CoLab Network

Health Technology Review

Efficacy and Safety of Long-Term Use of Omalizumab for the Treatment of Chronic Idiopathic Urticaria

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Key Messages

Omalizumab is accepted to treat moderate to severe chronic idiopathic urticaria for up to 24 weeks in most Canadian jurisdictions. However, some patients may require longer treatment or still experience symptoms despite optimal care.

We reviewed the current evidence on the potential benefits and harms of using omalizumab for 24 weeks or longer to treat patients with chronic idiopathic urticaria. Our review included 2 randomized controlled trials and 4 comparative cohort observational studies. We also included 4 single-group, prospective observational studies to supplement the comparative evidence.

Findings suggest that subcutaneous omalizumab taken every 4 weeks continues to provide symptom relief following a standard course of treatment for 24 weeks when compared to placebo. Two randomized controlled trials found clinically meaningful reductions in symptoms and improvement in quality of life with extended treatment. However, results should be considered with caution because of the high risk of bias in the 2 trials.

Findings suggest that extended use of omalizumab does not increase the risk of severe adverse events compared to placebo, hydroxychloroquine, or cyclosporine. Two randomized controlled trials at high risk of bias and 1 comparative cohort study at serious risk of bias reported these results. When omalizumab was compared to placebo, the randomized controlled trials found no increases in withdrawals due to adverse events.

The observational studies did not adjust for underlying factors, which may affect treatment outcomes. Therefore, these results may be confounded and should be interpreted with caution.

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Abbreviations

AE	adverse event
CI	confidence interval
CIU	chronic idiopathic urticaria
CU-Q2oL	Chronic Urticaria Quality of Life questionnaire
DLQI	Dermatology Life Quality Index
HCQ	hydroxychloroquine
HRQoL	health-related quality of life
IgE	immunoglobulin E
IRR	incidence rate ratio
ISS7	7-Day Itch Severity Score
JBI	Joanna Briggs Institute
MCID	minimal clinically important difference
MD	mean difference
NA	not applicable
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols
RCT	randomized controlled trial
RoB	risk of bias
ROBINS-I	Risk Of Bias in Non-Randomised Studies of Interventions
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SMD	standardized mean difference
UAS7	7-Day Urticaria Activity Score
UCT	Urticaria Control Test
WISS	Weekly Itch Severity Score

Introduction and Rationale

Background

Chronic idiopathic urticaria (CIU), also known as chronic spontaneous urticaria (CSU), is characterized by the presence of itchy hives persisting for at least 6 weeks, often with angioedema, and no identifiable external trigger.[1] This condition typically endures for 1 to 5 years, affecting more women than men and substantially impairing the emotional and physical health-related quality of life (HRQoL) of patients.[2] The financial impact of CIU on both patients and the health care system is significant, with patients in Canada living with the condition for more than 6 months incurring out-of-pocket expenses averaging nearly $1,000 annually.[3]

Traditionally, nonsedating H_1 antihistamines have been the cornerstone of initial CIU treatment.[4] Following clinical practice guidelines jointly issued by prominent organizations, clinicians in Canada typically updose the second-generation H_1 antihistamines to the maximum tolerated level, often exceeding the indicated dose by up to 4 times before considering additional treatments for inadequately controlled symptoms.[5] Unfortunately, many patients do not experience a response to H_1 antihistamines, even when administered at 3 to 4 times the approved dose.[6]

Omalizumab (Xolair) is a humanized monoclonal antibody that binds to immunoglobulin E (IgE), preventing its interaction with its high-affinity receptor on mast cells and basophils. This action reduces IgE-induced mast cell and basophil degranulation and histamine and other mediator release.[7,8]

Policy Issue

In 2015, the Canadian Drug Expert Committee recommended omalizumab for the treatment of adults and adolescents with moderate to severe CIU who remain symptomatic (experience hives and/or associated itching) despite optimal treatment with available oral therapies such as second-generation antihistamines.[9] Omalizumab was approved by Health Canada in 2004 for use in individuals with asthma, and in 2014 for those with CIU.[10] However, the evidence on the efficacy and safety of omalizumab for patients with CIU requiring re-treatment or use beyond 24 weeks is lacking.

While several systematic reviews have focused on omalizumab's efficacy for treating CIU, none have investigated its long-term (> 24 weeks) effectiveness and safety. Most of these reviews did not involve quantitative meta-analyses and relied solely on patient-reported outcomes.[11-14] Furthermore, many of these reviews limited their scope to randomized controlled trials (RCTs),[11,14-18] potentially overlooking evidence from relevant observational studies.[19,20] Some of these reviews were also sponsored by pharmaceutical companies, including the manufacturer of omalizumab,[11,13,15] introducing concerns about conflicts of interest potentially biasing reported findings. Table 1 outlines the approved indication for omalizumab in Canada. Current guidelines endorsed by the Canadian Society of Allergy and Clinical Immunology recommend that omalizumab be administered to patients at a dose of 300 mg every 4 weeks and, if necessary, to a maximum of 600 mg every 2 weeks.[8]

Key Take-Away

Nonsedating H_1 antihistamines are the first line of treatment for patients with CIU. However, some patients do not experience a response with them, even at higher doses. In such cases, omalizumab can be used. It is recommended for patients with moderate to severe CIU who remain symptomatic despite optimum management with available oral therapies.

Table 1: Product Description

Approved use	Presentation	Administration
Treatment of adults and adolescents (aged 12 years and older) with chronic idiopathic urticaria who remain symptomatic despite H_1 antihistamine treatment[a]	Prefilled syringe (75 mg or 150 mg)	150 mg or 300 mg administered subcutaneously every 4 weeks to the front and middle of thigh and/or the stomach area (self-administration) or upper arm (provider or caregiver only)

[a]Omalizumab is also approved for use in individuals with allergic asthma and chronic rhinosinusitis with nasal polyposis.

Source: Product monograph for Xolair (April 23, 2023).

Policy Question

1. Is long-term (≥ 24 weeks) treatment with omalizumab effective, and if so, for which patients?

Purpose

The purpose of this assessment was to evaluate the effectiveness and safety of omalizumab at or longer than 24 weeks in individuals with CIU using patient-reported and clinical outcomes, and to identify the characteristics of patients who use omalizumab for 24 weeks and beyond.

Research Questions

This health technology assessment addresses the policy question by exploring the following research questions:

1. What is the effectiveness of long-term use of omalizumab (i.e., ≥ 24 weeks)?
   a) What is the effectiveness of updosing (i.e., up to 600 mg every 4 weeks)?
   b) What is the effectiveness of reducing dosing intervals (i.e., from 4 weeks to 2 weeks)?
2. What is the safety of long-term use of omalizumab (i.e., ≥ 24 weeks)?
   a) What is the safety of updosing (i.e., up to 600 mg every 4 weeks)?
   b) What is the safety of reducing dosing intervals (i.e., from 4 weeks to 2 weeks)?

3. What are treatment-informing characteristics of patients who use omalizumab for 24 weeks or longer?

Key Take-Away

There were 2 objectives for this systematic review: to determine the efficacy and effectiveness of long-term use of omalizumab in patients with CIU, and to establish whether extended use is safe for patients.

Opportunities for Stakeholder Feedback

Stakeholders were given the opportunity to comment on the proposed project protocol that informed this report and were invited to provide feedback on the draft report.

Protocol Development

The protocol and review followed the methods of the Cochrane Handbook for Systematic Reviews for Interventions[21] and the PRISMA checklist for systematic reviews.[22] The protocol for this systematic review was written a priori, followed throughout the review process, and registered in advance through the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42023397714). Deviations from the planned protocol included consideration of data from single-group prospective studies or trials to inform the research and policy questions. One study not originally published in English was translated and included, and another could not be translated within the timeline of the current review.

Clinical Review

The research questions were addressed using a systematic review.

Literature Search Methods

An information specialist developed and conducted a literature search for clinical studies, using a peer-reviewed search strategy according to the Peer Review of Electronic Search Strategies (PRESS) checklist.[23] The complete search strategy is presented in Appendix 1.

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid, Embase via Ovid, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. The Ovid searches were run using the multifile option and deduplicated using the tool available on the Ovid platform.

The search strategy used a combination of controlled vocabulary (e.g., "omalizumab," "ephedrine," "chronic urticaria") and keywords (e.g., "xolair," "neo fedrin," "idiopathic urticaria"). Vocabulary and syntax were adjusted across the databases and, where possible, animal-only records and opinion pieces were removed. Grey literature was searched according the CADTH Grey Matters.

Limits were placed on the search for publication year (2005 to date of search). No other restrictions were used. We used EndNote version 9.3.3 (Clarivate Analytics) to download and manage records. The literature search results were uploaded to Covidence, a web-based systematic review platform (Covidence, Veritas Health Innovation). We uploaded the citations, abstracts, and full texts of the items to the Covidence database and removed duplicates.

The initial search was completed on March 28, 2023, and monthly alerts updated the database and grey literature searches until November 27, 2023.

Selection Criteria

Studies that met the population, intervention, comparators, and study design criteria were selected for inclusion. Studies were not included or excluded on the basis of reported outcomes (Table 2).[21]

Table 2: Selection Criteria

Criteria	Description
Population	Adults with moderate to severe CIU who remain symptomatic (presence of hives and/or associated itching) despite optimum management with available oral therapies
Intervention	Omalizumab ≥ 24 weeks (with or without antihistamines)
Comparators	• Omalizumab < 24 weeks (as monotherapy or in combination with an antihistamine) • Antihistamines (first or second generation) • Hydroxychloroquine • Cyclosporine • H_2 blockers (e.g., famotidine) • Leukotriene inhibitors (e.g., montelukast) • Placebo • No omalizumab
Outcomes	Efficacy and effectiveness: • Itchiness and hives using validated scales (e.g., WISS or ISS7, UAS7, WWS, UCT) • Relapse • Remission • Health-related quality of life using validated scales (e.g., DLQI, CU-Q2oL) • Number of responders • Rescue medication use Safety: • Serious adverse events • Withdrawals due to adverse events

Criteria	Description
Study designs	• Randomized controlled trials • Nonrandomized controlled trials • Quasi-experimental controlled trials • Comparative cohort studies

CIU = Chronic idiopathic urticaria; CU-Q2oL = Chronic Urticaria Quality of Life questionnaire; DLQI = Dermatology Life Quality Index; ISS7 = 7-Day Itch Severity Score; UAS7 = 7-Day Urticaria Activity Score; UCT = Urticaria Control Test; WISS = Weekly Itch Severity Score; WWS = Weekly Wheal Score.

Systematic reviews, protocols for studies in progress or without results, registered studies in progress, editorials, letters, commentaries, conference abstracts, presentations, theses, preprints, and duplicate studies were excluded. Studies not published in English were considered if they could be assessed for eligibility and translated to assess outcome data within the timeline of the review.

Population

The population of interest was adults with moderate to severe CIU who remain symptomatic (presence of hives and/or associated itching) despite optimum management with available oral therapies. For studies with mixed populations (e.g., diagnosis and age), at least 80% of the population must be eligible for the record to be included.

Intervention and Comparators

The intervention of interest was omalizumab used for 24 weeks or longer, in combination with or without antihistamines. All doses and dosing intervals were considered. Studies in which the omalizumab dose and/or duration were not given were excluded. Subgroups based on the dosing regimen were considered: 300 mg every 4 weeks, updosing strategies (i.e., 400 mg to 600 mg every 4 weeks), or changes in dosing interval (dose administered more frequently; e.g., every 2 or 3 weeks). Eligible comparators were omalizumab used for less than 24 weeks, first-generation or second-generation antihistamines, hydroxychloroquine (HCQ), cyclosporine, H_2 receptor antagonists (e.g., famotidine), leukotriene receptor agonists (e.g., montelukast) and placebo or no omalizumab.

Outcomes Definition

The efficacy or effectiveness outcomes of interest were symptom scales measuring hives and/or itchiness (e.g., WISS or ISS7, UAS7, WWS, UCT), incidence of relapse or remission of CIU, HRQoL (e.g., DLQI, CU-Q2oL), use of rescue medication, and total number of patients whose disease responds to study interventions. Nonvalidated outcome scales are considered out of scope. For the symptom scales, total scales were prioritized over subscales.

The safety outcomes were serious adverse events (SAEs) and withdrawals due to adverse events.

Outcomes were extracted at the end of treatment and the end of follow-up and for all treatment durations of interest.

Study Designs

The systematic review focused on comparative study designs including RCTs, nonrandomized controlled trials, quasi-experimental controlled trials, and comparative cohort studies. In a post hoc protocol deviation, single-group prospective studies or trials were included if they met the population and intervention criteria and reported on an outcome of interest.

Study Selection Process

Two independent reviewers applied the eligibility criteria to each title and abstract identified in the literature search. All records deemed potentially relevant by at least 1 reviewer were obtained in full-text format. The eligibility criteria were applied to the full-text records by both reviewers independently, and a final decision about eligibility was made. Conflicts were resolved by discussion. The reviewers were not blinded to study authors or the centre of publication before study selection. Study screening and assessment of eligibility were facilitated and standardized using Covidence software.

A pilot screening exercise was conducted before screening. Records were not excluded based on outcomes reported.

Quality Assessment

Risk of bias (RoB) was assessed for studies reporting outcomes of interest.

Randomized Controlled Trials

Two reviewers independently reviewed and assessed the included studies' RoB. RCTs were assessed using Cochrane's RoB 2.0 tool.[24] We assessed the following 5 domains: RoB arising from the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. A standardized form was used to complete all assessments. We evaluated the primary publication for each RCT and, when necessary, sought additional information from the protocol, study registration record, or additional study publications to confirm methods.

Observational Studies

We used the Risk of Bias in Non-Randomised Studies of Interventions (ROBINS-I) tool[25] to assess RoB in cohort studies based on consideration for 7 domains: confounding, selection bias, bias in measurement classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in outcome measurement, and bias in the selection of the reported result. ROBINS-I assesses RoB on an absolute scale for the causal inferences of any study design, where “low” RoB is comparable to a well-conducted RCT. We followed relevant guidance to assess both domain-level and study-level (overall) RoB. We used the Joanna Briggs Institute (JBI)’s critical appraisal checklist for studies reporting prevalence data. The JBI checklist is a 9-point checklist to assess the overall bias in single-cohort studies.[26] Briefly, it assesses the following domains to provide an overall estimation of the RoB: sample frame, study participants, sample size, description of study subjects and setting, validation of methods used to diagnose the condition, measurement of disease, statistical analysis, and adequacy of response rate.

Meta-bias

Planned approaches to determine the presence of publication bias were not feasible, as there were insufficient studies for assessment.

Data Extraction

Data were extracted by 1 reviewer using piloted and standardized data abstraction forms, and the extracted data were fully checked for accuracy by a second reviewer. Any disagreements were resolved by consensus and or discussion with a third reviewer.

The original primary record for each included study was used for data extraction, with supplementary data obtained from companion reports and ClinicalTrials.gov records where necessary to address the research questions. In situations where multiple publications for a unique study were available (e.g., supplemental online appendices, companion publications of specific outcomes, or populations from the original study), the most recently adjudicated data for each outcome were extracted, with preference given to published records.

The extracted data comprised:

- citation details: author, year, journal, country, companion records, study registration and protocol, and publication type
- methodology: setting, number of sites, treatment arms, study period, study aim, relevant definitions, inclusion and exclusion criteria, randomization, blinding or masking details, and design-specific variables
- population: age, sex, ethnicity, criteria defining CIU, disease and treatment history, comorbidities, and family history
- population characteristics: age, sex, duration of CIU, previous treatment and omalizumab use, and inadequate response to H_1 blockers
- intervention characteristics: study intervention description, including dose, treatment duration, dosing frequency, updosing or dose reduction, and route of administration
- control: control, placebo, and active drug description; drug name (brand or generic); dose; dosage form; route of administration; dosing frequency; treatment duration; and interval timing
- when efficacy outcomes (e.g., WISS or ISS7, UAS7, WWS, UCT, relapse, remission, DLQI, CU-Q2oL, number of responders, and rescue medication use) and safety outcomes (e.g., SAEs and withdrawals due to adverse events) were reported with multiple follow-up time points, relevant changes from baseline that were extracted for all time points of interest
- other: funding source and author declarations.

Missing data were identified and reported. Data extraction was limited to studies reporting outcomes of interest.

Microsoft Excel was utilized to document and tabulate data from the included studies, while WebPlotDigitizer[27] was used in extracting outcome data from figures.

Data Analyses and Synthesis

A descriptive summary of study selection, quality assessment, and study and patient characteristics is presented for each included study that reported at least 1 outcome of interest.

For comparing study groups, the effect estimate mean difference (MD) and 95% confidence intervals (CIs) were used for continuous outcomes, the relative risk (RR) and 95% CIs were used for dichotomous outcomes, and the incidence rate ratio (IRR) and 95% CIs were used for count outcomes. For continuous outcomes with varying outcome scales reported (e.g., HRQoL), effect estimates were expressed as standardized mean differences (SMDs). A description of included studies and relevant outcome data were provided when quantitative synthesis was not feasible. When meta-analysis for any outcome was not appropriate or feasible, a descriptive summary was included in the report.

When appropriate and when data were sufficient, a random effects meta-analysis was planned to pool study effects for each outcome of interest using RevMan 5.4. Clinical and methodological heterogeneity was assessed by comparing study design, patients' characteristics, and studied interventions of included studies. If feasible, statistical heterogeneity was measured using Cochrane's Q (statistically significant at $P < 0.10$) and the I^2 statistic (> 75% considered to represent high heterogeneity). If insufficient direct evidence was unavailable, indirect evidence synthesis based on a network meta-analysis was carried out using a Bayesian approach on WinBUGS version 1.4.3 (MRC Biostatistics Unit).[28]

Results

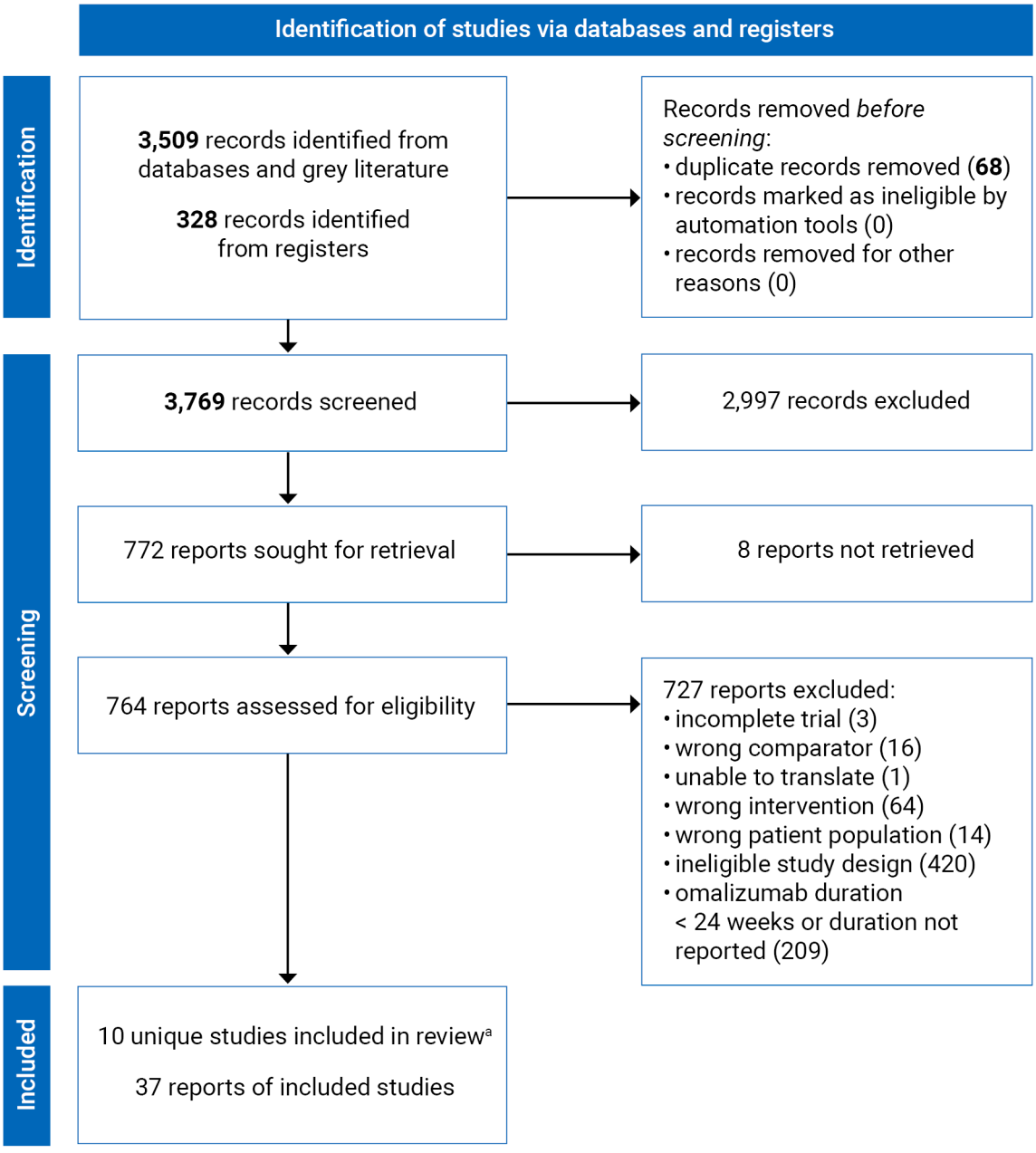
Selection of Primary Studies

Key Take-Away

A total of 37 publications met the final inclusion criteria. They reported findings from 2 RCTs on the use of omalizumab or placebo, 4 cohort studies comparing up to 2 years of treatment with omalizumab to other treatments or no treatment, and 4 single-group prospective studies.

