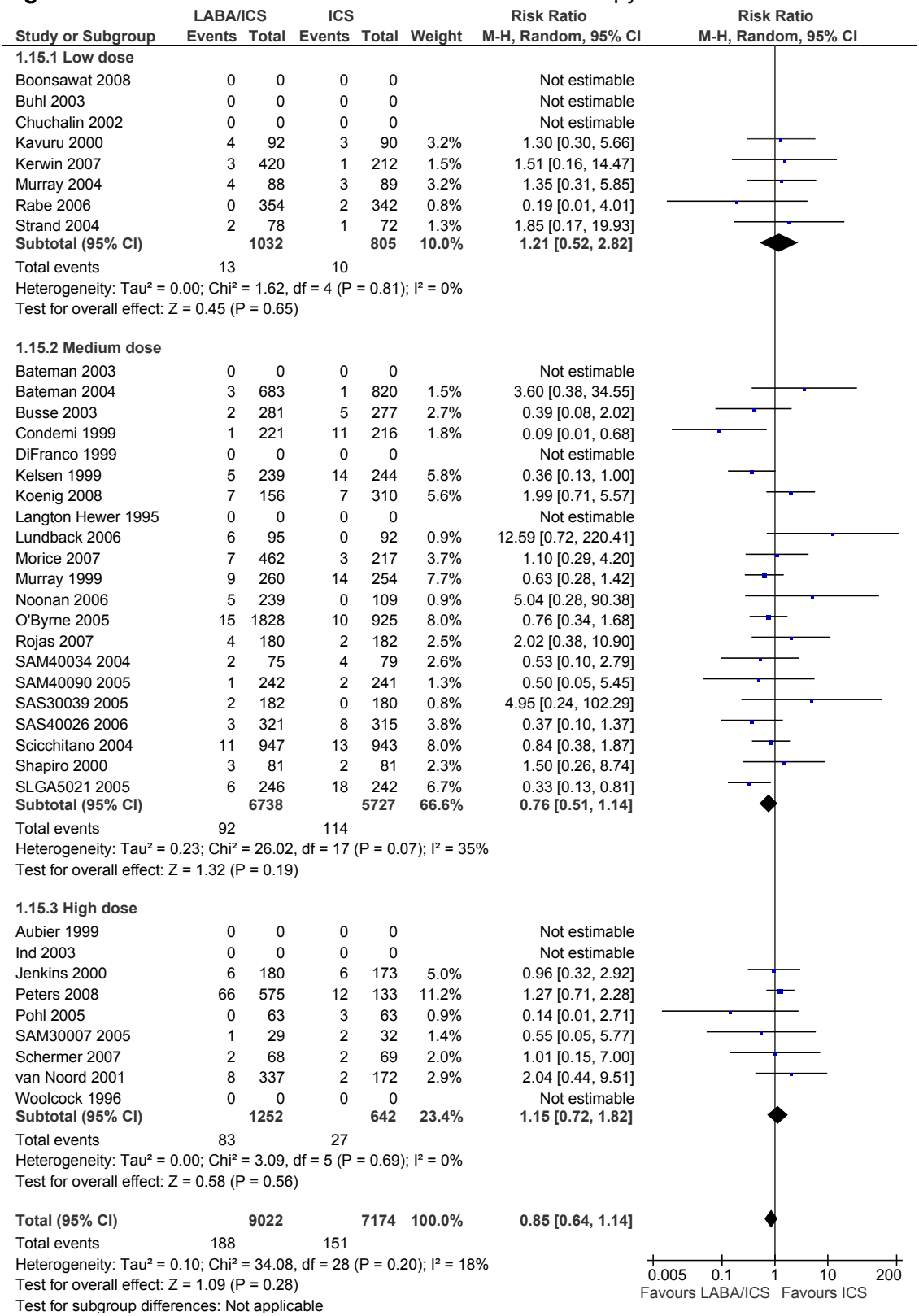


Figure 81: The effect of LABA/ICS versus ICS monotherapy on treatment-related AEs

Study or Subgroup	LABA/ICS Events	LABA/ICS Total	ICS Events	ICS Total	Weight	Risk Difference M-H, Random, 95% CI
1.16.1 Low dose						
Bateman 2001	31	333	14	165	0.2%	0.01 [-0.04, 0.06]
Boonsawat 2008	0	155	0	151	2.9%	0.00 [-0.01, 0.01]
Buhl 2003	0	352	0	171	5.9%	0.00 [-0.01, 0.01]
Corren 2007	0	0	0	0		Not estimable
Kerwin 2007	36	420	16	212	0.2%	0.01 [-0.03, 0.05]
Murray 2004	15	88	12	89	0.0%	0.04 [-0.07, 0.14]
Nelson 2003	16	95	16	97	0.0%	0.00 [-0.10, 0.11]
Pearlman 2004	0	92	0	89	1.0%	0.00 [-0.02, 0.02]
Rabe 2006	6	354	9	342	1.0%	-0.01 [-0.03, 0.01]
Subtotal (95% CI)		**1889**		**1316**	**11.4%**	**-0.00 [-0.01, 0.01]**
Total events	104		67			
Heterogeneity: Tau² = 0.00; Chi² = 2.65, df = 7 (P = 0.92); I² = 0%						
Test for overall effect: Z = 0.11 (P = 0.92)						
1.16.2 Medium dose						
Baraniuk 1999	0	118	0	114	1.7%	0.00 [-0.02, 0.02]
Bateman 2003	0	168	0	176	3.7%	0.00 [-0.01, 0.01]
Bateman 2004	4	1709	3	1707	51.7%	0.00 [-0.00, 0.00]
Bouros 1999	0	0	0	0		Not estimable
Busse 2003	0	281	0	277	9.7%	0.00 [-0.01, 0.01]
Condemi 1999	0	221	0	216	6.0%	0.00 [-0.01, 0.01]
Fitzgerald 1999	13	89	11	91	0.0%	0.03 [-0.07, 0.12]
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]
Kemp 1998	11	252	13	254	0.3%	-0.01 [-0.04, 0.03]
Molimard 2001	5	130	4	129	0.2%	0.01 [-0.04, 0.05]
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]
SAM40120 2005	0	8	0	10	0.0%	0.00 [-0.19, 0.19]
Subtotal (95% CI)		**4387**		**4135**	**77.6%**	**0.00 [-0.00, 0.00]**
Total events	113		88			
Heterogeneity: Tau² = 0.00; Chi² = 10.73, df = 14 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
1.16.3 High dose						
Aubier 1999	0	338	0	165	5.5%	0.00 [-0.01, 0.01]
Bergmann 2004	0	179	1	186	2.1%	-0.01 [-0.02, 0.01]
Peters 2008	144	575	26	133	0.1%	0.05 [-0.02, 0.13]
Pohl 2005	0	0	0	0		Not estimable
van Noord 2001	41	337	23	172	0.1%	-0.01 [-0.07, 0.05]
Woolcock 1996	2	487	2	251	3.1%	-0.00 [-0.02, 0.01]
Subtotal (95% CI)		**1916**		**907**	**11.0%**	**-0.00 [-0.01, 0.01]**
Total events	187		52			
Heterogeneity: Tau² = 0.00; Chi² = 7.95, df = 4 (P = 0.09); I² = 50%						
Test for overall effect: Z = 0.31 (P = 0.76)						
Total (95% CI)		**8192**		**6358**	**100.0%**	**0.00 [-0.00, 0.00]**
Total events	404		207			
Heterogeneity: Tau² = 0.00; Chi² = 20.60, df = 27 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
Test for subgroup differences: Not applicable						

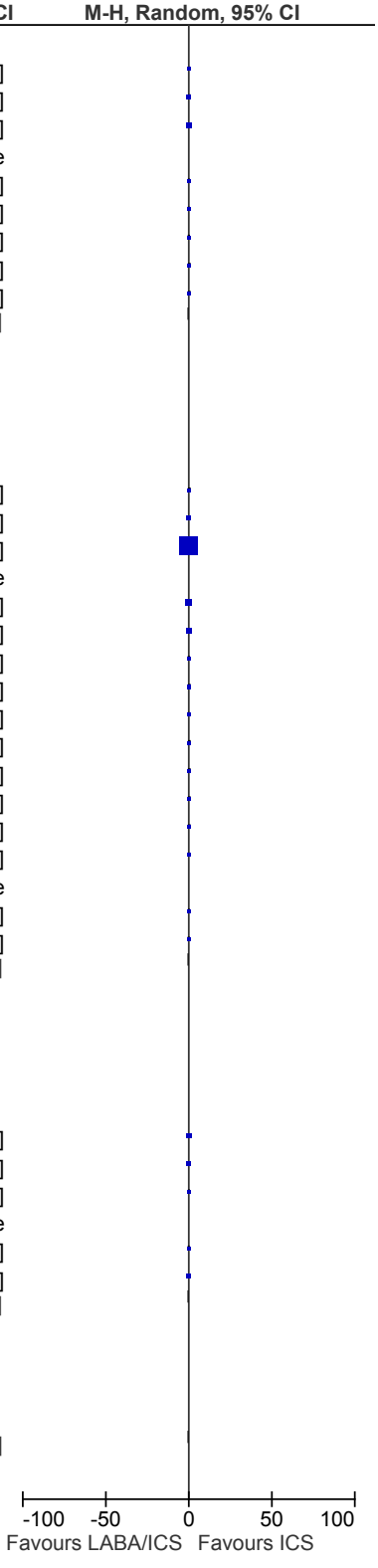


Figure 82: The effect of LABA/ICS versus ICS monotherapy on worsening asthma

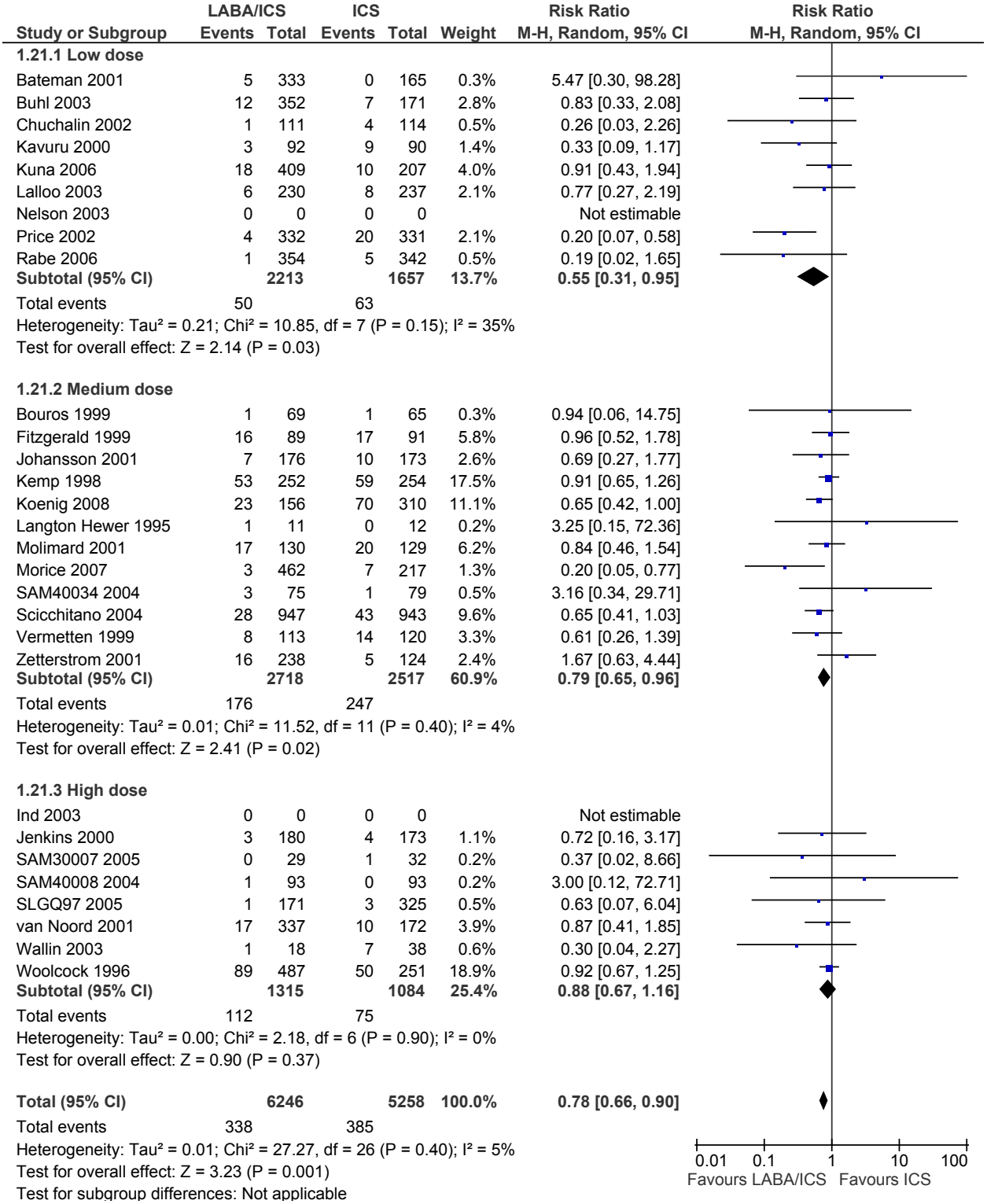


Figure 83: The effect of LABA/ICS versus ICS monotherapy on fatal SAEs

Study or Subgroup	LABA/ICS Events	LABA/ICS Total	ICS Events	ICS Total	Weight	Risk Difference M-H, Random, 95% CI
1.19.1 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]
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]**
Total events	0		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 9 (P = 1.00); I² = 0%						
Test for overall effect: Z = 1.03 (P = 0.30)						
1.19.2 Medium dose						
Busse 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]
SAM40034 2004	0	75	0	79	0.6%	0.00 [-0.03, 0.03]
SAM40065 2007	0	150	0	299	3.3%	0.00 [-0.01, 0.01]
SAM40090 2005	0	242	0	241	5.3%	0.00 [-0.01, 0.01]
SAM40120 2005	0	8	0	10	0.0%	0.00 [-0.19, 0.19]
SAS30002 2008	0	148	0	152	2.1%	0.00 [-0.01, 0.01]
SAS30039 2005	0	182	0	180	3.0%	0.00 [-0.01, 0.01]
SAS40026 2006	0	321	0	315	9.2%	0.00 [-0.01, 0.01]
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]**
Total events	0		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 10 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
1.19.3 High dose						
Aubier 1999	1	338	0	165	2.9%	0.00 [-0.01, 0.01]
Nielsen 1999	0	0	0	0		Not estimable
SAM30007 2005	0	29	0	32	0.1%	0.00 [-0.06, 0.06]
SAM40008 2004	0	93	0	93	0.8%	0.00 [-0.02, 0.02]
SLGQ97 2005	1	171	0	325	1.6%	0.01 [-0.01, 0.02]
van Noord 2001	1	337	0	172	3.0%	0.00 [-0.01, 0.01]
Subtotal (95% CI)		**968**		**787**	**8.5%**	**0.00 [-0.00, 0.01]**
Total events	3		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 4 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.98 (P = 0.33)						
Total (95% CI)		**5333**		**5288**	**100.0%**	**-0.00 [-0.00, 0.00]**
Total events	3		4			
Heterogeneity: Tau² = 0.00; Chi² = 3.15, df = 25 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
Test for subgroup differences: Not applicable						