A total of 3,769 citations were identified in the literature search. Following screening of titles and abstracts, 2,997 citations were excluded, and 772 potentially relevant records were retrieved for full-text review. Of these, 8 remain in process, as the full text could not be retrieved; 727 were excluded for various reasons; and 37 records[19,29-64] reporting 10 unique primary studies met the inclusion criteria (2 RCTs,[43,54] 4 comparative cohort studies,[19,42,50,62] and 4 single-group prospective studies)[30,38,48,59] (Figure 1). The list of included records, by unique study, is provided in Appendix 2 (Table 27).

Figure 1: PRISMA Flow Chart of Selected Reports



[a] Two RCTs, 4 comparative cohort studies, 4 single-group prospective studies.

Study Characteristics

The study characteristics for the 2 included RCTs are summarized in Table 3 and the comparative cohort studies in Table 4 and Table 5.

Key Take-Aways

All studies reported efficacy and safety outcomes for patients who were given a dose of 300 mg of omalizumab every 4 weeks. None of the studies reported outcomes for patients who received a higher dose or required more frequent dosing intervals.

Characteristics of RCTs

The included RCTs[43,54] were published in 2016 and 2018 and involved 225 participants in total. The larger of the RCTs was the XTEND-CIU trial with data for 134 participants with CIU published in 2018. The X-ACT trial included 91 participants, and results were first published in 2016. The XTEND-CIU trial was a multicentre trial involving approximately 40 study sites in the US, as detailed in the protocol.[43] The X-ACT trial took place at 24 centres in Germany (Table 3).[54] Both trials implemented a matching subcutaneous placebo.

XTEND-CIU Trial[43]

The XTEND-CIU trial was a phase IV, randomized, placebo-controlled, multicentre trial comparing the efficacy and safety of omalizumab up to 48 weeks in approximately 40 US centres.[29,32-37,40,41,43-46,51] The study enrolled patients aged 12 years to 75 years with symptomatic CIU, despite H_1 antihistamine treatment up to 4 times the approved dose. Following a 14-day screening period, all patients received omalizumab 300 mg every 4 weeks for 24 weeks (enrichment study). Responders from the initial 24-week treatment period (based on 7-Day Urticaria Activity Score [UAS7] ≤ 6 in weeks 23 and 24) were subsequently randomized to continue omalizumab 300 mg from weeks 24 to 48, or a matching subcutaneous placebo (i.e., stopped omalizumab). Following this double-blind period, patients were followed from weeks 48 to 60. Of the 205 patients enrolled in the XTEND-CIU study who received treatment in the initial treatment phase, 134 met the randomization criteria for the double-blind phase (i.e., weeks 24 to 48) and received either omalizumab 300 mg (n = 81) or placebo (n = 53). The reason for the allocation imbalance is unclear. Only 25 of the 53 patients allocated to placebo completed the double-blind period (47%).

The primary efficacy outcome was the percentage of patients with clinical worsening in CIU (UAS7 ≥ 12 for at least 2 consecutive weeks) from weeks 24 to 48. Secondary efficacy measures include time to and proportion with clinical worsening (UAS7 > 6 for at least 2 consecutive weeks), UAS7 change from week 24 to week 48, and re-treatment efficacy. Safety outcomes encompass the incidence and severity of adverse events, vital sign changes, and clinical laboratory evaluations.

X-ACT Trial[54]

The X-ACT trial was a double-blind, placebo-controlled, randomized, multicentre study in patients with H_1 antihistamine–resistant CIU. At 24 German centres, patients aged 18 years to 75 years with a history of angioedema were treated with 300 mg subcutaneous omalizumab every 4 weeks for 28 weeks (total of 7 treatments), or with placebo, and followed until week 36.[49,52-55,63,64] No updosing was reported as part of the permitted treatments. This study was designed to explore the impact of omalizumab on measures of quality of life (QoL), and the frequency and severity of angioedema in patients with CIU and angioedema who remained symptomatic despite the use of 2 to 4 times the recommended dose of a second-generation

H_1 antihistamine. A total of 91 participants (47 receiving omalizumab and 44 receiving placebo) were randomized; of these, 68 completed the 28-week treatment period (35 receiving omalizumab and 33 receiving placebo).

The primary outcome was HRQoL measured using the Chronic Urticaria Quality of Life questionnaire (CU-Q2oL) total score at 36 weeks. Relevant to the current review, the use of rescue medication during treatment (up to 28 weeks) and between weeks 33 and 36, change in UAS7, and change in Dermatology Life Quality Index (DLQI) score were measured at 28 weeks. Other secondary end points reported were angioedema burden and angioedema QoL at week 28.

Table 3: Characteristics of the Randomized Controlled Trials

Characteristic	Staubach et al. (X-ACT trial)[54]	Maurer et al. (XTEND-CIU trial)[43]
Trial registration number	NCT01723072	NCT02392624
Publication year	2016	2018
Study design	Randomized, double-blind, placebo-controlled trial	Randomized, double-blind, placebo-controlled trial, with enrichment phase (participants initially received open-label omalizumab 300 mg every 4 weeks for 24 weeks)
Locations	24 centres in Germany	Approximately 40 sites in the US
Patient enrolment dates	January 2013 to May 2014	May 2015 to March 2017
Randomized, N	91	134
Eligible population	Patients aged 18 years to 75 years with CIU refractory to H_1 antihistamine treatment	Patients aged 12 years to 75 years with CIU refractory to H_1 antihistamine treatment
Exclusion criteria	Patients with non–urticaria-associated angioedema, hypersensitivity to study drugs, rescue medication or drugs of similar chemical structure, evidence of parasitic infection, history of omalizumab treatment (≤ 6 months), history of anaphylactic shock, individuals who are pregnant or breastfeeding	Patients who have a history of omalizumab use (≤ 1 year), use of an investigational drug (≤ 30 days), body weight < 20 kg, other etiology for chronic urticaria, evidence of parasitic infection, specific skin diseases, use of specific drugs (≤ 30 days) of screening (including some study comparators), oral doxepin use (≤ 14 days prior), individuals who are pregnant or nursing (or those intending to become pregnant during study)
Randomized to intervention, n	44	81
Intervention	Omalizumab 300 mg every 4 weeks for 28 weeks (7 doses)	Omalizumab, 300 mg every 4 weeks for 24 weeks for all patients (i.e., 6 doses, single-arm); 300 mg every 4 weeks from weeks 24 to 48 for patients randomized to treatment arm (6 doses, treatment and placebo arms)

Characteristic	Staubach et al. (X-ACT trial)[54]	Maurer et al. (XTEND-CIU trial)[43]
Total treatment	2,100 mg	1,800 mg to 3,600 mg (includes enrichment phase)
Randomized to comparator, n	47	53
Comparator	Placebo for 28 weeks (7 doses)	Placebo, weeks 24 to 48 (6 doses)
Duration of follow-up	36 weeks (8 weeks posttreatment)	60 weeks (12 weeks posttreatment)
Outcomes	UAS7 CU-Q2oL DLQI SAEs	UAS7 DLQI Response or relapse SAEs

CIU = chronic idiopathic urticaria; CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology life Quality Index; UAS7 = 7-Day Urticaria Activity Score; NA = not applicable; SAE = serious adverse event.

Characteristics of Cohort Studies

The 4 included cohort studies[19,42,50,62] were published between 2019 and 2021. Of these, 1 was a prospective cohort study and 3 were retrospective cohort studies. One study was conducted in Cyprus,[62] 2 in the US,[19,50] and 1 in 12 European countries.[42] In all studies, omalizumab was consistently administered at 300 mg every 4 weeks, except for the study by Seth et al. (2019),[50] in which most patients received this dosing strategy but a small minority (proportion not reported) received 150 mg every 4 weeks or 375 mg every 2 weeks (Table 4 and Table 5).[50]

Maurer et al. (2020)[42] (AWARE Study)

The AWARE study was a prospective cohort study conducted in participants aged 18 years or older with antihistamine-resistant CIU.[42] This study took place at 418 centres in 12 European countries (Germany, Spain, the UK, Italy, Greece, Russia, France, Denmark, Belgium, Portugal, Norway, and Sweden). The study was sponsored by the manufacturer of omalizumab and aimed to examine disease burden, current treatment regimens, and use of clinical resources among patients with CIU. The study followed 2,727 patients for 24 months. Of these, 945 patients with CIU (32.3%) received omalizumab, although the breakdown of treatment and comparator exposure was unclear. The remainder of the participants received no treatment (6.4%) or were managed with cyclosporine, montelukast, nonsedating H_1 antihistamines (updosed, on demand or approved), sedative H_1 antihistamines, or combinations of sedative and nonsedative H_1 antihistamines (61.3%). Response to treatment was reported for participants taking these study medications or omalizumab (n = 288) at month 24.

Unsel (2021)[62]

This retrospective cohort study assessed the real-world effectiveness and safety of omalizumab monotherapy or combination therapy for 133 patients with antihistamine-refractory CIU at a single centre in Cyprus.[62] All participants received study drugs for at least 3 months between October 2017 and May 2020. Antihistamine treatment was discontinued in individuals experiencing complete remission of urticaria following the initiation of omalizumab therapy. Patients whose CIU recurred after cessation of antihistamine were again given up to 4 doses of antihistamine per day depending on their condition. Patients with a partial

response to omalizumab (and up to 4 doses of antihistamine) had cyclosporine added to their treatment regimen, and omalizumab was given every 2 weeks instead of 4. Patients with a complete response to omalizumab therapy stopped treatment after 24 weeks but were reinitiated if urticaria recurred. Early recurrence, defined as the reappearance of urticaria within 3 months of the last omalizumab injection, was monitored. Treatment duration for omalizumab was reported as a median of 6 months (range, 3 months to 60 months), and for cyclosporine it was reported as a median of 6.5 months (range, 2 months to 15 months). Data for treatment groups, nonresponders, and adverse events are described separately for individuals who received omalizumab monotherapy beyond 3 months (n = 89), and cyclosporine (n = 12).

Khan et al. (2019)[19]

This retrospective cohort study aimed to compare the real-world effectiveness of different treatments for patients with refractory CIU in 2 multiphysician clinical practices in the US (N = 264) between 2014 and 2019.[19] Patients were identified and screened for eligibility from electronic medical records. Subcutaneous monthly omalizumab 300 mg (n = 134) and oral HCQ 200 mg (n = 111) were the most commonly prescribed therapies for refractory CIU. Nineteen other participants received cyclosporine, sulfasalazine, colchicine, or dapsone but were not followed. The primary outcome was treatment response at 3 months, with complete response defined as a significant reduction in hives or itching, patient satisfaction, and no need for additional treatment. Participants with partial response (reduced symptoms but an incomplete control of CIU) or no response (no improvement in symptoms) at 3 months were eligible to switch medication (from omalizumab to HCQ or from HCQ to omalizumab) or to continue on their current treatment for an additional 8 months. A small proportion of participants continued omalizumab (n = 12) or HCQ (n = 31) to 1 year and were eligible for the current review.

Seth and Khan (2019)[50]

This retrospective cohort study was based on a chart review of electronic medical records from a single-centre allergy and immunology clinic within a major academic hospital in the US. The aim of the study was to examine the experience with alternative drugs in a group of patients with treatment-resistant chronic urticaria, with a specific focus on both subjective and objective adverse events.[50] Of the 126 eligible patients, a total of 24 patients were treated with omalizumab (300 mg every 4 weeks), 24 with cyclosporine (mean highest dose = 272.7 mg), and 45 with HCQ (mean highest dose = 402 mg). They were assessed for adverse events, SAEs, and reasons for discontinuation. Other study drugs reported were out of scope. When the treatment regimen for omalizumab varied for a small minority of patients, no details were reported outside of reduced dose (150 mg every 4 weeks) or increased dose and frequency (375 mg every 2 weeks). No subgroup data were available for these patients. Efficacy outcomes for all drugs were reported; however, the duration of treatment for those with treatment failure, partial response, partial control, complete control, and remission is unclear.

Table 4: Characteristics of Cohort Studies, Maurer et al. and Unsel et al.

Characteristic	Maurer et al. (AWARE)[42]	Unsel et al.[62]
Publication year	2020	2021
Study design	Multicentre, prospective cohort study	Single-centre, retrospective cohort study
Location and setting	418 sites in 12 countries (Germany, Spain, the UK, Italy, Greece, Russia, France, Denmark, Belgium, Portugal, Norway, and Sweden)	Hospital in Cyprus
Study period	March 2014 to October 2015	October 2017 to May 2020
Participants, N	2,727	133
Population	Patients aged ≥ 18 years with physician-confirmed CIU (with or without angioedema) for at least 2 months and inadequate response to standard doses of H_1 antihistamine treatment who provided informed consent	Patients who received omalizumab for at least 3 months due to antihistamine-refractory CIU
Exclusions	Patients who had urticaria present for < 2 months, had "unexpected follow-up difficulties" over the 2-year study period, or were simultaneously participating in any other clinical chronic urticaria study	Patients who continued their treatment at a different hospital after starting omalizumab or who did not adhere to scheduled treatment visits
Intervention, n	Omalizumab (881)	Omalizumab monotherapy (89)
Duration of treatment with intervention	2 years (104 weeks)	Median (range) = 6 months (3 months to 60 months)
Dose for intervention	NR	300 mg (every 4 weeks)
Comparators (n)	Cyclosporine (NR) Montelukast (NR) Nonsedating H_1 antihistamines (NR) Sedative H_1 antihistamines (NR) No treatment (NR)	Cyclosporine (12)
Duration of treatment with comparator	Varied, up to 2 years	Cyclosporine: median (range) = 6 months (2 months to 15 months)
Dose for comparators	NR	Cyclosporine (2.5 mg/kg/day)
Cointerventions	Cointerventions: Because 1 of the study intentions was to look at treatment patterns, all treatments received were tracked (34% continuously received omalizumab).	Cointerventions: Up to 4 doses of second-generation antihistamine (and/or addition of cyclosporine)
Updosing of omalizumab	Updosing was reported for 2 centres (n = 19 [14.2%] for Russia; n = 21 [22.8%] for France).[a]	A total of 4 participants had the frequency increased to 300 mg every 2 weeks due to nonresponse with standard dose and frequency.
Duration of follow-up	At least 2 years	NR
Outcomes	UCT	UAS7 Response

CIU = chronic idiopathic urticaria; NR = not reported; UAS7 = 7-Day Urticaria Activity Score; UCT = Urticaria Control Test.

[a]No additional definitions or doses were provided.

Table 5: Characteristics of Cohort Studies, Seth and Khan and Khan et al.

Characteristic	Seth and Khan[50]	Khan et al.[19]
Publication year	2017	2022
Study design	Single-centre retrospective cohort study	Multicentre retrospective cohort study (electronic medical records)
Location and setting	A single provider practising allergy and immunology at the University of Texas Medical Centre, US	Two multiphysician allergy and immunology practices (Cincinnati, Ohio and Indianapolis, Indiana) in US
Study period	January 1 2001 to April 22 2014	March 2014 to November 2019
Participants, n	126	264
Population	Physician-diagnosed chronic urticaria, traditional treatment for CIU has failed, and aged ≥ 18 years at the time of treatment with an alternative drug	Patients with CIU (with or without angioedema) ≥ 6 weeks and uncontrolled urticaria despite optimized doses of second-generation H_1 antihistamines, with or without montelukast, H_2 antagonists, and doxepin
Exclusions	Patient chart lacking sufficient documentation of follow-up and treatment with an alternative drug for indications other than chronic urticaria	Patients with nonidiopathic chronic urticaria including those with urticaria caused specifically by foods, medications, venom allergies, or other allergens
Intervention (n)	Omalizumab (24)	Omalizumab 300 mg every 4 weeks (134)
Duration of treatment with intervention	Mean (range) = 15 months (2 months to 70 months)	3 months (n = 134); number of eligible patients at 1 year = 12
Dose for intervention	Most patients received 300 mg every 4 weeks. Other regimens reported were 150 mg every 4 weeks and 375 mg every 2 weeks.[a]	300 mg (every 4 weeks)
Comparators (n)	HCQ (45) Cyclosporine (24)	HCQ (111)
Duration of treatment with comparator	HCQ: Mean (range) = 9.3 months (0.25 months to 96 months) Cyclosporine: Mean (range) = 13 months (2 months to 53 months)	3 months (n = 111) to 1 year (NR)
Dose for comparator(s)	HCQ: (mean = 402 mg) Cyclosporine: Starting dose usually approximately 3 mg/kg/d (mean = 272.2 mg)	200 mg/day
Co-interventions	Co-interventions: NR	Co-interventions: 32% of the patients initiated on omalizumab received oral corticosteroids after 3 months of therapy.
Duration of follow-up	NR	1 year
Outcomes	SAEs WDAEs	Response Rescue medications WDAEs

CIU = chronic idiopathic urticaria; HCQ = hydroxychloroquine; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a]No details on sample size for alternative dosing provided.

Patient Characteristics

The basic characteristics of patients are summarized for RCTs in Table 6 and for comparative cohort studies in Table 7, Table 8, Table 9, and Table 10.

Key Take-Aways

The studies included patients with a history of inadequate response to H_1 antihistamines, except for 2 studies that did not provide details on the treatment history. The studies reported on few participant characteristics and comorbidities. Previous use of medications such as H_1 antihistamines, steroids, and cyclosporine was noted in some studies, but details around dose, frequency, and duration were not available. Patients in the included studies were broadly generalizable to the current Canadian setting, but local differences in standard of care and access to health care may vary.

Characteristics of Patients in RCTs

In the RCTs, the mean age of patients ranged from 41.1 years to 48.5 years.[43,54] Mean duration of CIU varied greatly between the X-ACT and XTEND-CIU trials. Patients were predominantly female (68% to 78%) and white or Caucasian [wording from original source] (79% to 98%). Neither trial reported patients' comorbidities. Both patient groups were refractory to H_1 antihistamines (Table 6).