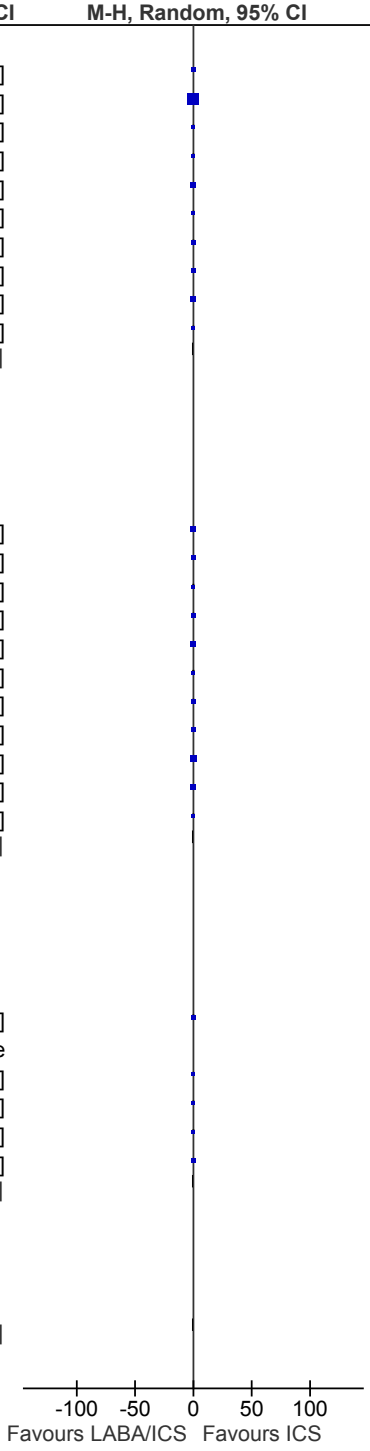


Figure 84: The effect of LABA/ICS versus ICS monotherapy on all-cause mortality

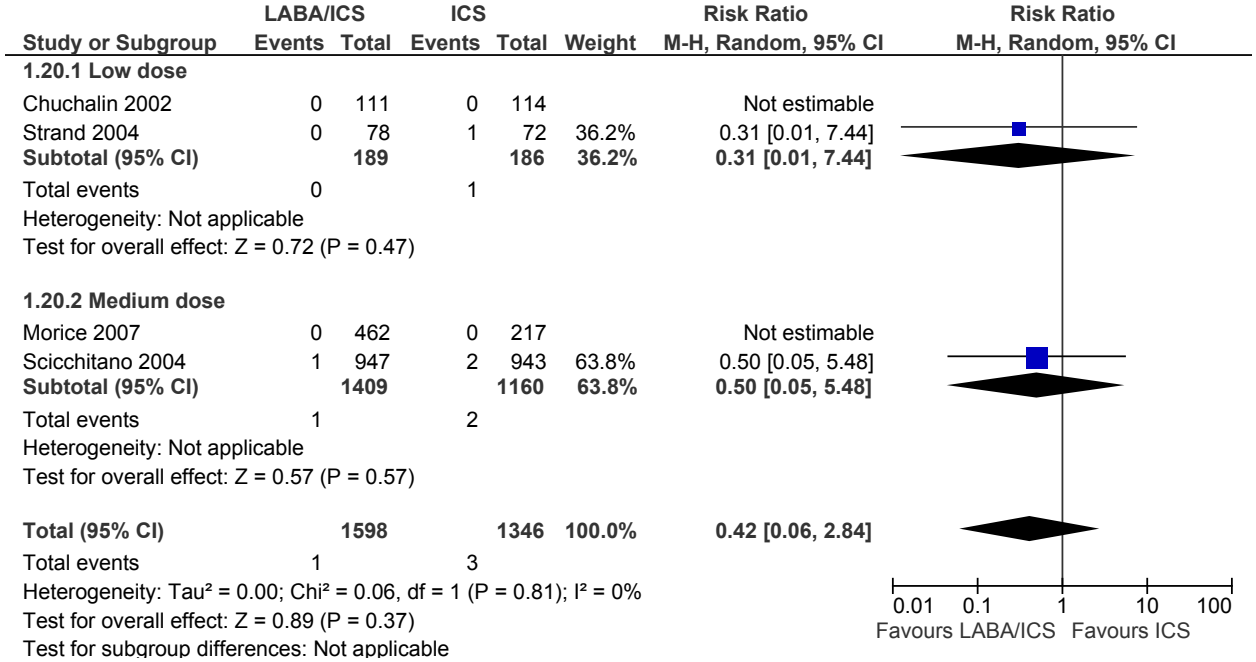
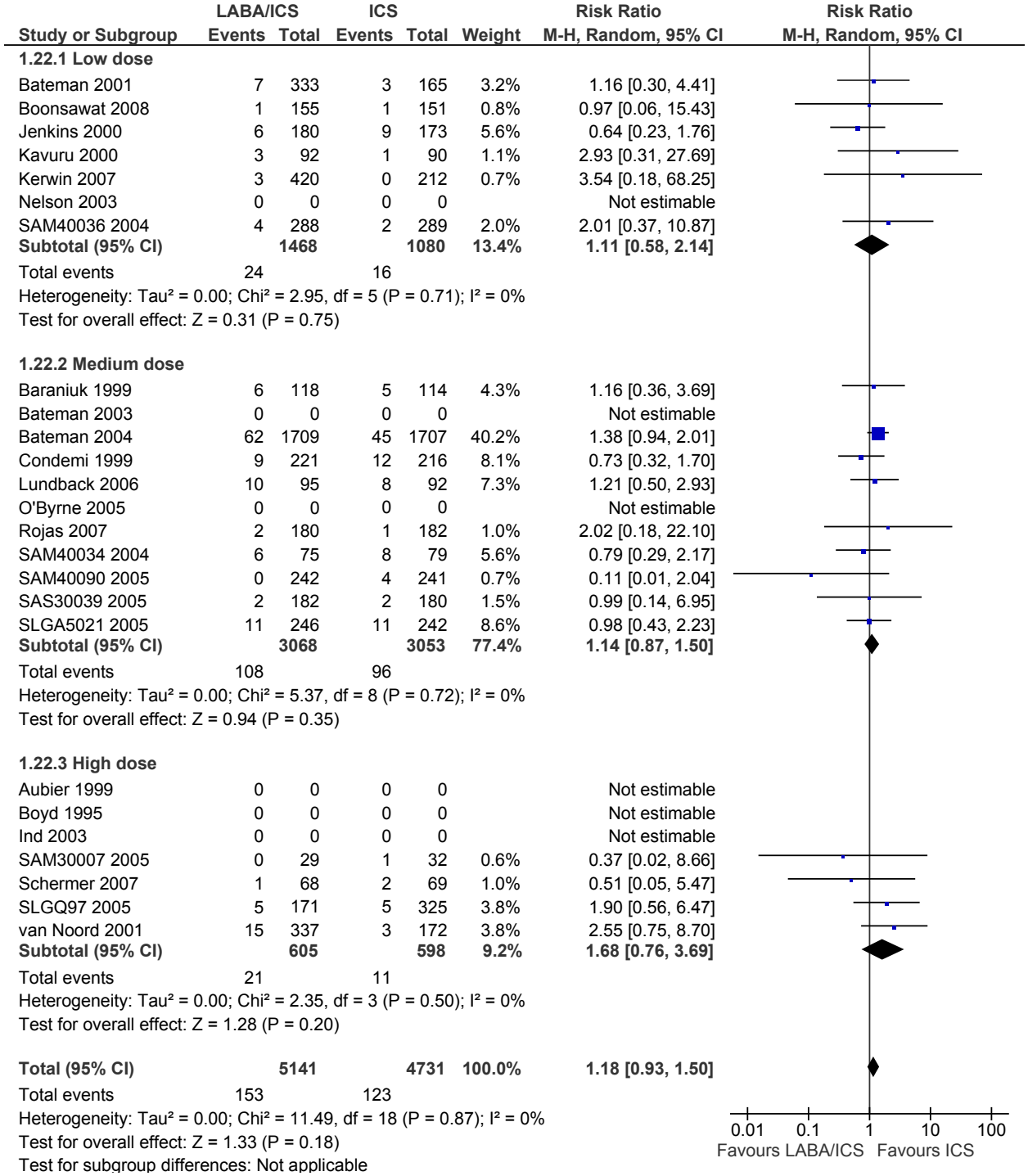


Figure 85: The effect of LABA/ICS versus ICS monotherapy on hoarseness



APPENDIX 8: APPRAISAL OF CANADIAN, NORTH AMERICAN, AND INTERNATIONAL CLINICAL PRACTICE GUIDELINES FOR THE USE OF LONG-ACTING BETA$_2$-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.[193,193] The AGREE Instrument has been used to compare the quality of corresponding clinical practice guidelines,[194,194] to identify predictors of high quality for clinical practice guidelines,[195,195] and to evaluate existing guidelines and make recommendations for the development of new guidelines.[196]

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™ 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™ 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.[193,193]

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™ 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™ table (Microsoft Corp. 2003) for analysis. Standardized domain scores were calculated for each guideline as described in the AGREE manual.[193] 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**.**

Figure 1: Domain scores for CACG, GINA and NAEPP guidelines

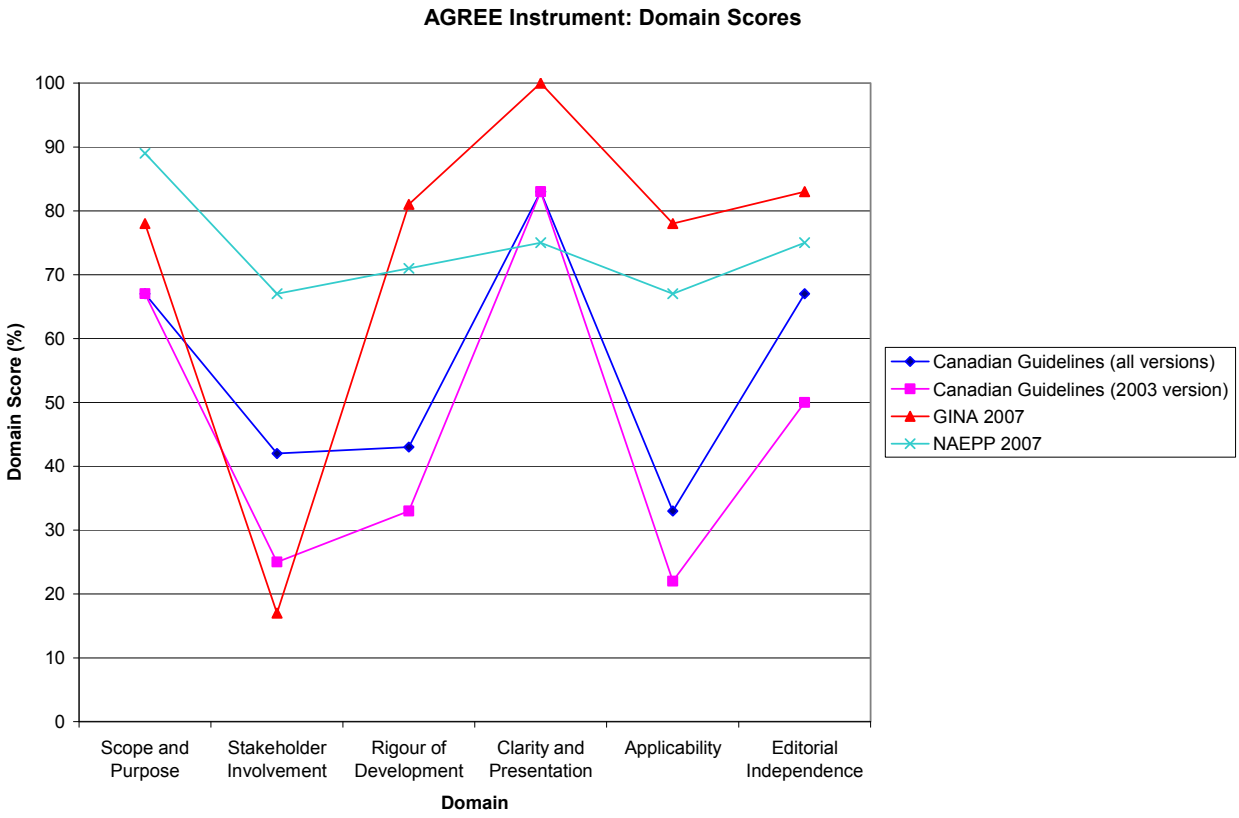


Table 1: AGREE instrument appraisal scores				
Domain and Item	**CACG (all)**	**CACG (2003)**	**GINA (2007)**	**NAEPP (2007)**
	Total %	**Total %**	**Total %**	**Total %**
Scope and Purpose				
1. The overall objective(s) of the guideline is (are) specifically described	**75**	**75**	**100**	**100**
2. The clinical question(s) covered by the guideline is (are) specifically described	**75**	**75**	**50%**	**75**
3. The patients to whom the guideline is meant to apply are specifically described	**75**	**75**	**100**	**100**
Domain Score	**67**	**67**	**78**	**89**
Stakeholder Involvement				
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	**42**	**25**	**17**	**67**
Rigour of Development				
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	**43**	**33**	**81**	**71**
Clarity and Presentation				
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	**83**	**83**	**100**	**75**
Applicability				
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	**33**	**22**	**78**	**67**
Editorial Independence				
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 these guidelines for use in practice?				
Recommendation	**Number of Experts**	**Number of Experts**	**Number of Experts**	**Number of Experts**
Strongly recommend:				**1**
Recommend	**1**	**1**	**1**	
Overall Recommendations:				
CACG (all)	**Recommend – stakeholder involvement, applicability, & rigour of development low**			
GINA (2007)	**Recommend - stakeholder involvement low**			
NAEPP (2007)	**Strongly Recommend**			

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.[194,194] 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.[193] 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,[4,9] and that the addition of LABAs can have a corticosteroid-sparing effect. [4]
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, [197,197] 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. [8,9,9] 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: Detailed AGREE assessment								
AGREE Instrument[193]	Canadian Asthma Consensus Guidelines [4,197-200](all versions)		Canadian Asthma Consensus Guidelines [4] (2003 version)		GINA Guidelines[8] 2007		NAEPP Guidelines[9] 2007	
	Score	Comments	Score	Comments	Score	Comments	Score	Comments
Scope and Purpose								
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 explicit.	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	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	Related to adults with mild asthma. (10A,12A) Not very specific.	4	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	4	Sections 4-5 Children 0-4 yrs; children 5-11 yrs; youths ≥12 years and adults. Categorized as intermittent or persistent asthma.
Domain Score	67%		67%		78%		89%	
Stakeholder Involvement								
4. Guideline Development Group	3	Physicians only.	3	Author list does not include group affiliation. Relevant professions inferred from author list.	2	Diversity of countries represented (50 countries), but no diversity professional groups represented. (i)	4	Wide range of involvement (physicians, researchers, nurses, consumers [representative from Mothers of Asthmatics], public health officials, etc. (xi)
5. Patients' Views	1	No indication patients' views canvassed.	1	No statement re: patient views being consulted. Patient preference allowed in treatment (recommendation 7)(12A)	1	No comments re: patient views/preferences	3	p.xi – Draft posted online for public review and comments before guidelines finalized and released → not clear that patients were the ones who responded. (xi) Some input from stakeholders.

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, 3rd-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%		17%		67%	
Rigour of Development								
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	p.7-8 – Evidence ranked to justify recommendations being made. Also specified strength of recommendations. (7-8) Findings discussed in small groups. Larger meetings to discuss findings, voting for consensus on final decision. No thresholds described for voting process.
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 2nd 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	1	Recommendations for future research questions (12A) Guidelines are updated, but no specifics on update process.	1	Process/timeline not clearly stated. No description.	4	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.
Domain Score	43%		33%		81%		71%	

Clarity and Presentation								
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	p.230 – Expert Panel conclusions – bold text, separate page. (230) Key Points: Safety of LABA – boxed and bulleted. (231) Size of document with recommendations buried in text makes them hard to locate. Could summarize all in one location.

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.	1	No description of tools to support application.
Domain Score	83%		83%		100%		75%	
Applicability								
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)	1	No mention in text.	4	Guideline Implementation Strategies, e.g. goal setting, strategies for asthma care, collaborations among professional groups. (88) Strategy for low-income countries. Multiple formats to disseminate in multiple venues. Designed for broad application.	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%		67%	
Editorial Independence								
22. Independence	3	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%		67%		83%		75%	
Further Comments	• Assessment complicated by number of documents to review (4 main docs, 2 summary docs) • No single document with all recommendations – all refer back to earlier versions of guidelines for certain topics. • Another guideline in 1995 is available but not used. • 2003 update the only guideline developed after the AGREE tool implemented. • Search strategy documentation very poorly described. • Search strategy and summary of supporting results poorly described. • Only 2003 update was developed after AGREE tool published. • No mention of specific measures of effect? • Recommendations not specifically linked to patient group or references. • No specific statement of expected impact or measures of effect. • Key search strategy, selection & summary poorly described.		• Methods should be recorded more rigorously. • Unsure about quality of recommendations (due to lace of methods). • Overall appears to be practical and accurate guideline but are not structured or reported according to AGREE guidelines therefore does not score well on all components of the tool.		• So much information, but the guideline states that it is meant to be complete source of information, e.g. p.2		• No meta-analytic statement of results – reports on single studies' results. • Best overall guideline of the 3 reviewed – greatest detail on most elements. Only drawback was lack of specificity on evidence – reference to trials. • Length of document a definite drawback. Why not put all recommendations at the end or beginning?	