Table 6: Characteristics of Patients in the Randomized Controlled Trials

Characteristics	Staubach et al. (2016) (X-ACT trial)[54]		Maurer et al. (2018) (XTEND-CIU trial)[43]	
	Omalizumab	Placebo	Omalizumab	Placebo
Total randomized, N	91		134	
Disease or symptoms duration in months, mean (SD)	8.4 (9.3)	7.4 (8.8)	77.0 (118.8)	73.6 (67.3)
Randomized, n	44	47	81	53
Age in years, mean	44.9 (range, 20 to 73)	41.1 (range, 20 to 61)	43.1 (SD = 14.7)	48.5 (SD = 13.2)
Sex Female, n (%) Male, n (%)	30 (68.2) 14 (31.8)	33 (70.2) 14 (29.8)	60 (74.1) 21 (25.9)	40 (75.5) 12 (24.5)
Race or ethnicity, n (%)				
White or Caucasian [wording from original source]	42 (95.5)	46 (97.9)	68 (84.0)	42 (79.2)
Black	NR	NR	6 (7.4)	7 (13.2)
Asian	1 (2.3)	1 (2.1)	2 (2.5)	3 (5.7)
American Indian or Alaska Native [wording from original source]	NR	NR	2 (2.5)	0

Characteristics	Staubach et al. (2016) (X-ACT trial)[54]		Maurer et al. (2018) (XTEND-CIU trial)[43]	
	Omalizumab	Placebo	Omalizumab	Placebo
Other	1 (2.3)	0 (0.0)	3 (3.7)	1 (1.9)
Current smokers, n (%)	19 (43.2)	18 (38.3)	16 (19.8)	12 (22.6)
Body mass index (kg/m^2), mean (SD)	NR	NR	29.8 (6.3)	30.8 (7.7)
Previous treatment	Second-generation H_1 antihistamines and no other treatment at least 30 days before omalizumab		Nonsedative H_1 antihistamine treatment (up to 4 times the approved dose) for CIU for at least 3 consecutive days immediately before screening visit with continued current use on the day of the initial screening visit	
Patients with comorbidities, n (%)	NR	NR	NR	NR

CIU = chronic idiopathic urticaria; NA = not applicable; NR = not reported; SD = standard deviation.

Characteristics of Patients in Comparative Cohort Studies

In the comparative cohort studies,[19,42,50,62] the mean age was 40.7 years to 46.7 years and a larger proportion of patients were female (range, 71% to 83%). No study reported patients' race or ethnicity, and details on other important patient characteristics were sparse (Table 7, Table 8, Table 9, Table 10).

Table 7: Characteristics of Patients in Comparative Cohort Studies, Maurer et al.

Characteristics	Maurer et al. (2020) (AWARE trial)[42]					
	Omalizumab[a]	Nonsedating H_1 antihistamines	Sedative H_1 antihistamines	Cyclosporine	Montelukast	No treatment
Participants, N	2,727					
Disease or symptoms duration in years, mean (SD)	4.7 (7.2)					
Patients, n (%)	881 (32.3)	473 (17.3)	NR (2.8)	71 (2.6)	97 (3.6)	1,008 (37)
Age in years, mean (SD)	46.7 (15.7)					
Sex Female, n (%) Male, n (%)	1,933 (70.9) 794 (29.1)					
Race or ethnicity, n (%)	NR	NR	NR	NR	NR	NR
Current smokers, n (%)	NR	NR	NR	NR	NR	NR
Body mass index (kg/m^2), mean (SD)	NR	NR	NR	NR	NR	NR

Characteristics	Maurer et al. (2020) (AWARE trial)[42]					
	Omalizumab[a]	Nonsedating H_1 antihistamines	Sedative H_1 antihistamines	Cyclosporine	Montelukast	No treatment
Previous treatment	Omalizumab, cyclosporin, montelukast, combination sedative and nonsedative H_1 antihistamines, sedative H_1 antihistamines, on-demand nonsedative H_1 antihistamines, updosed nonsedative H_1 antihistamines, approved nonsedative H_1 antihistamines or other treatments (not specified)					
Patients with comorbidities	20.6% of total patients had chronic inducible urticaria.					

NR = not reported; SD = standard deviation.

[a]Omalizumab for 2 years, frequency and dose not reported.

Table 8: Characteristics of Patients in Comparative Cohort Studies, Unsel et al.

Characteristics	Unsel (2021)[62]	
	Omalizumab	Cyclosporine
Participants, N	133 (89 used omalizumab)	
Disease or symptoms duration in months, median (range)	6 months (0.5 to 260)	
Interventions and dose	Omalizumab 300 mg, every 4 weeks in 118 patients (93.7%) Omalizumab 300 mg every 2 weeks in 8 patients (6.3%)	Cyclosporine (2.5 mg/kg/day)
Patients, n	89	12
Age in years, mean	40.7 (SD = 14.4; range, 12 to 86)	
Sex Female, n (%) Male, n (%)	 98 (73.7) 35 (26.3)	
Race or ethnicity, n (%)	NR	NR
Current smokers, n (%)	NR	NR
Body mass index (kg/m^2), mean (SD)	NR	NR
Previous treatment	Antihistamines (class, dose, and duration not specified)	
Patients with comorbidities, n (%)	NR	

NR = not reported; SD = standard deviation.

Table 9: Characteristics of Patients in Comparative Cohort Studies, Khan et al.

Characteristics	Khan et al. (2022)[19]	
	Omalizumab	HCQ
Participants, N	264 (134 used omalizumab)	
Disease or symptoms duration, mean months (SD)	NR	
Intervention	Omalizumab 300 mg for 3 months to 1 year (interval not specified)	HCQ 200 mg daily for 3 months to 1 year
Patients, n	134	111
Age in years, mean (range)	44 (3 to 80)	
Sex Female, n (%) Male, n (%)	 201 (83) 44 (17)	
Race or ethnicity, n (%)	NR	NR
Current smokers, n (%)	NR	NR
Body mass index (kg/m^2), mean (SD)	NR	NR
Previous treatment	Antihistamines, doxepin, montelukast, steroids	
Patients with comorbidities (n)	Thyroid disease (36) Other autoimmune conditions: (24)	Thyroid disease (78) Other autoimmune conditions: (18)

HCQ = hydroxychloroquine; NR = not reported; SD = standard deviation.

Table 10: Characteristics of Patients in Comparative Cohort Studies, Seth and Khan

Characteristics	Seth and Khan (2017)[50]		
	Omalizumab	HCQ	Cyclosporine
Locations	US		
Participants, N	126		
Disease or symptoms duration in months, mean (SD)	NR		
Intervention, dose, and duration	Omalizumab 300 mg, every 4 weeks for 15 months (range, 2 months to 70 months)	HCQ, mean highest dose 402 mg for 9.3 months (range, 0.25 months to 96 months)	Cyclosporin, mean highest dose 272.2 mg for 13 months (range, 2 months to 53 months)
Patients, n	3	45	24
Age in years, mean (range)	44 (18 to 69)		
Sex Female, % Male, %	 77 23		
Race or ethnicity, n (%)	NR	NR	NR
Current smokers, n (%)	NR	NR	NR

Characteristics	Seth and Khan (2017)[50]		
	Omalizumab	HCQ	Cyclosporine
Body mass index (kg/m^2), mean (SD)	NR	NR	NR
Previous treatment	NR		
Patients with comorbidities, n (%)	NR		

HCQ = hydroxychloroquine; NR = not reported.

Data Analysis and Synthesis

Key Take-Aways

Many analyses for efficacy and safety were not feasible due to a lack of data on outcomes of interest, variations in the studied treatments, and limitations in the study data. The analyses in the cohort studies did not consider confounding variables or adjust for imbalances in these factors across treatment groups. This may have led to a biased estimation of the treatment effects. Readers should use extreme caution when reviewing and interpreting these results.

Efficacy and Effectiveness Outcomes

Efficacy Outcomes Reported in RCTs

The results reported on the outcomes of interest in the RCTs, as well as additional results calculated based on the reported study results, are provided in Table 11. Outcome measures are described in Appendix 3 (Table 28).

UAS7: The UAS7 is a validated scoring system quantifying urticaria symptoms (weals and pruritus) on a scale from 0 to 3, as documented by the patient. The maximum score is 42, with a higher score meaning greater disease activity.[65] The minimal clinically important difference (MCID) is 9.5 to 10.5 points.[66]

In the X-ACT trial, omalizumab 300 mg administered for 28 weeks (7 doses) was significantly more efficacious than placebo (UAS7 = 11.1 for the active group and 24.6 for the placebo group), with an MD of 13.49 (95% CI, 12.29 to 14.69).[54] While the UAS7 MD was sustained throughout the treatment period, once treatment stopped, the MD for the active group decreased but the UAS7 score was still lower than placebo (MD = 5.05; 95%CI, 3.89 to 6.21) at follow-up (36 weeks).[54]

In the XTEND-CIU trial (the enrichment study),[43] the UAS7 for the group that was randomized to omalizumab 300 mg was compared to the group that was randomized to placebo for 24 weeks. At week 48, the MD in UAS7 was statistically significantly lower for the active group compared to the placebo group. In the group randomized to placebo for 24 weeks, UAS7 increased by 16.3 points. In the group randomized to an extra 24 weeks of omalizumab (i.e., the group treated for 48 weeks), UAS7 only increased by 3.5 points. The MD of these changes was statistically significant, favouring the active group (MD = 12.80; 95% CI, 5.01 to 20.59).

CU-Q2oL: The CU-Q2oL is an instrument assessing 23 items of symptoms and activities of daily living, with 5 possible responses on a Likert scale ranging from "never" to "very often." A higher score means worse QoL.[67] The MCID is 15 points.[68]

In the X-ACT trial, CU-Q2oL scores were statistically significantly lower for omalizumab 300 mg (CU-Q2oL score = 20.0) compared to placebo (CU-Q2oL score = 42.1) at 28 weeks (7 doses) (MD = 22.10; 95% CI, 20.58 to 23.62).[54] At the 36-week follow-up, the group previously treated with omalizumab for 28 weeks reported better QoL than the placebo group (mean score of 31.0 versus 41.5, respectively), although the MD was reduced (MD = 10.50; 95%CI, 8.98 to 12.02).

DLQI: The DLQI is a self-administered validated questionnaire consisting of 10 questions to determine a patient's perception of the impact of their skin disease on different aspects of their HRQoL over the previous week. The maximum score is 30 (extremely large impact on a person's life).[69] The MCID is 4 points.[70,71]

In the X-ACT trial, the change in DLQI score from baseline statistically significantly favoured omalizumab compared to placebo at 28 weeks (7 doses) (MD = 5.87; 95% CI, 2.48 to 9.27). After discontinuation of treatment at 28 weeks, the groups were followed for an additional 8 weeks (i.e., up to 36 weeks) and there were no significant differences in DLQI scores between the active and placebo groups (DLQI score of 7.8 for omalizumab versus 11.2 for placebo).[54]

In the XTEND-CIU trial,[43] change in DLQI score from week 24 to week 48 for the omalizumab 300 mg group was compared to the group randomized to placebo. At week 48, the MD in DLQI score was statistically significantly lower for the active group compared to the placebo group (MD = 6.70; 95% CI, 3.33 to 10.07). In addition, at week 48, the group randomized to extended omalizumab were less likely to experience worsening QoL (defined as a 4-point decrease in DLQI score) compared to the placebo group (80% RR reduction in DLQI worsening with the 48-week treated group compared to the 24-week treated group; RR = 0.30; 95% CI, 0.19 to 0.48).

Number of responders: The XTEND-CIU trial[43] assessed the number of patients with clinical worsening or relapse (i.e., UAS7 ≥ 6 for at least 2 consecutive weeks) in the group that was randomized to omalizumab 300 mg compared to the group that was randomized to placebo. The active group was less likely to experience worsening of clinical symptoms compared to the placebo group. This was shown with a statistically significant 51% RR reduction for the active group at week 48 (RR = 0.49; 95% CI, 0.34 to 0.72). When both groups were followed for an additional 12 weeks without treatment to week 60, there was no statistically significant difference (RR = 1.04; 95% CI, 0.70 to 1.55) (Table 11).

Table 11: Results by Outcome for Randomized Controlled Trials

Outcome measure	Time (dose)	Reported result: mean (SD) or %	Additional results calculated based on reported study results[a] (Results favour omalizumab when MD > 0 or RR < 1)
7-Day Urticaria Activity Score			
XTEND-CIU trial[b,43]			
UAS7 (Lower score is better)	Baseline	Omalizumab 300 mg extension (n = 81): 32.4 (7.2) Placebo extension (i.e., omalizumab 300 mg group that was randomized to stop omalizumab at 24 weeks) (n = 53): 32.9 (7.0)	MD (SE): 0.50 (1.26) 95% CI, −1.99 to 2.99
	24 weeks (6 doses)	Omalizumab 300 mg extension (n = 81): 0.6 (1.4) Placebo extension (n = 53): 0.9 (1.6)	MD (SE): 0.30 (0.26) 95% CI, −0.22 to 0.82
UAS7 change score (Week 48 score – week 24 score) (Lower change score is better)	24 weeks to 48 weeks (6 additional doses)	Omalizumab 300 mg extension (n = 81): 3.5 (9.23)[b] 95% CI, 1.51 to 5.54 Placebo extension (n = 53): 16.3 (33.6)[b] 95% CI, 12.30 to 30.35	MD (SE): 12.80 (3.94) 95% CI, 5.01 to 20.59
X-ACT trial[c,54]			
UAS7 (Lower score is better)	Baseline	Omalizumab, 300 mg (n = 44): 26.5 (8.2) Placebo (n = 47): 27.9 (8.7)	MD (SE): 1.4 (1.80) 95% CI, −2.13 to 4.93
	24 weeks (6 doses)	Omalizumab, 300 mg (n = 44): 11.47 (2.70) Placebo (n = 47): 23.71 (2.9)	MD (SE): 12.24 (0.59) 95% CI, 11.07 to 13.41
	28 weeks (7 doses)	Omalizumab, 300 mg (n = 44): 11.11 (2.80) Placebo (n = 47): 24.6 (2.96)	MD (SE): 13.49 (0.60) 95% CI, 12.29 to 14.69
	36 weeks (follow-up)	Omalizumab, 300 mg (n = 44): 18 (2.48) Placebo (n = 47): 23.05 (3.03)	MD (SE): 5.05 (0.58) 95% CI, 3.89 to 6.21
UAS7 change score compared to baseline at weeks 24, 28, and 36 (Lower change score is better)	24 weeks (6 doses)	Omalizumab, 300 mg (n = 44): −15.0 (15.0) Placebo (n = 47): −7.2 (14.7)	MD (SE): 7.80 (3.11) 95% CI, 1.61 to 13.99
	28 weeks (7 doses)	Omalizumab, 300 mg (n = 44): −16.8 (14.8) Placebo (n = 47): −6.5 (13.4)	MD (SE): 10.30 (2.96) 95% CI, 4.43 to 16.17
	36 weeks (End of follow-up)	Omalizumab, 300 mg (n = 44): −8.3 (15.3) Placebo (n = 47): −6.2 (13.3)	MD (SE): 2.10 (3.00) 95% CI, −3.86 to 8.06

Outcome measure	Time (dose)	Reported result: mean (SD) or %	Additional results calculated based on reported study results[a] (Results favour omalizumab when MD > 0 or RR < 1)
Chronic Urticaria Quality of Life questionnaire			
X-ACT trial[c,54]			
CU-Q2oL score (Lower score is better)	Baseline	Omalizumab 300 mg (n = 44): 55.4 (13.6) Placebo (n = 47): 56.1 (17.2)	MD (SE) = −7.00 (3.27) 95% CI, −5.79 to 7.19
	24 weeks (6 doses)	Omalizumab 300 mg (n = 44): 22 Placebo (n = 47): 41	NE
	28 weeks (7 doses)	Omalizumab 300 mg (n = 44): 20 (4.00) Placebo (n = 47): 42.1 (3.3)	MD (SE) = 22.10 (0.77) 95% CI, 20.58 to 23.62
	36 weeks (follow-up)	Omalizumab 300 mg (n = 44): 31 (3.50) Placebo (n = 47): 41.5 (3.8) P < 0.001	MD (SE) = 10.50 (0.77) 95% CI, 8.98 to 12.02
CU-2QoL change score compared to baseline at weeks 24, 28, and 36 (Lower change score is better)	24 weeks (6 doses)	Omalizumab 300 mg (n = 44): −31.4 (23.7) Placebo (n = 47): −16.2 (18.8)	MD (SE) = 15.20 (4.47) 95% CI, 6.32 to 24.08
	28 weeks (7 doses)	Omalizumab 300 mg (n = 44): −35.1 (24.2) Placebo (n = 47): −13.9 (17.7)	MD (SE) = 21.20 (4.43) 95% CI, 12.41 to 29.99
	36 weeks (follow-up)	Omalizumab 300 mg (n = 44): −23.1 (23.0) Placebo (n = 47): −14.7 (19.2)	MD (SE) = 8.4 (4.43) 95% CI, −0.40 to 17.20
Dermatology Life Quality Index			
XTEND-CIU trial[b,43]			
DLQI change score (Week 48 score – week 24 score) (Lower change score is better)	24 weeks to 48 weeks (6 additional doses)	Omalizumab 300 mg extension (n = 81): 1.5 (5.28) 95% CI, 0.3 to 2.6 Placebo extension (n = 53): 8.2 (10.02) 95% CI, 5.5 to 10.9 P < 0.0001	MD (SE) = 6.70 (1.33) 95% CI, 3.33 to 10.07
Percent of patients who experienced DLQI worsening (3 point increase) (Lower percent is better)	24 weeks to 48 weeks (6 additional doses)	Omalizumab 300 mg extension (n = 81): 19.8% 95% CI, 11.4 to 29.8 Placebo extension (n = 53): 66% 95% CI, 51.6 to 78.5	RR = 0.30 95% CI, 0.19 to 0.48

Outcome measure	Time (dose)	Reported result: mean (SD) or %	Additional results calculated based on reported study results[a] (Results favour omalizumab when MD > 0 or RR < 1)
X-ACT trial[54]			
DLQI change score compared to baseline at weeks 24, 28, and 36 (Lower change score is better)	24 weeks (6 doses)	Omalizumab, 300 mg (n = 44): −9.94 Placebo (n = 47): −4.00	NE
	28 weeks (7 doses)	Omalizumab, 300 mg (n = 44): −10.5 (8.3) Placebo (n = 47): −4.63 (8.0) P < 0.001	MD (SE) = 5.87 (1.71) 95% CI, 2.48 to 9.27
	36 weeks (follow-up)	Omalizumab, 300 mg (n = 44): −6.8 (8.6) Placebo (n = 47): −5.4 (8.3)	MD (SE) = 1.40 (1.77) 95% CI, −2.12 to 4.92
DLQI score (Lower score is better)	36 weeks (follow-up)	Omalizumab, 300 mg (n = 44): 7.8 (7.8) Placebo (n = 47): 11.2 (8.6)	MD (SE) = 3.40 (1.73) 95% CI, −0.03 to 6.83
Number of responders			
XTEND-CIU trial[b,43]			
Percent of patients who experienced clinical worsening (UAS7 > 6)[d]	At 24 weeks (6 doses)	Omalizumab 300 mg extension (n = 81): 21% Placebo extension (n = 43): 60.4% P < 0.0001	RR = 0.35 95% CI, 0.21 to 0.56
Percent of patients who experienced clinical worsening (UAS7 > 6)[d]	At 48 weeks (6 additional doses)	Omalizumab 300 mg extension (n = 81): 32.1% Placebo extension (n = 43): 64.2% P < 0.0004	RR = 0.49 95% CI, 0.34 to 0.72
Relapse: Clinical worsening after omalizumab discontinuation[e]	60 weeks[f] (12 weeks follow-up)	Omalizumab 300 mg extension (n = 71): 45.1% Placebo extension (n = 53): 43.4% P = 1.0	RR = 1.04 95% CI, 0.70 to 1.55

CI = confidence interval ; CU2-QoL = Chronic Urticaria Quality Of Life questionnaire; DLQI = Dermatology Life Quality Index; MD = mean difference; NE = not estimable; RR = relative risk; SD = standard deviation; SE = standard error; UAS7 = 7-day Urticaria Activity Score.