Table 2: Levels of evidence defined by the guidelines	
Canadian Asthma Consensus Guidelines (all versions)	GINA Guidelines 2007 and NAEPP Guidelines 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. 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.	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 Panel Consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.

Table 3: Guideline 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	• (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) • (NR) Fig.1 Continuum of asthma management (11A; Can 2003 Update) • (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) • (NR) The addition of a LABA to low-dose ICS therapy was superior to moderate-dose ICS use alone (13A; Can 2003 Update) • (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	• (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_2–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) • (Category A) Fig. 4.3-2 …at 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) • (Category A) Fig. 4.3-2 …at Step 4 the preferred treatment is to combine a med/high dose of ICS with a LABA. However in most patients, the	• (Category A) LABAs are not to be used as monotherapy for long-term control of asthma. (213) • (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) • (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) • (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

	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)	increase from medium to high-dose ICS provides relatively little additional benefit. (60) • (NR) [Formoterol] has been shown to be as effective as SABA in acute asthma exacerbations. (60) • (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)	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	• (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) • (NR) No comparison between the two types of combination devices.	• (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) • (Category A) Combination inhalers containing formoterol and budesonide may be used for both rescue and maintenance. (31, 60) • (NR) No statement comparing the two types of combination therapy.	• (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)
4A. Differences in safety between combination ICS/LABA and ICS monotherapy in treatment naïve adults	NR	NR	NR

4B. Differences in safety between combination ICS/LABA and ICS monotherapy in adults stabilized on ICS	1 (NR) "Neither salmeterol nor formoterol has been shown to have major adverse effects in patients with asthma when used in conjunction with ICSs." (17A; Can 2001 Update)	• (NR) Fewer systemic adverse effects, e.g. cardiovascular stimulation, skeletal muscle tremor, and hypokalemia, for therapy with inhaled LABA vs. oral therapy. (31) • (NR) Possible increased risk of asthma-related death associated with salmeterol use in small group of individuals. US FDA and Health Canada advisories that LABAs are not a substitute for ICS or OCS, and should be used in combination with appropriate clinically determined dose of ICS. (31) • (NR) Conflicting results regarding effects of regular use of salmeterol with/without use of ICSs on deterioration of asthma in individuals with unusual genotype for beta-adrenergic receptor. (31)	• (NR) Multiple studies have shown that individuals homozygous for Arg/Arg at position 16 of the protein have about a 3% reduction in peak flow when compared to Gly/Gly homozygotes. Studies of the influence of the homozygous Arg-16 genetic variant on response to LABA are inconclusive. (66) • (Category A) To reduce the potential for adverse effects, consider adding a LABA to a low or medium dose of ICS rather than using a higher dose of ICS to achieve or maintain control of asthma. (220) • (NR) The established, beneficial effects of LABA for the great majority of patients whose asthma is not well controlled with ICS alone should be weighed against the increased risk for severe 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)

LoE: level of evidence; **LABA**: long-acting beta$_2$-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.[148] 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 dosing of formoterol and ICS

Study	Price (2007)	Price (2004)	Bruggenjurgen (2005)
Country	Australia, UK	UK	Germany
Patient Population	Patients > 12 years of age with asthma for > 6 months on ICS for > 3 months with > 1month of 1000mcg/day	Patients >18 years of age with persistent asthma receiving 400-2000 mcg/day ICS.	Mild to moderate perennial asthma symptomatic on ICS.
Comparators	BUD/FORM 160/4.5 mcg 1 inhalation BID plus additional doses as needed (variable dose) (n=1107) BUD/FORM 160/4.5 mcg 1 inhalation BID plus rescue terbutaline (fixed dose) (n=1105) SALM/FP 25/125 mcg 2 inhalations BID plus rescue terbutaline (n=1123)	Four week run-in on either BUD/FORM 80/4.5 mcg or 160/4.5 mcg, two inhalations BID. Then randomized to: Same fixed dose of BUD/FORM (n=771) Self-adjustable maintenance dosing plan (n=782)	Fixed dose BUD/FORM 160/4.5 mcg 2 inhalations BID via single Turbuhaler Adjustable maintenance dosing BUD/FORM 160/4.5 mcg 1 inhalation BID (can increase to 2 or 4 inhalations BID)
Form of analysis	Cost effectiveness analysis	Cost minimization analysis	Cost minimization analysis
Resources included	Asthma medications and healthcare resources and productivity losses due to days off work.	Asthma medications and healthcare resources.	Asthma medications, healthcare resources and productivity losses due to days off work
Perspective	Healthcare system and societal	Healthcare system	Health insurance and societal
Study design	Randomised, double-blind, multicentre, parallel group study.	Pragmatic, randomized, open label, parallel-group, multicentre study	Randomised, open-label, parallel group study
Time horizon	6 months	12 weeks	12 weeks
Study results	Variable dose BUD/FORM resulted in a statistically significant reduction in severe exacerbations relative to both the fixed dose BUD/FORM and the SALM/FP groups. Direct and total costs were also lower in the variable dose BUD/FORM group compared with the fixed dose BUD/FORM group and the SALM/FP groups over the 6 month period from both the Australian and UK perspective.	There was no statistically significant difference between the two treatments with respect to improvement in QOL as measured by the AQLQ, although improvement was greater in the fixed dose group. The total per patient daily cost was £1.13 (95% CI £1.08-£1.18) in the adjusted dose group and £1.31 (95%CI £1.27-£1.34) in the fixed dose group.	There was no statistically significant difference between the two treatments with respect to improvement in QOL as measured by the AQLQ, although improvement was greater in the fixed dose group. Costs were lower in the adjustable dosing group with a mean cost per patient over 12 weeks of Euro 277 as compared with Euro 340 in the fixed dose group.
Comments	Lost productivity was measured by human capital approach which overestimates impact to society. Economic analysis using outcomes such as severe exacerbations rather than QALYs prevents comparisons with other therapeutic areas and does not facilitate decisions. Although the variable dose BUD/FORM arm had statistically fewer exacerbations than the other two groups the three treatments did not differ significantly with regards to other endpoints.	Although the adjustable dosing group appeared more cost effective, the teaching costs associated with this self management approach were not included in the analysis. The choice of cost minimization analysis is inappropriate as results suggest that the fixed dose may be more beneficial in terms of quality of life.	Lost productivity was measured by human capital approach which overestimates impact to society. The choice of cost minimization analysis is inappropriate as results suggest that the fixed dose may be more beneficial in terms of quality of life.
Study Quality	8 out of 10 items	7 out of 10 items	6 out of 10 items
Study Sponsorship	Astra Zeneca	Astra Zeneca	Astra Zeneca

Table 2: Head-to-head comparisons of salmeterol and ICS versus formoterol and ICS in asthma			
Study	Rutten-van Molken (1998)	Johansson (2006)	Miller (2007)
Country	Italy, Spain, France, Switzerland, Sweden and UK	Italy, France, UK and Germany	Canada
Patient Population	Patients ≥18 years of age with persistent asthma receiving ICS ≥400 mcg/day BDP or equivalent	Patients ≥ 12 years of age with persistent asthma receiving at least 1000 mcg/day BDP or equivalent.	Patients ≥ 12 years of age with moderate to severe asthma receiving 40 to 3000 mcg/day ICS.
Comparators	Formoterol 12 mcg dry powder capsules (Novartis) bid (n=241) Vs Salmeterol 50 mcg Diskhaler bid (n=241)	BUD/FORM 160/4.5 mcg 2 inhalations BID + prn (n=1067) SALM/FP 50/250 mcg 1 inhalation BID + rescue salbutamol prn (n=1076) -titrated up or down based on response	BUD/FORM 160/4.5 mcg 2 inhalations BID + additional inhalations prn (n=1067) SALM/FP 50/250 1 inhalation BID + rescue salbutamol prn (n=1076) - titrated up or down based on response
Form of analysis	Cost effectiveness analysis – cost per episode free day and clinically relevant improvement in QOL.	Cost effectiveness analysis – cost per severe exacerbation avoided	Cost effectiveness analysis – cost per severe exacerbation avoided
Resources included	Asthma medications, healthcare resources, travel expenses and productivity losses.	Asthma medications, healthcare resources and productivity losses.	Asthma medications, healthcare resources and productivity losses.
Perspective	Societal perspective	Healthcare system and societal perspective	Healthcare system and societal perspective
Study design	Open label, multicentre, randomized parallel clinical trial	Randomised, open, clinical trial	Randomised, open, clinical trial – same as Johansson
Time horizon	6 months	12 months	12 months
Study results	The average cost effectiveness ratio was US$11 per episode free day with formoterol and US$12 per episode free day with salmeterol. With respect to the cost per clinically relevant improvement in QOL it was US$1600 with formoterol and US$1825 with salmeterol.	The mean number of severe exacerbations per patient per year was 0.31 with SALM/FP and 0.24 with BUD/FORM. BUD/FORM was dominant in all countries from the societal perspective and in the UK and Germany from the healthcare system perspective. The ICER was €100 in Italy and €267 in France from the healthcare perspective.	The mean number of severe exacerbations per patient per year was 0.31 with SALM/FP and 0.24 with BUD/FORM. BUD/FORM was dominant from both a societal and healthcare perspective.
Comments	Country specific unit costs were applied to resource use but results are a synthesis presented in US dollars, therefore making it difficult to make overall conclusions. Formoterol inhaler used in this study was a dry powder capsule which is not comparable to the most commonly used delivery device. Results reported average cost effectiveness ratios which are meaningless for decision making. 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.	Lost productivity was measured by human capital approach which overestimates impact to society. Economic analysis using outcomes such as severe exacerbations rather than QALYs prevents comparisons with other therapeutic areas and does not facilitate decisions. The definition of severe exacerbations is a composite outcome including unscheduled visits required for dose changes. As all dose changes with salmeterol require physician visits, this may be biased.	Lost productivity was measured by human capital approach which overestimates impact to society. Economic analysis using outcomes such as severe exacerbations rather than QALYs prevents comparisons with other therapeutic areas and does not facilitate decisions.
Study Quality	6 out of 10 items	8 out of 10 items	9 out of 10 items
Study Sponsorship	Novartis	Astra Zeneca	Astra Zeneca

Table 2: Head-to-head comparisons of salmeterol and ICS versus formoterol and ICS in asthma (continued)		
Study	Miller (2008)	Ringdal (2002)
Country	Canada	Norway
Patient Population	Patients ≥ 12 years of age with asthma receiving ≥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[158,159,165] which are reviewed in detail in Appendix 5.1. In two of the studies[158,159] 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 or a fixed dose of salmeterol and ICS.

Two of the studies[158,159] 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[159].

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[130,160-163] 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[160]. 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[161-163]. The fourth study compared a fixed dosing schedule for both combinations[130]. Two studies derived efficacy data from randomized open trials[161,162] and two studies derived data from randomized controlled trials[130,163]. The studies ranged in duration from 12 weeks[130] to 6 months[162] to 12 months[161,163]. Studies were conducted from the perspective of Canada[162,163], Norway[130], and from multiple European countries[160,161]. All analyses were cost effectiveness analyses and all were from the healthcare system perspective with all but one[130] also including analysis from the societal perspective.

Two studies used efficacy data from the same clinical trial[161,162] 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 [130]. 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: 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	1 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	1 year	Healthcare system