[a]Additional calculations based on the reported data were made to derive effect estimates MD or RR and the 95% CI.

[b]Primary outcomes were mean differences after treatment with either omalizumab extension (i.e., omalizumab 300 mg group that was randomized to continue omalizumab at 24 weeks) or placebo extension (i.e., omalizumab 300 mg group that was randomized to stop omalizumab at 24 weeks) for 24 weeks.

[c]Patients were randomized 1:1 to omalizumab 300 mg or placebo (every 4 weeks up to week 24).

[d]UAS7 score had to be maintained for 2 weeks or more.

[e]Threshold used to define clinical worsening based on UAS7 not reported.

[f]Based on omalizumab discontinuation at 48 weeks (omalizumab 300 mg) or 24 weeks (placebo group). Time point for clinical worsening for the placebo group after discontinuation of omalizumab at 24 weeks unclear.

Effectiveness Outcomes Reported in Cohort Studies

The results for the outcomes of interest in the comparative cohort studies, as well as additional results calculated based on the study results, are provided in Table 12. Outcome measures are described in Appendix 3 (Table 28).

Urticaria Control Test (UCT): The UCT is an instrument used to determine the impact of urticaria based on 4 questions regarding symptoms and QoL. There are 5 possible choices of responses, with 0 being "very much" and 4 being "not at all." A score of 16 indicates complete disease control, whereas a score less than 12 means that a patient has poorly controlled chronic urticaria. The MCID is 3 points.[72,73]

In an unadjusted analysis for the AWARE study by Maurer et al. (2020),[42] the RR of poorly controlled response was statistically significantly lower in omalizumab compared to high-dose H_1 antihistamines with 52 weeks and 104 weeks of treatment (RR = 0.66 [95% CI, 0.54 to 0.81]; RR = 0.65 [95% CI, 0.48 to 0.87]; respectively) (Table 12). There was no statistical difference between omalizumab and cyclosporine, montelukast, or no treatment after 52 weeks, and there were no statistical differences between omalizumab and montelukast or no treatment at 104 weeks. At 104 weeks, only 1 patient remained in the cyclosporine group; hence, the RR is not robust. These additional analyses were not adjusted for possible confounding factors when comparing the treatment groups.

Number of responders: In the Unsel et al. (2021)[62] study, 77.8% of patients receiving omalizumab (98 of 133) had a complete response to treatment over 3 months to 60 months (defined as a UAS7 of 0). Results were not reported for cyclosporine. Those with no response to treatment (i.e., UAS7 of 28 to 42) included 1 patient in the omalizumab group and 3 patients in the cyclosporine group.

For the Khan et al. (2022)[19] study, after 52 weeks of treatment, there was a statistically significant number of patients with a sustained response with omalizumab (82% of patients) compared to HCQ (66% of patients) (RR = 1.26; 95% CI, 1.08 to 1.47). This analysis was not adjusted for possible confounding factors when comparing the treatment groups.

Table 12: Results for Outcomes of Interest in Comparative Cohort Studies

Outcome measure	Time (dose)	Reported result	Additional results calculated based on reported study results[a]
Urticaria Control Test			
Maurer et al. (2020)[42]			
UCT poorly controlled (UCT < 12)	Baseline	Omalizumab 300 mg (n = 79): 62.0% H_1 antihistamines (updosed) (n = 454): 76.4%	Unadjusted RR = 0.82 95% CI, 0.62 to 1.02
		Omalizumab 300 mg (n = 79): 62.0% Cyclosporin (n = 32): 78.1%	Unadjusted RR = 0.80 95% CI, 0.60 to 1.00
		Omalizumab 300 mg (n = 79): 62.0% Montelukast (n = 71): 69.0%	Unadjusted RR = 0.88 95% CI, 0.70 to 1.11
		Omalizumab 300 mg (n = 79): 62.0% No treatment (n = 792): 78.7%	Unadjusted RR = 0.80 95% CI, 0.66 to 0.94
	52 weeks	Omalizumab 300 mg (n = 415): 32.0% H_1 antihistamines (updosed) (n = 213): 48.4%	Unadjusted RR = 0.66 95% CI, 0.54 to 0.81

Outcome measure	Time (dose)	Reported result	Additional results calculated based on reported study results[a]
		Omalizumab 300 mg (n = 415): 32.0% Cyclosporin (n = 4): 50.0%	Unadjusted RR = 0.64 95% CI, 0.24 to 1.73
		Omalizumab 300 mg (n = 415): 32.0% Montelukast (n = 2): 50.0%	Unadjusted RR = 0.64 95% CI, 0.16 to 2.58
		Omalizumab 300 mg (n = 415): 32.0% No treatment (n = 262): 37.8%	Unadjusted RR = 0.85 95% CI, 0.6880 to 1.05
	104 weeks	Omalizumab 300 mg (n = 288): 27.1% H_1 antihistamines (updosed) (n = 105): 41.9%	Unadjusted RR = 0.65 95% CI, 0.48 to 0.87
		Omalizumab 300 mg (n = 288): 27.1% Cyclosporin (n = 1): 100%	Unadjusted RR = 0.27 95% CI, 0.22 to 0.33
		Omalizumab 300 mg (n = 288): 27.1% Montelukast (n = 10): 50.0%	Unadjusted RR = 0.54 95% CI, 0.28 to 1.04
		Omalizumab 300 mg (n = 288): 27.1% No treatment (n = 264): 27.7%	Unadjusted RR = 0.98 95% CI, 0.75 to 1.29
Number of responders			
Unsel (2021)[a62]			
Complete response (UAS7 = 0)	Treatment duration 6 months (range, 3 months to 60 months)	Omalizumab 300 mg: 98 of 133 (77.8%) Cyclosporin: NR	NE
Well-controlled response (UAS7 = 1 to 6)	Treatment duration 6 months (range, 3 months to 60 months)	Omalizumab 300 mg: 23 of 133 (18.3%) Cyclosporin: NR	NE
No response (UAS7 = 28 to 42)	Treatment duration 6 months (range, 3 months to 60 months)	Omalizumab 300 mg: 1 of 133 (0.8%) Cyclosporin: 3 of 12 (25%)	Unadjusted RR = 0.030 95% CI, 0.003 to 0.267
Khan et al. (2022)[19]			
Sustained response (complete response after 1 year)	52 weeks	Omalizumab 300 mg: 111 of 134 (82%) Hydroxychloroquine: 73 of 111 (66%)	Unadjusted RR = 1.26 95% CI, 1.08 to 1.47

CI = confidence interval; NE = not estimable; RR = relative risk; UAS7 = 7-day Urticaria Activity Score; UCT = Urticaria Control Test.

[a]Additional calculations based on the reported data were made to derive effect estimates RR and the 95% CI. Care should be exercised when interpreting results as no adjustment has been made for potential confounding variables.

No health-related or general QoL data were reported in the comparative cohort studies specific to omalizumab or the other comparators of interest.

Safety Outcomes

Safety Outcomes Reported in RCTs

The safety outcomes of interest reported in the RCTs, and additional results calculated based on the reported study results, are presented in Table 13.

SAEs: No statistically significant difference was found in the number of patients with SAEs between those receiving omalizumab 300 mg and those receiving placebo in either RCT (RR = 2.23; 95% CI, 0.43 to 11.57;[43] and RR = 0.43; 95% CI, 0.08 to 2.52),[54] although the RRs of SAEs for the 2 studies were in opposite directions. In addition, the numbers of SAEs (IRR = 4.81; 95% CI, 0.99 to 45.72)[54] were not statistically different between those receiving omalizumab 300 mg (9 events in 4 patients) and those receiving placebo (2 events in 2 patients). The observed SAEs were not considered attributable to the study medication following adjudication by investigators in both RCTs.

All-cause mortality: The X-ACT trial considered mortality as an outcome. No deaths were reported in either the omalizumab 300 mg group or the placebo group.[54]

WDAEs: The XTEND-CIU trial (Maurer et al. [2018])[43] reported 1 WDAE in a patient who received omalizumab and 2 WDAEs in the placebo group. No additional details were provided to clarify whether the withdrawals in the placebo group were attributable to specific adverse events or to the subcutaneous delivery of the study medications. No WDAEs were documented in the X-ACT trial (Staubach et al. [2016]).[54]

Table 13: Summary of Safety Outcomes Reported in the Randomized Controlled Trials

Outcome measure	Reported result	Additional results calculated based on reported study results
Serious adverse events		
XTEND-CIU[43]		
Number of patients	Omalizumab 300 mg extension (i.e., omalizumab 300 mg group that was randomized to continue omalizumab at 24 weeks) (n = 81): 2 (2.5%) Placebo extension (i.e., omalizumab 300 mg group that was randomized to stop omalizumab at 24 weeks) (n = 53): 3 (5.6%)	RR = 0.43 95% CI, 0.08 to 2.52
X-ACT trial[a,54]		
Number of patients	Omalizumab 300 mg (n = 44): 4 (9.1%) Placebo (n = 47): 2 (4.3%)	RR = 2.23 95% CI, 0.43 to 11.57
Number of events	Omalizumab 300 mg (n = 44): 9 events in 4 patients Placebo (n = 47): 2 events in 2 patients	IRR = 4.81 95% CI, 0.99 to 45.72
Withdrawals due to adverse events		
XTEND-CIU trial[43]		
Number of patients	Omalizumab 300 mg (n = 81): 1 (1.2%) Placebo (n = 53): 2 (3.8%)	RR = 0.33 95% CI, 0.03 to 3.52
X-ACT trial[54]		
Number of patients	Omalizumab 300 mg (n = 44): 0 Placebo (n = 47): 0	RD = 0

CI = confidence interval; IRR = incidence rate ratio; RD = risk difference; RR = relative risk.

[a]This study also considered all-cause mortality. Zero mortality was documented in omalizumab or placebo arms.

Safety Outcomes Reported in Comparative Cohort Studies

The safety outcomes of interest reported in comparative cohort studies and additional results calculated based on the reported study results are presented in Table 14.

SAEs: No SAEs were reported in Seth and Khan (2017)[50] for omalizumab, cyclosporine, or HCQ.

WDAEs: No patients withdrew from the study due to adverse events in Khan et al. (2022).[19] In Seth and Khan (2017),[50] no patients withdrew from omalizumab or cyclosporine due to adverse events, whereas 4 patients withdrew from HCQ due to adverse events.[50]

Table 14: Summary of Adverse Events Reported in the Comparative Cohort Studies

Outcome measure	Reported result	Additional results calculated based on reported study results
Serious adverse events		
Seth and Khan (2017)[50]		
Number of patients	Omalizumab 300 mg (n = 134): 0 (0%) Cyclosporin (n = 8): 0 (0%)	RD = 0
Number of patients	Omalizumab 300 mg (n = 134): 0 (0%) Hydroxychloroquine (n = 45): 0 (0%)	RD = 0
Withdrawals due to adverse events		
Khan et al. (2022)[19]		
Number of patients	Omalizumab 300 mg (n = 134): 0 Hydroxychloroquine (n = 111): 0	RD = 0
Seth and Khan (2017)[50]		
Number of patients	Omalizumab 300 mg (n = 134): 0 (0%) Cyclosporin (n = 8): 0 (0%)	RD = 0
Number of patients	Omalizumab 300 mg (n = 134): 0 (0%) Hydroxychloroquine (n = 45): 3 (6.7%)	Unadjusted RD = 6.7% 95% CI, −1.06% to 14.40%

CI = confidence interval; RD = risk difference; RR = relative risk.

Important Subgroups

Two cohort studies reported updosing of omalizumab for a small number of patients.[42,62] No additional details or related outcomes specific to the patients receiving updosed omalizumab were provided. One other cohort study[50] reported updosing to omalizumab 375 mg while reducing the treatment intervals to 2 weeks in a small number of patients whose symptoms were unresponsive to omalizumab (n = 4 of 133 patients). No outcome data were reported for these patients.

Additional Patient Information From Single-Group Prospective Studies

Given the paucity of comparative data from studies reporting long-term use of omalizumab, outcomes from 3 prospective single-arm studies and 1 arm of the OPTIMA trial were also included to inform the results of this review.

Study Characteristics

The study characteristics of the included single-group prospective studies[30,38,48] are summarized in Table 15, Table 16, and Table 17.

All studies were published between 2019 and 2023 and had populations of 15 to 315 eligible participants with CIU. In all studies, omalizumab was administered at 300 mg every 4 weeks. Treatment duration for omalizumab was not standardized and varied among the patients with few details provided (range, 6 months to ≥ 24 months). Participants in the OPTIMA trial[59] were allocated initially to either 150 mg or 300 mg omalizumab for 24 weeks; however, only the 300 mg dose is described in the current review. Data hereafter in this review are focused on participants who were randomized initially to the 300 mg omalizumab arm and continued for an additional 12 weeks. The single-group prospective studies were conducted in various international locations, including multicentre studies in France,[30] Italy,[38] and Russia.[48] The OPTIMA trial was conducted in 8 countries: Argentina, Canada, Chile, the Dominican Republic, Guatemala, Panama, Brazil, and Mexico.[59]

Sussman et al. (2020) (OPTIMA Trial)[59]

The OPTIMA trial was a prospective, randomized (3:4), open-label trial.[59] The focus on the OPTIMA trial in the current review is to examine the specific benefit of treatment extension for those patients whose symptoms were not well controlled following their initial course of treatment with omalizumab 300 mg. Patients who received 150 mg and whose dose was then increased to 300 mg are hereafter not considered.

Patients initially received 300 mg of omalizumab every 4 weeks for 24 weeks. Patients on 300 mg could extend treatment for an additional 12 weeks if their symptoms were not controlled at the 300 mg dose. The main goal was to evaluate optimized re-treatment's impact on patients with CIU who relapsed (UAS7 > 16) after being clinically well controlled (UAS7 ≤ 6) during the initial omalizumab treatment. The study also examined the time to relapse for patients whose symptoms were well controlled following the initial 24 weeks; the benefits of extending treatment for those whose symptoms remained uncontrolled; and omalizumab's safety, tolerability, and efficacy during the initial dosing period.

Barbaud et al. (2020) (LUCIOL Study)[30]

The LUCIOL study,[30] requested by the French Health Authority as a postlisting study, was designed to gather data regarding the effectiveness and safety of omalizumab for treating CIU in real-world conditions in France. The LUCIOL study was a nationwide, multicentre, observational, prospective study that, over 12 years, followed patients (with a mean age of 43.7 years) who had initiated omalizumab treatment. The primary outcome measure was the proportion of patients with good symptom control (UAS7 score ≤ 6) at 12 months. The study also assessed QoL using DLQI or CDLQI scores and examined the practical aspects of omalizumab use as part of its primary evaluation. This study was only reported as an abstract.

Damiani et al. (2019)[38]

This multicentre, prospective, real-life observational study was conducted at 3 university centres and aimed to assess the effectiveness of omalizumab in a cohort of patients with severe urticaria. Omalizumab was administered subcutaneously at 300 mg every 4 weeks to patients who had a UAS7 greater than 3 or a UAS7 greater than 16 and whose symptoms were unresponsive to a fourfold increase in antihistamine dosage. Patients were categorized into 4 groups based on their UAS7 scores: urticaria-free (UAS7 = 0, complete response), well-controlled disease (UAS7 = 1 to 6, optimal response), mild urticaria (UAS7 = 7 to 15, partial response), and moderate to severe urticaria (UAS7 = 16 to 27 and > 27, nonresponse). The treatment involved 2 cycles: the first cycle lasting 24 weeks, followed by an 8-week "wait and see" period, and then the second cycle, which lasted 20 weeks.[38]

Olisova and Skander (2023)[48]

This prospective multicentre study aimed to compare the efficacy of omalizumab treatment in patients with chronic idiopathic urticaria. All patients received omalizumab therapy at a dose of 300 mg subcutaneously once a month, as per the approved regimen in the Russian Federation, when antihistamine therapy was ineffective. The treatment duration ranged from 6 months to 12 months, with the primary focus on improving QoL, reducing disease severity, and enhancing symptom control of urticaria as the optimal therapeutic outcome. In addition, participants were monitored for 2 months following the conclusion of treatment to assess the duration of remission and the impact on relapse rates.[48]

Table 15: Characteristics of Single-Group Prospective Studies (Barbaud et al. and Damiani et al.)

Characteristic	Barbaud et al. 2020 (LUCIOL)[30]	Damiani et al. 2019[38]
Design	Single-arm, prospective cohort study (published as an abstract)	Multicentre, prospective cohort study
Location and setting	Multicentre, France	3 university centres, Italy
Study period	NR	NR
Eligible population	Patients aged > 12 years with CIU	Patients with severe urticaria eligible for omalizumab use; all patients had history of urticaria > 6 weeks and had symptoms that were unresponsive to antihistamines.
Exclusions	NR	NR
Participants, n	265	88
Intervention, dose (n)	Omalizumab 300 mg every 4 weeks (265)	Omalizumab 300 mg every 4 weeks (88)
Duration of intervention	12 months	44 months (cycle 1 for 24 weeks, and cycle 2 for 20 weeks); in between 8 weeks as withdrawal period
Total dose of intervention	1,800 mg to 3600 mg	Not clear (up to 13,200 mg)

Characteristic	Barbaud et al. 2020 (LUCIOL)[30]	Damiani et al. 2019[38]
Cointerventions and titration	Cointerventions: 88.7% took at least 1 concomitant treatment associated with omalizumab during the follow-up, mainly antihistamines, leukotriene, and corticosteroids. Titration: NR	Cointerventions: NR Titration: NR
Outcomes	Response DLQI Safety (measured but not reported)	Response Safety (measured but not reported)

CIU = chronic idiopathic urticaria; DLQI = Dermatology Life Quality Index; NR = not reported.

Table 16: Characteristics of Single-Group Prospective Studies, Olisova and Skander

Characteristic	Olisova and Skander (2023)[48]
Design	Multicentre, prospective cohort study
Location and setting	Multicentre, Russia
Study period	2018 to 2022
Eligible population	Patients with chronic urticaria, ≥ 6 weeks
Exclusions	Age younger than 18 years, course of the disease < 6 weeks, hypersensitivity to omalizumab, pregnancy and/or lactation, and severe mental or physical disorders
Participants, n	30 (15 with CIU)
Intervention, dose (n)	Omalizumab 300 mg (15)
Duration of intervention	6 months to 12 months
Total dose of intervention	Not clear
Cointerventions and titration, (n)	Cointerventions: NR Titration: NR
Outcomes	UAS7 DLQI CU-QoL UCT Safety

CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index; NR = not reported; UAS7 = 7-Day Urticaria Activity Score; UCT = Urticaria Control Test.

Table 17: Characteristics of Single-Group Prospective Studies, Sussman et al. (OPTIMA Trial)

Characteristic	Sussman et al. (2020) (OPTIMA trial)[59]
Trial registration number	NCT02161562
Design	Randomized, open-label, noncomparator trial[a] (evidence from 1 arm (omalizumab 300 mg) in the open-label randomized controlled trial included in the review))
Location and setting	34 centres in 8 countries: Argentina, Canada, Chile, Dominican Republic, Guatemala, Panama, Brazil, Mexico
Study period	August 2014 to November 2016
Eligible population	Patients aged 18 years or older with CIU and presence of symptoms for ≥ 6 months, and itch and hives for ≥ 6 consecutive weeks despite concurrent use of nonsedating H_1 antihistamine
Exclusions	Other etiology for CIU, skin disease that may interfere with trial outcomes, evidence of parasitic infection, history of malignancy, pregnant and/or nursing, individuals with child-bearing potential (unless contraceptive currently used), willing and able to comply with study procedures and follow-up
Participants, N	314
Intervention, dose (n)	Omalizumab 300 mg every 4 weeks (134), with 6 doses in the initial treatment phase and an additional 3 doses in the extended or re-treatment phase
Duration of intervention	First phase = 24 weeks; second phase = 12 weeks
Cointerventions and titration (n)	Unclear
Other important study details	Intermission between initial and extended treatments: 8 weeks Posttreatment follow-up: 4 weeks Extended treatment with 300 mg (n = 44); re-treatment (n = 49)
Outcomes	UAS7 DLQI Relapse Response

CIU = chronic idiopathic urticaria; DLQI = Dermatology Life Quality Index; UAS7 = Urticaria Activity Score.

[a]This is the study design assigned by investigators.

Patient Characteristics

The characteristics of the participants reported in the single-group prospective studies are summarized in Table 18, Table 19, and Table 20.

Patients in the single-group prospective studies who received omalizumab had an average age of 44 years and 53% to 73% were female. None of the studies, except for the study by Sussman et al. (2020),[59] provided details on patient health status, smoking history, BMI, or race or ethnicity. One study[48] did not report any details regarding the patients' treatment history; however, patients in the other studies were reported to have experience with first-generation H_1 antihistamines,[30,38,59] second-generation or third-generation H_1 antihistamines,[59] H_2 antihistamines,[59] leukotriene receptor antagonists,[30,59] short-course corticosteroids,[38] montelukast,[38] cyclosporine,[38] or other medications.[38]

Table 18: Characteristics of Patients in Single-Group Prospective Studies (Barbaud et al. and Damiani et al.)

Characteristics	Patients receiving omalizumab in Barbaud et al. (2020)[30]	Patients receiving omalizumab in Damiani et al. (2019)[38]
Participants, n	265	127
Disease or symptoms duration in months, mean (SD) and range	NR	52 (65.7) Range, 6 to 540
Intervention, dose	Omalizumab 300 mg	Omalizumab 300 mg
Number of patients receiving omalizumab	265	88
Age in years, mean (SD)	43.7 (NR)	50.8 (16.5)
Sex Female, n (%) Male, n (%)	 178 (66.4) 89 (33.6)	 75 (59.1) 52 (40.9)
Race or ethnicity, n (%)	NR	NR
Current smokers, n (%)	NR	NR
Body mass index (kg/m^2), mean (SD)	NR	NR
Previous treatment	Fourfold dose of antihistamines (49.15%), licensed dose of antihistamines (36.2%), twofold dose of antihistamines (22.6%), antileukotriene (17.4%)	In addition to H_1 antihistamines, 62% of this cohort previously used short-course corticosteroids, 18.1% montelukast, 13.4% cyclosporine, and 5.5% others.
Patients with comorbidities, n (%)	NR	NR

CIU = chronic idiopathic urticaria; H_1 = antihistamine; NR = not reported; SD = standard deviation.

Table 19: Characteristics of Patients in Single-Group Prospective Studies (Olisova and Skander)

Characteristics	Patients receiving omalizumab in Olisova and Skander (2023)[48]
Participants, N	30 (15 with CIU)
Disease or symptoms duration in years, mean (range)	> 6 weeks (mean NR)
Intervention, dose	Omalizumab 300 mg
Number of patients receiving omalizumab	30
Age in years, mean (range)	39 (18 to 62)
Sex Female, n (%) Male, n (%)	 20 (67) 10 (33)
Race or ethnicity, n (%)	NR

Characteristics	Patients receiving omalizumab in Olisova and Skander (2023)[48]
Current smokers, n (%)	NR
Body mass index (kg/m^2), mean (SD)	NR
Previous treatment	NR
Patients with comorbidities, n (%)	NR

CIU = chronic idiopathic urticaria; NA = not applicable; NR = not reported; SD = standard deviation.

Table 20: Characteristics of Patients in Single-Group Prospective Studies, Sussman et al. (OPTIMA Trial)

Characteristics	Patients receiving omalizumab in Sussman et al. (2020) (OPTIMA trial)[59]
Total randomized participants, N	314[a]
Disease or symptoms duration in months, mean (SD)	Not clear (84.3% of patients had disease for more than 1 year)
Number of patients receiving omalizumab	136
Age in years, mean (SD)	45.8 (13.60)
Sex Female, n (%) Male, n (%)	 99 (72.8) 37 (27.2)
Ethnicity, n (%)	
Hispanic or Latino	29 (21.3)
Not Hispanic or Latino	106 (77.9)
NR or unknown	1 (0.7)
Race, n (%)	
White	113 (83.1)
Black	6 (4.4)
Asian	10 (7.4)
American Indian or Alaska Native [wording from original source]	NR
Other	7 (5.1)
Current smokers, n (%)	NR
Body mass index (kg/m^2), mean (SD)	NR
Previous treatment	First-generation H_1 antihistamines, second-generation or third-generation H_1 antihistamines, H_2 antihistamines, and leukotriene receptor antagonists
Patients with comorbidities, n (%)	NR
Categories of comorbidities, n (%)	NR

NR = not reported; RCT = randomized controlled trial; SD = standard deviation; vs. = versus.

[a]The comparison of interest in this RCT (150 mg omalizumab vs. 300 mg omalizumab) is not eligible for the review and thus the 300 mg arm of the study is being used to inform the efficacy and safety outcomes of interest alongside the 4 single-group cohort studies.

Outcomes Reported in Single-Group Prospective Studies

Effectiveness Outcomes Reported in Single-Group Prospective Studies

The results reported on the efficacy outcomes of interest in the single-group prospective studies are provided in Table 21, for treatment with omalizumab 300 mg.

UAS7: The UAS7 was reported in 2 single-group prospective studies.[48,59] Olisova and Skander (2023)[48] evaluated omalizumab 300 mg in 15 patients for 48 weeks (13 doses); after a sharp reduction in the UAS7 following initial treatment, the UAS7 held constant at this reduced level over the treatment period to week 24 (7 doses) (mean = 2.81). The reductions in UAS7 score were maintained when treatment was extended to week 48 (13 doses) (mean = 2.81).

Sussman et al. (2020)[59] evaluated omalizumab 300 mg in 44 patients, with a total of 9 doses administered over 2 cycles. In the first cycle, the UAS7 sharply reduced from baseline (mean = 30.27) to week 24 (6 doses) (mean = 1.14). After an 8-week withdrawal period from week 24 to week 32 (no omalizumab received), the UAS7 increased (mean = 28.30). Following a second treatment cycle, the UAS7 again reduced at week 36 (7 doses) (mean = 6.19) and then further reduced by week 44 (9 doses) (mean = 2.3). When the extended treatment with omalizumab was stopped, the UAS7 increased gradually over the final 4-week follow-up (mean = 11.86).

CU-Q2oL: Olisova and Skander (2023)[48] evaluated omalizumab 300 mg in 15 patients for 48 weeks (13 doses). Study results showed a large increase in CU-Q2oL score from baseline (1 dose) (mean = 55.06) to week 24 (7 doses) (mean = 83.53), which seems to contradict results in the same study for improvement in urticaria symptoms, and it was not possible to further elucidate this data anomaly. The CU-Q2oL score held constant at the same level until week 48 (13 doses) (mean = 83.71).

UCT: Olisova and Skander (2023)[48] evaluated omalizumab 300 mg in 15 patients for 48 weeks (13 doses). The UCT score improved from baseline (1 dose) (mean = 8.19) to week 24 (7 doses) (mean = 14.23) and further improved when treatment was extended to week 48 (13 doses) (mean = 14.23).

DLQI: The DLQI was reported in 3 single-group prospective studies.[30,48,59] Olisova and Skander (2023)[48] evaluated omalizumab 300 mg in 15 patients for 48 weeks (13 doses); after a sharp decrease in DLQI score from baseline (1 dose) (mean = 16.05) to week 24 (7 doses) (mean = 3.30), reductions were sustained when treatment was extended to week 48 (13 doses) (mean = 3.31). Barbaud et al. (2020)[30] evaluated omalizumab 300 mg in patients for 52 weeks and found there was a sharp decrease in DLQI score from baseline (mean = 11.0) to 52 weeks (mean = 1.77). Sussman et al. (2020)[59] evaluated omalizumab 300 mg in 44 patients, and found a decrease in DLQI score from baseline to 36 weeks (6 to 9 doses) (mean change = −8.49).

Number of responders: The number of responders categorized at different levels of control of CIU were reported in 2 single-group prospective studies[30,48] based on cut-points of the UAS7. In Barbaud et al. (2020), the percentage of patients whose symptoms were well_controlled (i.e., UAS7 ≤ 6) was 68.9% at week 24[35] and 74.9% at week 52. For 90% of the participants taking 300 mg omalizumab, their symptoms were well controlled by week 36 in the OPTIMA trial. Similarly, the proportion of patients with a well-controlled

response in Damiani et al. (2019)[38] at 32 weeks was 47%, but this response was not sustained at week 44 (2.5%). In this same study, the percentage of patients whose symptoms were completely controlled (i.e., UAS7 = 0) was 58.4% (week 44),[38] and similar proportions of complete responders were observed in Barbaud et al. (2020)[30] at week 52. Barbaud et al. (2020)[30] also found that 84.5% were in remission at week 52 of treatment. Sussman et al. (2020)[59] found that 50% of patients at week 24 (6 doses) had relapsed (i.e., UAS7 ≥ 16), and that the mean time to relapse for those patients was 4.7 weeks (SD = 2.3 weeks).

Table 21: Results of Efficacy Outcomes Reported in the Single Cohort Prospective Studies

Outcome measure	Time (dose)	Reported result: mean (SD) or %
7-Day Urticaria Activity Score		
Olisova and Skander (2023):[48] omalizumab 300 mg		
UAS7 (Lower score is better)	Baseline (1 dose)	(n = 15): 29.78 (5.62)
	24 weeks (7 doses)	(n = 15): 2.81 (8.99)
	28 weeks (8 doses)	(n = 15): 2.53 (8.71)
	32 weeks (9 doses)	(n = 15): 3.09 (8.71)
	36 weeks (10 doses)	(n = 15): 2.81 (8.99)
	40 weeks (11 doses)	(n = 15): 3.09 (8.71)
	44 weeks (12 doses)	(n = 15): 3.09 (8.43)
	48 weeks (13 doses)	(n = 15): 2.81 (8.71)
Sussman et al. (2020):[59] omalizumab 300 mg		
UAS7 (Lower score is better)	Baseline	(n = 44): 30.27 (7.5)
	24 weeks (6 doses)	(n = 44): 1.14 (2.20)
	32 week (end of 8-week follow-up [withdrawal])	(n = 44): 28.30 (8.00)
	36 weeks (7 doses)	(n = 44): 6.19 (10.62)
	40 weeks (8 doses)	(n = 44): 3.84 (7.8)
	44 weeks (9 doses)	(n = 44): 2.3 (5.1)
	48 weeks (4-week posttreatment follow-up)	(n = 44): 11.86 (12.74)
UAS7 change score (Week 36 score – week 24 score) (Lower change score is better)	24 weeks to 36 weeks (3 additional doses)	(n = 41): −2.0 95% CI, −5.3 to 1.4
Chronic Urticaria Quality of Life questionnaire		
Olisova and Skander (2023):[48]omalizumab 300 mg		
CU-Q2oL score (Lower score is better)	Baseline (1 dose)	(n = 15): 55.06 (6.47)

Outcome measure	Time (dose)	Reported result: mean (SD) or %
	24 weeks (7 doses):	(n = 15): 83.53 (13.53)
	28 weeks (8 doses):	(n = 15): 83.53 (13.53)
	32 weeks (9 doses):	(n = 15): 83.12 (12.94)
	36 weeks (10 doses):	(n = 15): 83.71 (13.53)
	40 weeks (11 doses):	(n = 15): 83.71 (12.94)
	44 weeks (12 doses):	(n = 15): 83.71 (13.53)
	48 weeks (13 doses):	(n = 15): 83.71 (12.94)
Urticaria Control Test		
Olisova and Skander, (2023):[48] omalizumab 300 mg		
UCT score (Higher score is better)	Baseline (1 dose)	(n = 15): 8.19 (2.01)
	24 weeks (7 doses):	(n = 15): 14.23 (1.88)
	28 weeks (8 doses):	(n = 15): 14.23 (1.88)
	32 weeks (9 doses):	(n = 15): 14.23 (1.88)
	36 weeks (10 doses):	(n = 15): 14.23 (2.01)
	40 weeks (11 doses):	(n = 15): 14.23 (2.15)
	44 weeks (12 doses):	(n = 15): 14.23 (2.01)
	48 weeks (13 doses):	(n = 15): 14.23 (2.01)
Dermatology Life Quality Index		
Barbaud et al. (2020):[30] omalizumab 300 mg		
DLQI score (Lower score is better)	Baseline	11 (NR)
	52 weeks	1.77 (NR)
Olisova and Skander (2023):[48] omalizumab 300 mg		
DLQI score (Lower score is better)	Baseline (1 dose)	(n = 15): 16.05 (2.99)
	24 weeks (7 doses)	(n = 15): 3.70 (4.35)
	28 weeks (8 doses)	(n = 15): 3.25 (4.72)
	32 weeks (9 doses)	(n = 15): 3.73 (5.35)
	36 weeks (10 doses)	(n = 15): 3.43 (5.35)
	40 weeks (11 doses)	(n = 15): 3.44 (5.19)
	44 weeks (12 doses)	(n = 15): 3.30 (5.19)
	48 weeks (13 doses)	(n = 15): 3.31 (5.19)
Sussman et al. (2020):[59] omalizumab 300 mg		
DLQI, change score	Baseline to 36 weeks (6 to 9 doses)	(n = 44): −8.49 (7.42) (−55%)

Outcome measure	Time (dose)	Reported result: mean (SD) or %
Number of responders		
Barbaud et al. (2020):[30] omalizumab 300 mg		
Percent of patients whose symptoms were well controlled (UAS7 ≤ 6)	24 weeks	(n = 143) 68.9%
	52 weeks	(n = 140) 74.9%
Percent of patients whose symptoms were completely controlled (UAS7 = 0)	52 weeks	(n = 109) 58.3%
Percent of patients who were in remission	24 weeks	(n = 143) 77.8%
	52 weeks	(n = 109) 84.5%
Sussman et al. (2020):[59] omalizumab 300 mg		
Percent of patients whose symptoms were well controlled (UAS7 ≤ 6)	24 weeks (6 doses)	(n = 134) 65.7%
	36 weeks (9 doses)	(n = 37) 90.0%
Percent of patients who relapsed (UAS7 ≥ 16)	24 weeks (6 doses)	(n = 88) 50.0%
Time to relapse (UAS7 ≥ 16) in weeks	24 weeks (6 doses)	(n = 44): 4.7 (2.31)
Damiani et al. (2019):[38] omalizumab 300 mg		
Percent of patients whose symptoms were completely controlled (UAS7 = 0)	32 weeks	22.0%[a]
	36 weeks	43.0%
	40 weeks	46.2%
	44 weeks	58.4%
Percent of patients who were well controlled (UAS7 < 6)	32 weeks	47.0%
	36 weeks	33.0%
	40 weeks	38.0%
	44 weeks	2.5%
No or poor response (UAS7 > 27)	32 weeks	3.0%
	36 weeks	0%
	40 weeks	0%
	44 weeks	0%

CU2-QoL = Chronic Urticaria Quality of Life questionnaire; DLQI = Dermatology Life Quality Index; SD = standard deviation; UAS7 = 7-Day Urticaria Activity Score; UCT = Urticaria Control Test.

Safety Outcomes Reported in Single-Group Prospective Studies

The safety outcomes in the single-group prospective studies are presented in Table 22.

SAEs: SAEs were reported in only 1 study. Sussman et al. (2020)[43] reported that 2.5% of patients experienced an SAE. These estimates were based on patients who received 150 mg and 300 mg of omalizumab.

SAEs, anaphylaxis, and all-cause mortality: Two studies reported on specific types of SAEs, including anaphylaxis and all-cause mortality. Olisova and Skander (2023)[48] and Damiani et al. (2019)[38] reported no occurrences of anaphylaxis or all-cause mortality.

WDAEs: Two studies reported WDAEs. Olisova and Skander (2023)[48] reported no WDAEs; Sussman et al. (2020)[59] reported that 13 patients (4.1%) withdrew during treatment and that 1 patient (0.3%) withdrew during follow-up.

Table 22: Summary of Safety Outcomes Reported in the Single-Group Prospective Studies

Outcome measure	Reported result, n of N (%)
Serious adverse events	
Sussman et al. (2020)[43]	
Number of patients	Omalizumab 150 mg and 300 mg combined: 8 of 314 (2.5)
Severe adverse events (anaphylaxis or all-cause mortality)	
Olisova and Skander (2023)[48]	
Number of patients	Omalizumab 300 mg: 0 of 15 (0)
Damiani et al. (2019)[38]	
Number of patients	Omalizumab 300 mg: 0 of 15 (0)
Withdrawal due to adverse events	
Olisova and Skander (2023)[48]	
Number of patients	Omalizumab 300 mg: 0 of 15 (0)
Sussman et al. (2020)[59]	
Number of patients	Omalizumab 150 and 300 mg combined: 13 of 314 (4.1) during treatment 1 of 314 (0.32) during follow-up period

Summary of Critical Appraisal

Key Take-Aways

The included RCTs had a high RoB due to the discontinuation of study participants and the handling of missing data. The cohort studies had a serious to critical RoB due to potential selection bias, confounding, and the measurement of outcomes. The cohort studies also failed to account for variables that could distort the association between the studied treatments and health outcomes of interest.

Randomized Controlled Trials

We reported the RoB assessment for the RCTs in Table 23. Both of the included RCTs were assessed to be at a high overall RoB. There were some concerns with the randomization process in the X-ACT trial[54] due to a lack of information in the available reports regarding allocation and concealment procedures;

however, discontinuation of study participants and methods for handling missing outcome data were also a concern. Less than 80% of the patients in the omalizumab group and 62% of patients in the placebo group received all 7 doses as planned in the protocol. A total of 75.0% of patients who received omalizumab and 55.3% in the placebo group completed the follow-up. For patients who discontinued the trial early, the last observation carried forward (LOCF) was used for the primary end point and other outcomes. In the XTEND-CIU trial,[43] there were some concerns regarding a lack of information in the available reports regarding the randomization and allocation procedures, given the unexplained differences in group size and unclear reporting for some of the quantitative outcome data, which added uncertainty to the interpretation of the results. Approximately 48% of the placebo patients crossed over to the intervention group, and all efficacy analyses were performed using a modified intention-to-treat population. For continuous outcomes, an LOCF approach was used, but these methods should not be assumed to correct for any potential bias. It is unclear as to whether safety data were censored at the time of transition for patients who switched treatment.

Table 23: Risk of Bias Assessment for Randomized Controlled Trials

First author (year) Name of trial	Risk of bias domain[a]					Overall risk of bias
	Randomization	Deviation	Missing data	Measurement	Results selection	
Staubach et al. (2016) X-ACT trial[54]	Some	Low	High	Low	Low	High
Maurer et al. (2018) XTEND-CIU trial[43]	High	Some	Low	Some	Some	High

[a]Randomization: bias arising from the randomization process; Deviation: bias due to deviations from the intended intervention; Missing data: bias due to missing outcome data; Measurement: bias in the measurement of the outcome; Results selection: bias in the selection of the reported results.