Table 2: Comparison of addition of LABA to ICS versus ICS in patients with mild to moderate asthma			
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: ≤ 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 analysis	Cost effectiveness analysis – cost per symptom free day	Cost effectiveness analysis – cost per symptom free day	Cost utility analysis
Resources included	Asthma medications and healthcare resources and productivity losses due to days off work	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	1 year	1 year	1 year
Study results	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.	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.	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 asthmatics			
7 STUDY	**8 COMPARATORS**	**9 TIME HORIZON**	**10 PERSPECTIVE**
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 Population	Moderate to severe asthmatics, >12 years of age symptomatic on 800-1200 mcg/day BDP or 400-800 mcg/day FP.	Adult and adolescent asthmatics receiving 2000 mcg/day BDP or equivalent	Adult and adolescent asthmatics receiving 462 to 672 mcg/day BDP or equivalent
Comparators	SALM/FP 50/250 BID via Diskus or Accuhaler (n=180) BUD 800 mcg BID via Turbuhaler (n=173)	SALM/FP 50/500 mcg BID via Diskus (n=167) FP 500 mcg BID via Diskus (n=165)	SALM/FP 50/250 mcg BID via Diskus (n=81) FP 250 mcg BID via Diskus (n=81)
Form of analysis	Cost effectiveness analysis – cost per successfully treated week, episode free day and symptom free day	Cost effectiveness analysis - cost per successfully treated week, episode free day and symptom free day	Cost effectiveness analysis – cost per successfully treated week, episode free day and symptom free day
Resources included	Asthma medications and healthcare resources.	Asthma medication and healthcare resources	Asthma medications and healthcare 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 costly. The ICER was US$3.9 for an additional successfully treated week, US$0.93 for an additional episode free day and US$1.12/day for an additional symptom free day.	SALM/FP was significantly more effective and more costly. The ICER for successfully treated week was US$23.31 for the combination vs FP and US$8.10 per symptom-free day and US$14.56 per episode-free day.	SALM/FP was significantly more effective and more costly. The ICER for SALM/FP vs FP was US$1.52 per successfully treated week, US$0.47 per episode-free day and US$0.47 per symptom-free day.
Comments	The reporting of the ICER using outcomes such as SFDs rather than QALYs prevents comparisons with other therapeutic areas and does not facilitate decisions.	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 outcomes such as SFDs rather than QALYs prevents comparisons with other therapeutic areas and does not facilitate decisions.	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 outcomes such as SFDs rather than QALYs prevents comparisons with other therapeutic areas and does not facilitate decisions.
Study Quality	9 out of 10 items	8 out of 10 items	8 out of 10 items
Study Sponsorship	Glaxo Smith Kline	Glaxo Smith Kline	Glaxo Smith Kline

Table 4: Comparison 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

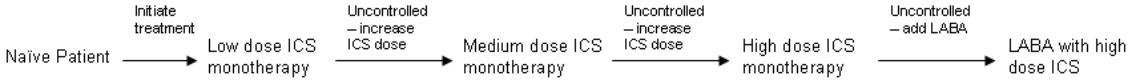
APPENDIX 13: METHODOLOGICAL QUALITY OF ECONOMIC STUDIES REVIEWED IN MAIN REPORT

Table 1: Quality Assessment of Economic Evaluations

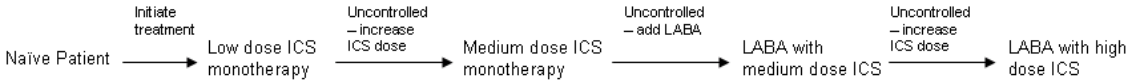
	Jonsson 2004	Andersson 2001	Briggs 2006	Johansson 1999	Price 2002	Shih 2007	Lundbäck 2000	Pieters 1999	Palmqvist 1999	Ericsson 2006	Price 2007	Price 2004	Bruggenjurgen 2005	Rutten-van Molken 1998	Johansson 2006	Miller 2007	Miller 2008	Ringdal 2002
Q1	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Q2	Y	Y	Y	Y	Y	N	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

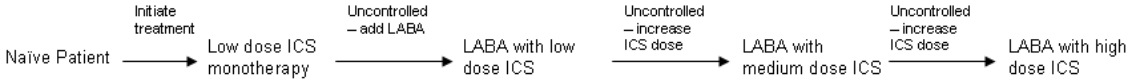
Figure 1: Treatment strategies



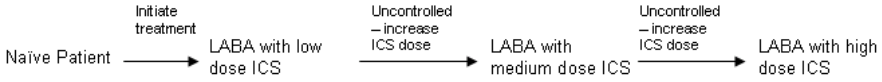
a. Introduce LABA after uncontrolled on high dose ICS monotherapy



b. Introduce LABA after uncontrolled on medium dose ICS monotherapy



c. Introduce LABA after uncontrolled on low dose ICS monotherapy



d. Introduce LABA to ICS naïve patients

Table 1: Definition of low, moderate, and high dose ICS			
ICS Therapy	**Low**	**Medium**	**High**
BUD Turbuhaler	≤ 400 mcg/day	400-800 mcg/day	> 800 mcg/day
FP MDI	≤ 250 mcg/day	251-500 mcg/day	> 500 mcg/day
FP Diskus	≤ 250 mcg/day	251-500 mcg/day	> 500 mcg/day
BDP	≤ 500 mcg/day	501-1000 mcg/day	> 1000 mcg/day

Source: Lemiere et al. 2004[4]

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: Parameter values for relative 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
Weekly Rate of Exacerbation			
Naïve Patients			
Low dose ICS vs LABA+low dose ICS	0.800	0.577	Lognormal
Uncontrolled on low dose ICS			
Medium dose ICS vs LABA+low dose ICS	0.825	0.245	Lognormal
Uncontrolled on medium dose ICS			
High dose ICS vs LABA+medium dose ICS	0.705	0.848	Lognormal
Uncontrolled on high dose ICS			
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 [#]
Non medical	0.57	0.078	Lognormal [#]
GP	0.57	0.078	Lognormal [#]
ER	0.57	0.078	Lognormal [#]
Inpatient	0.33	0.014	Lognormal [#]

[#] Distribution represents uncertainty around the disutility associated with health states

Table 5: Calculation 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)		
Scenario	Strategy B vs Strategy A	Strategy C vs Strategy B	Strategy D vs 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 Briggs)	$213,467	$1,792,988	$3,631,911
Lowest relative risk for withdrawals with LABA	$188,500	$1,610,466	$2,841,837
Highest relative risk for withdrawals with LABA	$208,834	$1,704,341	$7,892,327
Lowest relative risk for exacerbations with LABA	$159,095	$811,005	$981,913
Highest relative risk for exacerbations with LABA	Strategy A dominant	Strategy B dominant	Strategy C 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 (72.67, 78.18)	0.179819 (0.176, 0.184)	
Strategy B	74.93 (72.69, 78.20)	0.179819 (0.176, 0.184)	$577,812.43[1]
Strategy C	78.86 (75.48, 83.11)	0.179821 (0.176, 0.184)	$1,929,583.70[2]
Strategy D	183.93 (180.30,190.78)	0.179829 (0.176, 0.184)	$12,570,692.83[3]
One year			
Strategy A	353.54 (335.84,375.39)	0.778954 (0.762,0.795)	
Strategy B	355.11 (336.87,377.64)	0.778956 (0.762,0.795)	$637,687.25[1]
Strategy C	426.67 (381.67,481.71)	0.778988 (0.762,0.795)	$2,236,925.59[2]
Strategy D	$849.59 (806.02,918.33)	0.7789541 (0.762,0.795)	Dominated by Strategy C

Figures in parenthesis are 95% certainty intervals
[1] versus Strategy A, [2] versus Strategy B, [3] 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 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	$9,486,533	$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 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	$9,476,653	$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 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	$9,466,773	$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