Comparative Cohort Studies

We assessed the comparative cohort studies, comprising 1 prospective and 3 retrospective studies, using the ROBINS-I tool (Table 24). Among these studies, all of the reported results were unadjusted, so baseline and unmeasured confounding was a critical concern. All studies were assessed to have a serious RoB related to the measurement of outcomes. The interpretations of the domain level judgments are as follows: “low” means the study is comparable to a well-performed randomized trial; “moderate” means the study is sound for a nonrandomized study but cannot be considered comparable to a well-performed randomized trial; “serious” means the study has some important problems; and “critical” means the study is too problematic to provide any useful evidence on the effects of the intervention.[25] All studies had at least 1 important problem, and 2 of the studies[42,62] were assessed to have critical problems in at least 1 domain (and therefore were rated “critical” for RoB overall).

Table 24: Risk of Bias Assessment for Comparative Cohort Studies

First author (year)	Risk of bias domain							Overall risk of bias
	Confounding	Participant selection	Classification	Deviation	Missing data	Measurement	Results selection	
Khan et al. (2022)[19]	Critical	Low	Low	Low	Unclear	Serious	Low	Serious
Maurer et al. (2020)[42]	Critical	Serious	Unclear	Moderate	Critical	Serious	Low	Critical
Unsel (2021)[62]	Critical	Critical	Serious	Low	Low	Serious	Low	Critical
Seth (2017)[50]	Critical	Low	Low	Unclear	Low	Serious	Low	Serious

Notes: In the table headings, confounding refers to bias due to confounding; participant selection refers to bias in selection of participants; classification refers to bias in classification of interventions; deviation refers to bias due to deviations from intended interventions; missing data refers to bias due to missing data; measurement refers to bias in measurement of outcomes; and results selection refers to bias in selection of reported results.

Single-Group Prospective Studies

The group of patients receiving 300 mg of omalizumab in the OPTIMA trial[59] was considered as a single group for evidence synthesis; however, it was assessed for RoB as a complete RCT, including both 150 mg and 300 mg omalizumab arms (Table 25). We assessed the OPTIMA trial[59] to broadly have a low RoB; however, we could not rule out RoB associated with the measurement of outcomes due to a lack of information in the available reports.

We assessed the RoB for the other 3 single-group prospective studies using the JBI Critical Appraisal Checklist for Prevalence Studies (Table 26).[30,38,48] Assessment focused on items pertaining to the RoB (appropriateness of the sample frame or sampling, ascertainment of the exposure, and the outcome and response rate) rather than quality of reporting, generalizability, or statistical measures or sample size. A judgment of "no" indicated that the item under consideration was not handled appropriately or in a way that minimized RoB for the study. There were concerns in all studies over sampling procedures and adequacy of response rate,[30,38,48] as well as exposure ascertainment due to gaps in information in the study reports.

Table 25: Risk of Bias Assessment for Sussman et al. (OPTIMA Trial)

First author (year) Name of study	Risk of bias domain					Overall risk of bias
	Randomization	Deviation	Missing data	Measurement	Results selection	
Sussman et al. (2020) OPTIMA trial[59,a]	Low	Low	Low	Some	Low	Some

Notes: In the table headings, randomization refers to bias arising from the randomization process; deviation refers to bias due to deviations from the intended intervention; missing data refers to bias due to missing outcome data; measurement refers to bias in the measurement of the outcome; and results selection refers to bias in the selection of the reported results.

[a]This study was assessed as an RCT but contributed data for only 1 arm of omalizumab 300 mg.

Table 26: Risk of Bias Assessment for Single-Group Prospective Studies

First author (year)	Risk of bias assessment								
	Sample frame	Sampling	Sample size	Subjects and setting description	Data analysis coverage	Identification of condition	Measurement of condition	Statistics	Response rate
Barbaud et al. (2020)[30]	No	No	No	No	No	Yes	Unclear	No	No
Damiani et al. (2019)[38]	Yes	No	No	Yes	No	Unclear	Unclear	No	No
Olisova (2023)[48]	No	No	No	No	No	Yes	Unclear	Unclear	No

Notes: The table headings refer to the following questions:
Sample frame: Was the sample frame appropriate to address the target population?
Sampling: Were study participants sampled in an appropriate way?
Sample size: Was the sample size adequate?
Subjects and setting description: Were the study subjects and the setting described in detail?
Data analysis coverage: Was the data analysis conducted with sufficient coverage of the identified sample?
Identification of condition: Were valid methods used for the identification of the condition?
Measurement of condition: Was the condition measured in a standard, reliable way for all participants?
Statistics: Was there appropriate statistical analysis?
Response rate: Was the rate adequate, and if not, was the low response rate managed appropriately?

Discussion

Summary of Evidence

The aim of this systematic review was twofold: to determine the efficacy and effectiveness of long-term use of omalizumab in patients with CIU, and to establish whether extended use is safe for patients. The project scope was informed by engaging with clinical experts and decision-makers to better understand the considerations for treatment with omalizumab for longer than 24 weeks and the potential health system impacts. A total of 37 publications met the final inclusion criteria, and reported findings from 2 RCTs on the use of omalizumab or placebo (omalizumab 300 mg for up to 48 weeks) and 4 cohort studies comparing up to 2 years of treatment with omalizumab to other treatments (cyclosporine, HCQ, montelukast, updosed H_1 antihistamines) or no treatment. Efficacy or safety outcomes were all reported according to dosing regimens based on 300 mg of omalizumab every 4 weeks. No study reported outcomes for patients updosing from a 300 mg dose or who required more frequent dosing intervals.

Patients in all studies were eligible to receive omalizumab in the included studies if they had a history of inadequate response to H_1 antihistamines, except for 2 single, prospective cohort studies,[30,48] which did not use previous treatment experience as a criterion for patient entry or did not provide details for participants' treatment history. The ages of included participants were broadly greater than 12 years,[30,43,62] 18 years or

older,[42,48,50,54,59] or any age.[19,38] Based on the reported age range of study participants, patients were in their mid to low 40s, and 1 study noted the inclusion of a child aged 3 years.[19] Very few participant characteristics and comorbidities were reported outside of the RCTs, which included predominantly white women (> 70% of included participants). Duration of disease varied greatly across the study populations (6 weeks to 14 years) in studies that reported this information. Outside of the eligibility criteria, few details were available to assess patients' treatment history. In the studies that reported previous use of medications, H_1 antihistamines, steroids, and cyclosporine were more frequently noted, although details pertaining to dose, frequency, and duration were not available. Patients in the included studies are likely to be broadly generalizable to the current Canadian setting, although local differences in standard of care and access to health care where the studies were conducted may differ from Canadian guidelines.

Many analyses for efficacy and safety were not feasible owing to the paucity of data on outcomes of interest, heterogeneity in the studied treatments, and/or limitations in the study data. Analyses from included cohort studies did not consider confounding variables or otherwise adjust for imbalances in these factors across treatment groups. This may have led to biased estimation of omalizumab treatment effects. Readers should use extreme caution when reviewing and interpreting these results.

The RoB in the included RCTs was high due to discontinuation of study participants and handling of missing data in the study populations, which may be attributable to the open-label design used for all or part of the trial designs. The RoB across the included cohort studies ranged from serious to critical, with potential selection bias, confounding, and ascertainment of outcome data being the primary concerns. The overall limitation of the included cohort studies was failing to account for variables that could distort the association between the studied treatments and the health outcomes of interest.

Interpretation of Clinical Results

Key Take-Aways

Findings suggest extended treatment with omalizumab beyond the standard course of 24 weeks continues to provide symptom relief. Findings suggest that extended use of omalizumab does not increase the risk of severe adverse events compared to placebo, HCQ, or cyclosporine.

Changes in Urticaria Activity Following Long-Term Treatment With Omalizumab

Data on change in urticaria activity, as measured using the validated UAS7 instrument in response to omalizumab or placebo in CIU, were available from 2 RCTs collectively involving 225 patients up to 28 weeks and 48 weeks, respectively. Patients who had an extended or second full treatment course experienced a clinically meaningful change in their symptoms of CIU with 300 mg omalizumab compared to placebo (equivalent to a 9.5-point to 10.5-point reduction in UAS7). This may indicate that extended treatment may continue to provide symptom relief for individuals who experience an adequate response in a standard duration course of omalizumab, or who may require re-treatment with omalizumab upon relapse for patients who experienced an adequate response during the previous treatment course. Reductions in symptom relief were documented after treatment was stopped; however, improvements in symptoms remained and were

clinically meaningful. The XTEND CIU trial was well designed to compare extended omalizumab treatment to 48 weeks versus standard 24-week treatment. Although the XTEND CIU trial had an enrichment design, the appropriate comparison using trial data would be following randomization, and not 48 weeks versus 24 weeks as reported. However, the study outcomes were useful to compare long-term treatment in patients with CIU. The study groups were broadly similar at baseline and after treatment with omalizumab 300 mg for 24 weeks based on symptom and QoL outcomes; however, changes at week 48 provided information for what patients may experience when they continue or stop omalizumab treatment after 24 weeks.

Based on data from 1 prospective cohort study, fewer participants taking omalizumab had uncontrolled symptoms (UCT < 12) compared with updosed H_1 antihistamines at the end of month 24, which was statistically and clinically meaningful, but the number of intervention doses could not be confirmed. When compared to no treatment at month 24, there were no statistical or clinically meaningful differences in the proportion of participants with uncontrolled disease.

Changes in QoL Following Long-Term Treatment With Omalizumab

Based on data from the 2 included RCTs, meaningful changes in disease-specific (measured using the CU-Q2oL) and dermatologic QoL (measured using the DLQI) align with improvements observed with clinical symptoms. Changes were clinically meaningful based on assessments at week 28, and in 1 study, week 48. These important differences did subside, and reductions were not sustained following treatment discontinuation. In 1 trial, improvements in disease-specific QoL were still better than placebo, but differences were not sustained at a level that was clinically meaningful. No real-world or observational data on QoL were reported.

SAEs Following Long-Term Treatment With Omalizumab

There were no meaningful differences in the frequency of SAEs in 2 RCTs. No SAEs were documented in the cohort studies.

Strengths and Limitations of the Systematic Review

Strengths

We designed, implemented, and conducted a systematic review and meta-analysis following the best practices outlined in the Cochrane Handbook of Systematic Reviews of Interventions. The literature search was continuously updated to include the most recent studies published up to November 28, 2023. The systematic review included real-world evidence.

Limitations

Two main limitations of this report were the lack of identified clinical evidence for any key subgroups of interest and the varying clinical end point timing and instruments, which limited the analyses that could be conducted. Another limitation is the potential for confounding due to the inability to adjust for variables distorting associations between treatments and the outcomes of interest. Unadjusted results were reported in all of the cohort studies for all outcomes considered. Due to the paucity of data from RCTs and comparative cohort studies, this report considered data from single-group prospective studies reporting patient use of omalizumab. Although these data were presented in the interest of transparency to provide a

complete synthesis of the available evidence, we strongly recommend interpreting these results with caution. Although we conducted comprehensive searches for evidence, there were few primary studies eligible for inclusion. No formal evidence grading was used to assess the trustworthiness of the reported effects.

Conclusions and Implications for Decision- or Policy-Making

Key Take-Away

Based on studies described, there is some evidence that omalizumab remains effective after 24 weeks, and there was no indication of increased harm, but the studies had several limitations, as previously noted.

What Is the Efficacy and Safety of Omalizumab Used for Longer Than 24 Weeks in Patients With CIU?

To determine the efficacy, effectiveness, and safety of long-term use of omalizumab in patients with CIU, a systematic review of RCTs and real-world studies was undertaken. Two RCTs, 4 cohort studies, and 4 single-group studies were included in this review. No formal evidence grading was used to assess the trustworthiness of the reported effects.

The product monograph did not specify treatment duration or any stopping rules, but clinical practitioners are advised to periodically reassess the need for continued therapy. Efficacy data from 2 RCTs demonstrate that continued therapy with omalizumab is likely efficacious in patients with CIU who experience symptom relief during their initial course, and in those who require re-treatment for relapse following the end of their initial treatment. The 2 RCTs investigated the use of 300 mg omalizumab administered subcutaneously every 4 weeks or matching placebo in a group of patients with CIU whose symptoms were refractory to H_1 antihistamines. Treatment duration and follow-up in 1 RCT were 28 weeks and 36 weeks, and were 48 weeks and 60 weeks in the second RCT. Although the allocation procedures were poorly documented and attrition was high, there were no other substantial concerns over RoB.

In the limited data for safety collected from the studies included in this review, we may conclude that re-treatment with or long-term use of omalizumab does not put patients at increased risk of any additional severe harms, nor does it differ significantly from the known safety profile associated with a standard course of the drug. We cannot rule out rare and unexpected harms that the studies included in the current review were unlikely to capture.

Which Patients Are Most Likely to Benefit From Long-Term Treatment With Omalizumab?

Clinical populations in the X-ACT and XTEND-CIU trials are likely broadly comparable to populations in Canada.

Participants who show a meaningful difference in clinical outcomes up to 24 weeks are likely to benefit from continued treatment with omalizumab. When patients experience meaningful reductions in symptoms and gains in QoL, these benefits may wane when treatment is stopped, so re-treatment may be considered.

We did not give specific consideration to any clinically relevant subgroups for which there could be differential effectiveness; however, none of the studies reported population subgroups based on age, sex or gender, or important comorbidities. The X-ACT trial enrolled patients with CIU and angioedema, but no angioedema-specific clinical outcomes were considered in this review.

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Clinical Review

George A. Wells acted as the principal investigator by developing and leading the approach, and contributed to validation of the results, interpretation of the results, drafting, and finalizing the report.

Said Yousef Abdelrazeq contributed by screening studies; extracting data; analyzing and interpreting results, figures, and tables; verifying and assessing risk of bias; and drafting and revising the report.

Shariq Najeeb contributed by screening studies; extracting data; analyzing and interpreting results, figures, and tables; verifying and assessing risk of bias; and drafting and revising the report.

Shannon Kelly contributed to the conceptualization and design of the approach, provided research oversight, and contributed to the interpretation of results and drafting and finalizing the report.

Nazmun Nahar contributed by drafting tables and assisting with referencing of the report.

Melissa Brouwers contributed to the conceptualization and design of the approach and provided final approval of the report.

Research Information Science

Becky Skidmore designed and executed the literature search strategy, monitored search alerts, prepared the search methods section and appendix, and provided final approval of her sections of the report.

Contributors

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Conflicts of Interest

No conflicts of interest were declared.

Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Final Strategy; 2023 Mar 28

Ovid Multifile

Database: Embase Classic+Embase <1947 to 2023 March 27>, Ovid MEDLINE(R) ALL <1946 to March 27, 2023>, EBM Reviews - Cochrane Central Register of Controlled Trials <February 2023>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 22, 2023>

Search Strategy:

1. Omalizumab/ (13780)
2. (omalizumab or ct-p39 or ctp39 or fb 317 or fb317 or gbr 310 or gbr310 or hu 901 or hu901 or ige 25 or ige25 or “ige 025” or ige025 or olizumab$2 or rg 3648 or rg3648 or rhumab 25 or rhumab e25 or “sti 004” or sti004 or “syn 008” or syn008 or xolair$2 or 2p471x1z11 or 242138-07-4).tw,kw,kf,ot,hw,rn,nm. (16248)
3. ((anti-IgE or antiIgE) adj4 (antibod* or anti-bod*)).tw,kw,kf,ot. (3411)
4. Loratadine/ (8677)
5. (loratadine or aerotina$2 or alavert$2 or alerfast$2 or alernitis$2 or alerpriv$2 or alertadin$2 or alertrin$2 or allerta$2 or allertyn$2 or allohex$2 or ambrace$2 or analergal$2 or anhissen$2 or anlos$ or ardin$2 or biloina$2 or bonalerg$2 or caradine$2 or carin$2 or civeran$2 or clalodine$2 or claratyne$2 or clarid$2 or clarium$2 or claritin$2 or claritine$2 or clarityn$2 or clarityne$2 or cronitin$2 or cronopen$2 or curyken$2 or demazin$2 or ezasmin$2 or ezede$2 or finska$2 or frenaler$2 or fristamin$2 or genadine$2 or halodin$2 or hislorex$2 or histalor$2 or histaloran$2 or j-tadine$2 or klarihist$2 or klinset$2 or laredine$2 or lergia$2 or lertamine$2 or lesidas$2 or lindine$2 or lisino$2 or lobeta$2 or lodain$2 or lora-lich$2 or lora-tabs$2 or lorabasics$2 or loracert$2 or loraclar$2 or loraderm$2 or loradex$2 or loradif$2 or loradin$2 or lorahist$2 or loralerg$2 or lorano$2 or loranox$2 or lorantis$2 or lorapaed$2 or lorastine$2 or loratadura$2 or loratan$2 or loratazine$2 or loratidin$2 or loratidine$2 or loraton$2 or loratrim$2 or loratyne$2 or loraver$2 or loraxin$2 or loreen$2 or lorfast$2 or lorihis$2 or lorin$2 or lorita$2 or loritine$2 or lotadine$2 or lotarin$2 or lowadina$2 or mosedin$2 or noratin$2 or notamin$2 or nularef$2 or onemin$2 or optimin$2 or polaratyne$2 or proactin$2 or pylor$2 or restamine$2 or ridamin$2 or rihest$2 or rinityn$2 or rityne$2 or roletra$2 or rotifar$2 or sanelor$2 or sch-2985 or sch2985 or sch 29851 or sch29851 or sensibit$2 or sohotin$2 or tadine$2 or tidilor$2 or tirlor$2 or toradine$2 or velodan$2 or versal$2 or voratadine$2 or zeos$2 or 7AJO3BO7QN or 79794-75-5).tw,kw,kf,ot,hw,rn,nm. (357622)

6. (fexofenadine or allegra$2 or allegratab$2 or almerg$2 or fexallegra$2 or fexofenadin$2 or fexofenadine$2 or “m 016455” or m016455 or mdl 16455 or mdl16455 or mdl 16455a or mdl16455a or telfast$2 or treathay$2 or E6582LOH6V or 138452-21-8).tw,kw,kf,ot,hw,rn,nm. (7243)
7. (desloratadine or aerius$2 or alerdin$2 or aleric$2 or allex$2 or aviant$2 or azomyr$2 or claramax$2 or clarinex$2 or dasselta$2 or decarbethoxyloratadine$2 or denosin$2 or desalergo$2 or desalex$2 or descarboethoxyloratadine$2 or deslor$2 or escontral$2 or mk 4117 or mk4117 or neoclaritine$2 or neoclarityn$2 or opulis$2 or sch 34117 or sch34117 or sinalerg$2 or supraler$2 or FVF865388R or 100643-72-9 or 100643-71-8).tw,kw,kf,ot,hw,rn,nm. (4332)
8. Cetirizine/ (11114)
9. (cetirizine or ac 170 or ac170 or acidrine$2 or actifed allergie$2 or adezio$2 or agelmin$2 or alairgix$2 or alercet$2 or alerid$2 or alerlisin$2 or alertop$2 or alerviden$2 or aletir$2 or alled$2 or aller tec$2 or allertec$2 or alltec$2 or alzytec$2 or benaday$2 or benadryl$2 or betarhin$2 or cabal$2 or cerazine$2 or cerini$2 or cerotec$2 or cesta$2 or cetalerg$2 or ceterifug$2 or cethis$2 or ceti tab$2 or ceti-puren$2 or cetilich$2 or cetiderm$2 or cetidura$2 or cetil von ct $2 or cetimin$2 or cetin$2 or cetirigamma$2 or cetirax$2 or cetirin$2 or cetirizin$2 or cetirizina$2 or cetirizinum$2 or cetirlan$2 or cetizin$2 or cetrimed$2 or cetrine$2 or cetrizet$2 or cetrizin$2 or cetryn$2 or cetymin$2 or cistmine$2 or deallergy$2 or drill allergie$2 or falergi$2 or finallerg$2 or formistin$2 or generit$2 or histazine$2 or histica$2 or humex$2 or incidal-od$2 or jdp 205 or jdp205 or jdp 207 or jdp207 or lergium$2 or livoreactine$2 or nosemin$2 or nosmin$2 or ot 1001 or ot1001 or ozen$2 or “p 071” or p071 or piriteze allergy$2 or pollenase$2 or pollenshield$2 or prixlae$2 or quzyttir$2 or qzytir$2 or raingen$2 or razene$2 or reactine$2 or rhizin$2 or risima$2 or ritecam$2 or ryvel$2 or ryzen$2 or sancotec$2 or selitex$2 or setizin$2 or setir$2 or simtec$2 or sutac$2 or symitec$2 or terizin$2 or terizine$2 or vick-zyrt$2 or virlix$2 or voltric$2 or xarlin$2 or zenriz$2 or zensil$2 or zeran$2 or zertine$2 or zerviate$2 or zetir$2 or zicet$2 or zinex$2 or ziptek$2 or ziralton$2 or zirtec$2 or zirtek$2 or zirtin$2 or zyllergy$2 or zymed$2 or zyrac$2 or zyrazine$2 or zyrcon$2 or zyrlex$2 or zyrtec$2 of zyrtecset$2 or zyrtek$2 or YO7261ME24 or 64O047KTOA or 83881-51-0 or 83881-52-1). tw,kw,kf,ot,hw,rn,nm. (32708)
10. (levocetirizine or allerwet$2 or cetirmar$2 or levocetira$2 or levocetirizina$2 or levrix$2 or muntel$2 or novocetrin$2 or rinozal$2 or sopras$2 or vozet$2 or xarlin$2 or xazal$2 or xozal$2 or xusal$2 or xyzal$2 or xyzall$2 or 6U5EA9RT2O or SOD6A38AGA or W69HSF2416 or 130018-77-8 or 130018-77-8).tw,kw,kf,ot,hw,rn,nm. (3212)
11. exp Diphenhydramine/ (31209)
12. (diphenhydramine or alledryl$2 or allerdryl$2 or allergina$2 or amidryl$2 or antistominum$2 or antomin$2 or bagodryl$2 or banaril$2 or baramine$2 or beldin$2 or belix$2 or benachlor$2 or benadril$2 or benadrin$2 or benadryl$2 or benadyl$2 or benapon$2 or benhydramin$2 or benocten$2 or benodin$2 or benodine$2 or benylan$2 or benylin$2 or benzantine$2 or benzhydramine$2 or benzhydril$2 or betramin$2 or broncho d$2 or caladryl$2 or carphenamine$2 or carphenex$2

or cathejell$2 or compoz$2 or dabylen$2 or debendrin$2 or dermistina$2 or dermodrin$2 or desentol$2 or diabenyl$2 or diabylen$2 or dibadorm$2 or dibendrin$2 or dibenil$2 or dibondrin$2 or dibrondrin$2 or difedryl$2 or difenhydramin$2 or difenhydramine$2 or dihidral$2 or dimedrol$2 or dimedryl$2 or dimidril$2 or dimiril$2 or diphantine$2 or diphedryl$2 or diphen$2 or diphenacen$2 or diphendramine$2 or diphenhydramide$2 or diphenhydramin$2 or diphenydramine$2 or diphenylhydramin$2 or diphenylhydramine$2 or dobacen$2 or dormin$2 or dryhistan$2 or drylistan$2 or dylamon$2 or dytan$2 or emesan$2 or histaxin$2 or histergan$2 or hyadrine$2 or hydramine$2 or hyrexin$2 or ibiodral$2 or medidryl$2 or mephadryl$2 or nausen$2 or neosynodorm$2 or novamina$2 or nytol quickgels$2 or pm 255 or pm255 or probedryl$2 or q-dryl$2 or reisegold$2 or resmin$2 or restamin$2 or sediat$2 or sedryl$2 or silphen$2 or sleepeze$2 or sominex$2 or syntedril$2 or trux-adryl$2 or tzoali$2 or unisom sleepgels$2 or valdrene$2 or valu-dryl$2 or venasmin$2 or vertirosan$2 or “vicks formula 44” or vilbin$2 or wehdryl$2 or ziradryl$2 or 8GTS82S83M or 4OD433S209 or TC2D6JAD40 or 147-24-0 or 58-73-1 or 88637-37-0).tw,kw,kf,ot,hw,rn,nm. (130328)

13. Hydroxyzine/ (12113)

14. (hydroxyzine or abacus$2 or “ah3 n” or antizine$2 or arcanax$2 or atarax$2 or ataraxone$2 or aterax$2 or attarax$2 or bestalin$2 or bobsule$2 or centilax$2 or cerax$2 or darax$2 or disron$2 or dormirex$2 or durrax$2 or efidac$2 or hiderax$2 or hizin$2 or hydroxizine$2 o r hyzine$2 or idroxizina$2 or iremofar$2 or iterax$2 or novohydroxyzin$2 or orgatrax$2 or otarex$2 or paxistil$2 or phymorax$2 or postarax$2 or prurid$2 or qualidrozine$2 or quiess$2 or “r-rax” or “tran q” or trandozine$2 or tranquijust$2 or ucb 4492 or ucb4492 or ucerax$2 or unamine$2 or vistacot$2 or vistaject$2 or vistaril$2 or 30S50YM8OG or 76755771U3 or M20215MUFR or 10246-75-0 or 2192-20-3 or 68-88-2).tw,kw,kf,ot,hw,rn,nm. (14549)

15. Methotrexate/ (257024)

16. (methotrexate or “a methopterine” or abitextrate$2 or abitrexate$2 or “adx 2191” or adx2191 or amethopterin$2 or amethopterine$2 or ametopterine$2 or antifolan$2 or biotrexate$2 or brimexate$2 or canceren$2 or cl 14377 or cl14377 or emt 25299 or emt25299 or emtexate$2 or emthexat$2 or emthexate$2 or emtrexate$2 or enthexate$2 or farmitrexat$2 or farmitrexate$2 or farmotrex$2 or folex$2 or ifamet$2 or imeth$2 or intradose MTX or jylamvo$2 or lantarel$2 or ledertrexate$2 or lumexon$2 or maxtrex$2 or metatrexan$2 or metex$2 or methoblastin$2 or methohexate$2 or methotrate$2 or methotrexat$2 or methotrexate$2 or methotrexato$2 or methoxtrexate$2 or methrotrexate$2 or methylaminopterin$2 or methylaminopterine$2 or meticil$2 or metoject$2 or metothrexate$2 or metotrexat$2 or metotrexate$2 or metotrexin$2 or metrex$2 or metrotex$2 or mexate$2 or mpi 2505 or mpi2505 or mpi 5004 or mpi5004 or neotrexate$2 or nordimet$2 or novatrex$2 or nsc 740 or nsc740 or otrexup$2 or r 9985 or r9985 or rasuvo$2 or reditrex$2 or reumatrex$2 or rheumatrex$2 or texate$2 or texorate$2 or tremetex$2 or trexall$2 or trexeron$2 or wr 19039 or wr19039 or xaken$2 or xatmep$2 or zexate$2 or zlatal$2 or YL5FZ2Y5U1 or 3IG1E710ZN or 133073-73-1 or 15475-56-6 or 51865-79-3 or 59-05-2 or 60388-53-6 or 86669-44-5).tw,kw,kf,ot,hw,rn,nm. (291643)

17. Colchicine/ (55988)

18. (colchicine or aqua colchin$2 or colchichine$2 or colchicin$2 or colchicina$2 or colchicinum$2 or colchicum$2 or colchily$2 or colchimedio$2 or colchineos$2 or colchiquim$2 or colchisol$2 or colchysat$2 or colcin$2 or colcine$2 or colcrys$2 or colctab$2 or colgout$2 or colrefuz$2 or colsaloid$2 or colstat$2 or condylon$2 or gloperba$2 or goutichine$2 or goutnil$2 or kolkicin$2 or kolkisin$2 or mitigare$2 or “mpc 004” or mpc004 or myinfla$2 or tolchicine$2 or SML2Y3J35T or 54192-66-4 or 64-86-8 or 75520-89-7).tw,kw,kf,ot,hw,rn,nm. (69246)

19. Dapsone/ (26723)

20. (dapsone or aczone$2 or atrisone$2 or avlosulfan$2 or avlosulfon$2 or avlosulfone$2 or bn 2405 or bn2405 or croysulfone$2 or dapsoderm$2 or dapson$2 or dapsona$2 or diamino diphenyl sulfone$2 or diaminodiphenyl sulfone$2 or diaminodiphenylosulfone$2 or diaminodiphenylsulfon$2 or diaminodiphenylsulfone$2 or diammodiphenylsulfone$2 or diaphenyl sulfone$2 or diaphenylsulfon$2 or diaphenylsulfone$2 or diaphenylsulphone$2 or diphenason$2 or diphenasone$2 or diphone$2 or disulone$2 or dopsan$2 or dumitone$2 or eporal$2 or f 1358 or f1358 or lepravir$2 or novasulfon$2 or novophone$2 or servidapson$2 or servidapsone$2 or sulfadione$2 or sulfadoine$2 or sulfona$2 or sulfone mere$2 or udolac$2 or 8W5C518302 or 80-08-0).tw,kw,kf,ot,hw,rn,nm. (65909)

21. Indomethacin/ (112669)

22. (indomethacin or algiflam$2 or algometacin$2 or amuno$2 or antalgin dialicels$2 or areumatin$2 or argilex$2 or arthrexin$2 or articulen$2 or artracin$2 or artrilona$2 or artrinovo$2 or artrocid$2 or asimet$2 or benocid$2 or betacin$2 or bonidon$2 or boutycin$2 or catlep$2 or chrono indocid$2 or chronoindocid$2 or confortid$2 or docin$2 or dolazal$2 or dolazol$2 or dolcidium$2 or dometin$2 or durametacin$2 or elmego spray$2 or elmetacin$2 or endometacin$2 or flamaret$2 or flexin continus$2 or grindocin$2 or helvecin$2 or idicin$2 or im-75 or imbrilon$2 or imet$2 or inacid$2 or indacin$2 or indaflex$2 or indalgin$2 or inderapollon$2 or indicin$2 or indo phlogont$2 or indo-lemmon$2 or indo-tablinen$2 or indocap$2 or indocid$2 or indocin$2 or indocolir$2 or indocollyre$2 or indogesic$2 or indolag$2 or indolar$2 or indolemmon$2 or indomecin$2 or indomed$2 or indomee$2 or indomelan$2 or indomelol$2 or indomet$2 or indometacin$2 or indometacine$2 or indomethacin$2 or indomethacine$2 or indomethacinum$2 or indomethegan$2 or indometicina$2 or indometin$2 or indomexum$2 or indomin$2 or indono$2 or indoptic$2 or indoptol$2 or indorektal$2 or indorem$2 or indos$2 or indosan$2 or indosima$2 or indosmos$2 or indotard$2 or indovis$2 or indoxen$2 or indoy$2 or indren$2 or indrenin$2 or indylon$2 or inflazon$2 or inmetsin$2 or inteban$2 or lauzit$2 or luiflex$2 or malival$2 or mcn r 1166 or mcn r1166 or metacen$2 or methacin$2 or methindol$2 or methindole$2 or methocaps$2 or metindol$2 or mezolin$2 or miometacen$2 or mk 615 or mk615 or mobilan$2 or novomethacin$2 or osmogit$2 or osmosin$2 or reumacid$2 or reusin$2 or rheumacid$2 or rheumacin$2 or salinac$2 or servimeta$2 or sidocin$2 or tannex$2 or taye$2 or tivorbex$2 or vi-gel$2 or vonum$2 or XXE1CET956 or 104614-77-9 or 113560-66-0 or

125770-88-9 or 28811-31-6 or 28811-32-7 or 53-86-1 or 58201-41-5 or 62509-41-5 or 70938-94-2 or 74252-25-8 or 7681-54-1 or 86947-68-4 or 88170-06-3).tw,kw,kf,ot,hw,rn,nm. (144852)

23. Hydroxychloroquine/ (51372)

24. (hydrochloroquine or chloroquinol$2 or dolquine$2 or ercoquin$2 or hydroxychlorochin$2 or oxychlorochin$2 or oxychloroquine$2 or plaquenil$2 or polirreumin$2 or quensyl$2 or sn 8137 or sn8137 or tlc 19 tlc19 or win 1258 or win1258 or 4QWG6N8QKH or 8Q2869CNVH or 118-42-3 or 747-36-4).tw,kw,kf,ot,hw,rn,nm. (49493)

25. Doxepin/ (11097)

26. (doxepin or adapin$2 or anten$2 or aponal$2 or co dox$2 or curatin$2 or deptran$2 or desidox$2 or doneurin$2 or doxal$2 or doxepia$2 or doxepine$2 or expadox$2 or expan$2 or gilex$2 or mareen$2 or p 3693a or p3693a or prudoxin$2 or quitaxon$2 or silenor$2 or sinequan$2 or sinquan$2 or sinquane$2 or xepin$2 or zonalon$2).tw,kw,kf,ot,hw,rn,nm. (293600)

27. Capsaicin/ (35049)

28. (capsaicin or abc-pflaster$2 or adlea$2 or algrx 4975 or algrx4975 or axsain$2 or biozone$2 or capsaicine$2 or capsicaine$2 or capsicum$2 or capsidol$2 or capsig$2 or captrix$2 or capzasin$2 or casacine$2 or cgs 200 or cgs200 or cntx 4975 or cntx4975 or dolenon$2 or dolorac$2 or gelcen$2 or katrum$2 or ngx 1998 or ngx1998 or ngx 4010 or ngx4010 or qutenza$2 or styptysat$2 or transacin$2 or zacin$2 or zostrix$2 or S07O44R1ZM or 404-86-4).tw,kw,kf,ot,hw,rn,nm. (53646)

29. Ephedrine/ (22533)

30. (ephedrine or biophedrin$2 or eciphin$2 or efedra$2 or efedrin$2 or efedrine$2 or efidrin$2 or eggophedrin$2 or ephadrosan$2 or ephalone$2 or ephedra$2 or ephedral$2 or ephedrin$2 or ephedrosan$2 or ephedrosst$2 or et 203 or et203 or fedrin$2 or i sedrin$2 or kratedyn$2 or mandrin$2 or neo fedrin$2 or primatene$2 or rezipres$2 or sanedrin$2 or sanedrine$2 or zephrol$2 or GN83C131XS or NLJ6390P1Z or U6X61U5ZEG or 299-42-3).tw,kw,kf,ot,hw,rn,nm. (30351)

31. Famotidine/ (12533)

32. (famotidine or agufam$2 or amfamox$2 or antodine$2 or apogastine$2 or ausfam$2 or beilande$2 or bestidine$2 or blocacid$2 or brolin$2 or cepal$2 or durater$2 or ep 335 or ep335 or facid$2 or fadin$2 or fadine$2 or fadul$2 or fafotin$2 or famoabz$2 or famoc$2 or famocid$2 or famodar$2 or famodil$2 of famodin$2 or famodine$2 or famogal$2 or gamogard$2 or gamogast$2 or famohexal$2 or famolta$2 or famonerton$2 or famopril$2 or famopsin$2 or famos$2 or famosan$2 or famosia$2 or famotal$2 or famotep$2 or famotin$2 or famotine$2 or famowal$2 or famox$2 or famoxal$2 or fanox$2 or fararidin$2 or farmotex$2 or farotin$2 or ferotine$2 or fibonel$2 or fluxid$2 or foxadul$2 or fudone$2 or fuweidin$2 or ganor$2 or gardin$2 or gaster$2 or gastren$2 or gastridin$2 or gastrion$2 or gastro$2 or gastrodomina$2 or gastroflux$2 or h2 bloc or incifam$2 or kemofam$2 or kimodin$2 or l 643341 or l643341 or mk 208 or mk208 or motiax$2 or motidine$2

or pecidine$2 or pepcid$2 or pepcidin$2 or pepcidina$2 or pepcidine$2 or pepdif$2 or pepdine$2 or pepdul$2 or pepfamin$2 or peptan$2 or pepticon$2 or peptifam$2 or pepzan$2 or purifam$2 or quamatel$2 or quamtel$2 or rapitab$2 or restadin$2 or rogasti$2 or sedanium$2 or stadin$2 or stomax$2 or supertidine$2 or tamin$2 or topcid$2 or ulcatif$2 or ulcefam$2 or ulcelac$2 or ulcenol$2 or ulcetrax$2 or ulcofam$2 or ulcusan$2 or ulfadin$2 or ulfagel$2 or ulfam$2 or ulfamid$2 or ulped$2 or voker$2 or weimok$2 or winiful$2 or wiretin$2 or yamarin$2 or ym 11170 or ym11170 or 5QZO15J2Z8 or 108885-67-2 or 76824-35-6).tw,kw,kf,ot,hw,rn,nm. (112717)

33. (montelukast or actamone$2 or airathon$2 or aircast$2 or airing$2 or alvokast$2 or apilone$2 or ascafi$2 or ascolin$2 or asmenol$2 or asprevent$2 or astecon$2 or asthator$2 or asthmasan$2 or asthmont$2 or astmirex$2 or astmodil$2 or atentus$2 or atlabiclo$2 or belokast$2 or brolyt$2 or castispir$2 or chesmon$2 or deprive$2 or elukan$2 or elunkast$2 or eonic$2 or ephyra$2 or filkast$2 or fulmont$2 or imvlo$2 or ispyrra$2 or jepafex$2 or kipres$2 or l 706631 or l706631 or lanair$2 or leukast$2 or lukair$2 or lukanof$2 or lukas aiwa$2 or lukasm$2 or lukastang$2 or lukavent$2 or melarth$2 or metigreunul$2 or milukante$2 or mintalos$2 or miralust$2 or “mk 0476” or mk 476 or mk0476 or modrian$2 or modulair$2 or mofenstra$2 or mokast$2 or molucar$2 or monalux$2 or monart$2 or monast$2 or moncas$2 or mondeo$2 or monkasta$2 or monlast$2 or monlucare$2 or monspes$2 or monstonol$2 or montair$2 or montast$2 or montecell$2 or montecon$2 or montefar$2 or montegen$2 or montek$2 or montelair$2 or montelak$2 or montelar$2 or montelex$2 or montelax$2 or montelubronch$2 or montelucaste$2 or montelukast$2 or montelukaste$2 or montelukastteva$2 or montelukastum$2 or montelukasturn$2 or montelux$2 or montemyl$2 or montep$2 or monterast$2 or monteresp$2 or montespir$2 or montewin$2 or montexal$2 or monthan$2 or montol$2 or montul$2 or montus$2 or moolpas$2 or nal 6336 or nal6336 or orilukast$2 or otelus$2 or pentafeno$2 or perasm$2 or pluralais$2 or pneumo-kast$2 or promonta$2 or rasec$2 or relukas$2 or respilukas$2 or romilast$2 or saslong$2 or singodem$2 or singulair$2 or singulergy$2 or solok$2 or spirokast$2 or spiromon$2 or stangen$2 or surfair$2 or symlukast$2 or telelux$2 or telukast$2 or teluki$2 or tevalukast$2 or thordel$2 or valnuen$2 or velukast$2 or xaira$2 or yekast$2 or zakomoxit$2 or MHM278SD3E or U1O3J18SFL or 158966-92-8). tw,kw,kf,ot,hw,rn,nm. (98508)

34. (zafirlukast or accolate$2 or accoleit$2 or aeronix$2 or ici 204219 or ici204219 or olmoran$2 or respix$2 or vanticon$2 or zafirst$2 or zuvair$2 or XZ629S5L50 or 107753-78-6). tw,kw,kf,ot,hw,rn,nm. (3687)

35. Nizatidine/ (2709)

36. (nizatidine or acinon$2 or actidine$2 or antizid$2 or axadine$2 or axid$2 or calmaxid$2 or cronizat$2 or distaxid$2 or dixtasid$2 or gastrax$2 or jadin$2 or ly 139037 or ly139037 or nacid$2 or naxidine$2 or nixaxid$2 or nizax$2 or panaxid$2 or tazac$2 or tinza$2 or ulxit$2 or zanitidine$2 or zanitin$2 or zanizal$2 or zatidine$2 or zinga$2 or zl 101 or zl101 or P41PML4GHR or 76963-41-2). tw,kw,kf,ot,hw,rn,nm. (10794)

37. Ranitidine/ (33927)
38. (ranitidine or achedos$2 or acidex$2 or aciloc$2 or acloral$2 or acran$2 or ah 19065 or ah19065 or aldin$2 or alquen$2 or anistal$2 or antagonin$2 or ardoral$2 or atural$2 or ausran$2 or avintac$2 or axoban$2 or azantac$2 or baroxal$2 or biotidin$2 or consec$2 or coralen$2 or cygran$2 or d 14951 or d14951 or duractin$2 or eltidine$2 or eu-ran$2 or ezopta$2 or galidrin$2 or gastran$2 or gastrial$2 or gastridina$2 or gastrosedol$2 or hexer$2 or histac$2 or histak$2 or hyzan$2 or incid$2 or istomar$2 or iqfadina$2 or kemoranin$2 or kiradin$2 or logast$2 or lumaren$2 or lydin$2 or mauran$2 or microtid$2 or midaven$2 or nadine$2 or neoceptin$2 or pilorex$2 or ponaltin$2 or ptinolin$2 or quantor$2 or quicran$2 or r-loc$2 or radinat$2 or radine$2 or rafitaz$2 or ranacid$2 or rancet$2 or randin$2 or “rani 2” or ranial$2 or raniben$2 or ranibloc$2 or ranicalm$2 or ranidil$2 or ranidine$2 or ranidura$2 or ranigast$2 or ranihexal$2 or ranimex$2 or ranin$2 or raniogas$2 or raniplex$2 or ranisan$2 or ranisen$2 or ranitab$2 or ranital$2 or ranitax$2 or raniter$2 or ranitidin$2 or ranitidina$2 or ranitil$2 or ranitin$2 or ranitine$2 or ranolta$2 or rantac$2 or rantacid$2 or rantin$2 or ranuber$2 or ranzac$2 or ratic$2 or raticina$2 or raxide$2 or retamin$2 or rolan$2 or rosimol$2 or sampep$2 or simetac$2 or sostril$2 or tanidina$2 or taural$2 or terodul$2 or toriol$2 or ulcaid$2 or ulceran$2 or ulcex$2 or ulcin$2 or ulcocur$2 or ulsal$2 or ultak$2 or ultidine$2 or urantac$2 or verlost$2 or vesyca$2 or vizerul$2 or weichilin$2 or weidos$2 or xanidine$2 or zantab$2 or zantac$2 or zantadin$2 or zantic$2 or zinetac$2 or 884KT10YB7 or BK76465IHM or 66357-35-5 or 66357-59-3).tw,kw,kf,ot,hw,rn,nm. (53625)
39. or/1-38 [OMALIZUMAB + OTHER DRUGS OF INTEREST] (1741865)
40. Chronic Urticaria/ (7634)
41. Urticaria/ and Chronic Disease/ (3753)
42. ((idiopathic* or spontaneous*) adj2 urticaria*).tw,kw,kf. (7343)
43. (CIU adj1 CSU).tw,kw,kf. (209)
44. ((CIU or CSU) adj6 urticaria*).tw,kw,kf. (3481)
45. ((autoimmun* or auto-immun*) adj2 urticaria*).tw,kw,kf. (787)
46. or/40-45 [CHRONIC SPONTANEOUS URTICARIA] (14185)
47. 39 and 46 [OMALIZUMAB + OTHER DRUGS - CHRONIC SPONTANEOUS URTICARIA] (6023)
48. exp Animals/ not Humans/ (17567483)
49. 47 not 48 [ANIMAL-ONLY REMOVED] (4910)
50. (editorial or news or newspaper article).pt. (1651561)
51. 49 not 50 [OPINION PIECES REMOVED] (4841)

52. (exp Child/ or exp Infant/) not (exp Adult/ or Adolescent/) (3594454)
53. 51 not 52 [CHILD-, INFANT-ONLY REMOVED] (4671)
54. limit 53 to yr="2005-current" [DATE LIMIT APPLIED] (3709)
55. 54 use medall [MEDLINE RECORDS] (1090)
56. omalizumab/ (13780)
57. (omalizumab or ct-p39 or ctp39 or fb 317 or fb317 or gbr 310 or gbr310 or hu 901 or hu901 or ige 25 or ige25 or "ige 025" or ige025 or olizumab$2 or rg 3648 or rg3648 or rhumab 25 or rhumab e25 or "sti 004" or sti004 or "syn 008" or syn008 or xolair$2 or 2p471x1z11 or 242138-07-4).tw,kw,kf,ot,hw,rn. (16248)
58. ((anti-IgE or antiIgE) adj4 (antibod* or anti-bod*)).tw,kw,kf,ot. (3411)
59. loratadine/ (8677)
60. (loratadine or aerotina$2 or alavert$2 or alerfast$2 or alernitis$2 or alerpriv$2 or alertadin$2 or alertrin$2 or allerta$2 or allertyn$2 or allohex$2 or ambrace$2 or analergal$2 or anhissen$2 or anlos$ or ardin$2 or biloina$2 or bonalerg$2 or caradine$2 or carin$2 or civeran$2 or clalodine$2 or claratyne$2 or clarid$2 or clarium$2 or claritin$2 or claritine$2 or clarityn$2 or clarityne$2 or cronitin$2 or cronopen$2 or curyken$2 or demazin$2 or ezasmin$2 or ezede$2 or finska$2 or frenaler$2 or fristamin$2 or genadine$2 or halodin$2 or hislorex$2 or histalor$2 or histaloran$2 or j-tadine$2 or klarihist$2 or klinset$2 or laredine$2 or lergia$2 or lertamine$2 or lesidas$2 or lindine$2 or lisino$2 or lobeta$2 or lodain$2 or lora-lich$2 or lora-tabs$2 or lorabasics$2 or loracert$2 or loraclar$2 or loraderm$2 or loradex$2 or loradif$2 or loradin$2 or lorahist$2 or loralerg$2 or lorano$2 or loranox$2 or lorantis$2 or lorapaed$2 or lorastine$2 or loratadura$2 or loratan$2 or loratazine$2 or loratidin$2 or loratidine$2 or loraton$2 or loratrim$2 or loratyne$2 or loraver$2 or loraxin$2 or loreen$2 or lorfast$2 or lorihis$2 or lorin$2 or lorita$2 or loritine$2 or lotadine$2 or lotarin$2 or lowadina$2 or mosedin$2 or noratin$2 or notamin$2 or nularef$2 or onemin$2 or optimin$2 or polaratyne$2 or proactin$2 or pylor$2 or restamine$2 or ridamin$2 or rihest$2 or rinityn$2 or rityne$2 or roletra$2 or rotifar$2 or sanelor$2 or sch-2985 or sch2985 or sch 29851 or sch29851 or sensibit$2 or sohotin$2 or tadine$2 or tidilor$2 or tirlor$2 or toradine$2 or velodan$2 or versal$2 or voratadine$2 or zeos$2 or 7AJO3BO7QN or 79794-75-5).tw,kw,kf,ot,hw,rn. (357578)
61. fexofenadine/ (5072)
62. (fexofenadine or allegra$2 or allegratab$2 or almerg$2 or fexallegra$2 or fexofenadin$2 or fexofenadine$2 or "m 016455" or m016455 or mdl 16455 or mdl16455 or mdl 16455a or mdl16455a or telfast$2 or treathay$2 or E6582LOH6V or 138452-21-8).tw,kw,kf,ot,hw,rn. (7243)
63. desloratadine/ (2786)

64. (desloratadine or aerius$2 or alerdin$2 or aleric$2 or allex$2 or aviant$2 or azomyr$2 or claramax$2 or clarinex$2 or dasselta$2 or decarbethoxyloratadine$2 or denosin$2 or desalergo$2 or desalex$2 or descarboethoxyloratadine$2 or deslor$2 or escontral$2 or mk 4117 or mk4117 or neoclaritine$2 or neoclarityn$2 or opulis$2 or sch 34117 or sch34117 or sinalerg$2 or supraler$2 or FVF865388R or 100643-72-9 or 100643-71-8).tw,kw,kf,ot,hw,rn. (4332)

65. cetirizine/ (11114)

66. (cetirizine or ac 170 or ac170 or acidrine$2 or actifed allergie$2 or adezio$2 or agelmin$2 or alairgix$2 or alercet$2 or alerid$2 or alerlisin$2 or alertop$2 or alerviden$2 or aletir$2 or alled$2 or aller tec$2 or allertec$2 or alltec$2 or alzytec$2 or benaday$2 or benadryl$2 or betarhin$2 or cabal$2 or cerazine$2 or cerini$2 or cerotec$2 or cesta$2 or cetalerg$2 or ceterifug$2 or cethis$2 or ceti tab$2 or ceti-puren$2 or cetilich$2 or cetiderm$2 or cetidura$2 or cetil von ct $2 or cetimin$2 or cetin$2 or cetirigamma$2 or cetirax$2 or cetirin$2 or cetirizin$2 or cetirizina$2 or cetirizinum$2 or cetirlan$2 or cetizin$2 or cetrimed$2 or cetrine$2 or cetrizet$2 or cetrizin$2 or cetryn$2 or cetymin$2 or cistmine$2 or deallergy$2 or drill allergie$2 or falergi$2 or finallerg$2 or formistin$2 or generit$2 or histazine$2 or histica$2 or humex$2 or incidal-od$2 or jdp 205 or jdp205 or jdp 207 or jdp207 or lergium$2 or livoreactine$2 or nosemin$2 or nosmin$2 or ot 1001 or ot1001 or ozen$2 or “p 071” or p071 or piriteze allergy$2 or pollenase$2 or pollenshield$2 or prixlae$2 or quzyttir$2 or qzytir$2 or raingen$2 or razene$2 or reactine$2 or rhizin$2 or risima$2 or ritecam$2 or ryvel$2 or ryzen$2 or sancotec$2 or selitex$2 or setizin$2 or setir$2 or simtec$2 or sutac$2 or symitec$2 or terizin$2 or terizine$2 or vick-zyrt$2 or virlix$2 or voltric$2 or xarlin$2 or zenriz$2 or zensil$2 or zeran$2 or zertine$2 or zerviate$2 or zetir$2 or zicet$2 or zinex$2 or ziptek$2 or ziralton$2 or zirtec$2 or zirtek$2 or zirtin$2 or zyllergy$2 or zymed$2 or zyrac$2 or zyrazine$2 or zyrcon$2 or zyrlex$2 or zyrtec$2 of zyrtecset$2 or zyrtek$2 or YO7261ME24 or 64O047KTOA or 83881-51-0 or 83881-52-1). tw,kw,kf,ot,hw,rn. (32708)

67. levocetirizine/ (2282)

68. (levocetirizine or allerwet$2 or cetirmar$2 or levocetira$2 or levocetirizina$2 or levrix$2 or muntel$2 or novocetrin$2 or rinozal$2 or sopras$2 or vozet$2 or xarlin$2 or xazal$2 or xozal$2 or xusal$2 or xyzal$2 or xyzall$2 or 6U5EA9RT2O or SOD6A38AGA or W69HSF2416 or 130018-77-8 or 130018-77-8).tw,kw,kf,ot,hw,rn. (3212)

69. diphenhydramine/ (30625)

70. (diphenhydramine or alledryl$2 or allerdryl$2 or allergina$2 or amidryl$2 or antistominum$2 or antomin$2 or bagodryl$2 or banaril$2 or baramine$2 or beldin$2 or belix$2 or benachlor$2 or benadril$2 or benadrin$2 or benadryl$2 or benadyl$2 or benapon$2 or benhydramin$2 or benocten$2 or benodin$2 or benodine$2 or benylan$2 or benylin$2 or benzantine$2 or benzhydramine$2 or benzhydril$2 or betramin$2 or broncho d$2 or caladryl$2 or carphenamine$2 or carphenex$2 or cathejell$2 or compoz$2 or dabylen$2 or debendrin$2 or dermistina$2 or dermodrin$2 or desentol$2 or diabenyl$2 or diabylen$2 or dibadorm$2 or dibendrin$2 or dibenil$2 or dibondrin$2 or

dibrondrin$2 or difedryl$2 or difenhydramin$2 or difenhydramine$2 or dihidral$2 or dimedrol$2 or dimedryl$2 or dimidril$2 or dimiril$2 or diphantine$2 or diphedryl$2 or diphen$2 or diphenacen$2 or diphendramine$2 or diphenhydramide$2 or diphenhydramin$2 or diphenydramine$2 or diphenylhydramin$2 or diphenylhydramine$2 or dobacen$2 or dormin$2 or dryhistan$2 or drylistan$2 or dylamon$2 or dytan$2 or emesan$2 or histaxin$2 or histergan$2 or hyadrine$2 or hydramine$2 or hyrexin$2 or ibiodral$2 or medidryl$2 or mephadryl$2 or nausen$2 or neosynodorm$2 or novamina$2 or nytol quickgels$2 or pm 255 or pm255 or probedryl$2 or q-dryl$2 or reisegold$2 or resmin$2 or restamin$2 or sediat$2 or sedryl$2 or silphen$2 or sleepeze$2 or sominex$2 or syntedril$2 or trux-adryl$2 or tzoali$2 or unisom sleepgels$2 or valdrene$2 or valu-dryl$2 or venasmin$2 or vertirosan$2 or “vicks formula 44” or vilbin$2 or wehdryl$2 or ziradryl$2 or 8GTS82S83M or 4OD433S209 or TC2D6JAD40 or 147-24-0 or 58-73-1 or 88637-37-0).tw,kw,kf,ot,hw,rn. (126431)

71. hydroxyzine/ (12113)

72. (hydroxyzine or abacus$2 or “ah3 n” or antizine$2 or arcanax$2 or atarax$2 or ataraxone$2 or aterax$2 or attarax$2 or bestalin$2 or bobsule$2 or centilax$2 or cerax$2 or darax$2 or disron$2 or dormirex$2 or durrax$2 or efidac$2 or hiderax$2 or hizin$2 or hydroxizine$2 o r hyzine$2 or idroxizina$2 or iremofar$2 or iterax$2 or novohydroxyzin$2 or orgatrax$2 or otarex$2 or paxistil$2 or phymorax$2 or postarax$2 or prurid$2 or qualidrozine$2 or quiess$2 or “r-rax” or “tran q” or trandozine$2 or tranquijust$2 or ucb 4492 or ucb4492 or ucerax$2 or unamine$2 or vistacot$2 or vistaject$2 or vistaril$2 or 30S50YM8OG or 76755771U3 or M20215MUFR or 10246-75-0 or 2192-20-3 or 68-88-2).tw,kw,kf,ot,hw,rn. (14549)

73. methotrexate/ (257024)

74. (methotrexate or “a methopterine” or abitextrate$2 or abitrexate$2 or “adx 2191” or adx2191 or amethopterin$2 or amethopterine$2 or ametopterine$2 or antifolan$2 or biotrexate$2 or brimexate$2 or canceren$2 or cl 14377 or cl14377 or emt 25299 or emt25299 or emtexate$2 or emthexat$2 or emthexate$2 or emtrexate$2 or enthexate$2 or farmitrexat$2 or farmitrexate$2 or farmotrex$2 or folex$2 or ifamet$2 or imeth$2 or intradose MTX or jylamvo$2 or lantarel$2 or ledertrexate$2 or lumexon$2 or maxtrex$2 or metatrexan$2 or metex$2 or methoblastin$2 or methohexate$2 or methotrate$2 or methotrexat$2 or methotrexate$2 or methotrexato$2 or methoxtrexate$2 or methrotrexate$2 or methylaminopterin$2 or methylaminopterine$2 or meticil$2 or metoject$2 or metothrexate$2 or metotrexat$2 or metotrexate$2 or metotrexin$2 or metrex$2 or metrotex$2 or mexate$2 or mpi 2505 or mpi2505 or mpi 5004 or mpi5004 or neotrexate$2 or nordimet$2 or novatrex$2 or nsc 740 or nsc740 or otrexup$2 or r 9985 or r9985 or rasuvo$2 or reditrex$2 or reumatrex$2 or rheumatrex$2 or texate$2 or texorate$2 or tremetex$2 or trexall$2 or trexeron$2 or wr 19039 or wr19039 or xaken$2 or xatmep$2 or zexate$2 or zlatal$2 or YL5FZ2Y5U1 or 3IG1E710ZN or 133073-73-1 or 15475-56-6 or 51865-79-3 or 59-05-2 or 60388-53-6 or 86669-44-5).tw,kw,kf,ot,hw,rn. (291642)

75. colchicine/ (55988)

76. (colchicine or aqua colchin$2 or colchichine$2 or colchicin$2 or colchicina$2 or colchicinum$2 or colchicum$2 or colchily$2 or colchimedio$2 or colchineos$2 or colchiquim$2 or colchisol$2 or colchysat$2 or colcin$2 or colcine$2 or colcrys$2 or colctab$2 or colgout$2 or colrefuz$2 or colsaloid$2 or colstat$2 or condylon$2 or gloperba$2 or goutichine$2 or goutnil$2 or kolkicin$2 or kolkisin$2 or mitigare$2 or “mpc 004” or mpc004 or myinfla$2 or tolchicine$2 or SML2Y3J35T or 54192-66-4 or 64-86-8 or 75520-89-7).tw,kw,kf,ot,hw,rn. (69246)

77. dapsone/ (26723)

78. (dapsone or aczone$2 or atrisone$2 or avlosulfan$2 or avlosulfon$2 or avlosulfone$2 or bn 2405 or bn2405 or croysulfone$2 or dapsoderm$2 or dapson$2 or dapsona$2 or diamino diphenyl sulfone$2 or diaminodiphenyl sulfone$2 or diaminodiphenylosulfone$2 or diaminodiphenylsulfon$2 or diaminodiphenylsulfone$2 or diammodiphenylsulfone$2 or diaphenyl sulfone$2 or diaphenylsulfon$2 or diaphenylsulfone$2 or diaphenylsulphone$2 or diphenason$2 or diphenasone$2 or diphone$2 or disulone$2 or dopsan$2 or dumitone$2 or eporal$2 or f 1358 or f1358 or lepravir$2 or novasulfon$2 or novophone$2 or servidapson$2 or servidapsone$2 or sulfadione$2 or sulfadoine$2 or sulfona$2 or sulfone mere$2 or udolac$2 or 8W5C518302 or 80-08-0).tw,kw,kf,ot,hw,rn. (65115)

79. indomethacin/ (112669)

80. (indomethacin or algiflam$2 or algometacin$2 or amuno$2 or antalgin dialicels$2 or areumatin$2 or argilex$2 or arthrexin$2 or articulen$2 or artracin$2 or artrilona$2 or artrinovo$2 or artrocid$2 or asimet$2 or benocid$2 or betacin$2 or bonidon$2 or boutycin$2 or catlep$2 or chrono indocid$2 or chronoindocid$2 or confortid$2 or docin$2 or dolazal$2 or dolazol$2 or dolcidium$2 or dometin$2 or durametacin$2 or elmego spray$2 or elmetacin$2 or endometacin$2 or flamaret$2 or flexin continus$2 or grindocin$2 or helvecin$2 or idicin$2 or im-75 or imbrilon$2 or imet$2 or inacid$2 or indacin$2 or indaflex$2 or indalgin$2 or inderapollon$2 or indicin$2 or indo phlogont$2 or indo-lemmon$2 or indo-tablinen$2 or indocap$2 or indocid$2 or indocin$2 or indocolir$2 or indocollyre$2 or indogesic$2 or indolag$2 or indolar$2 or indolemmon$2 or indomecin$2 or indomed$2 or indomee$2 or indomelan$2 or indomelol$2 or indomet$2 or indometacin$2 or indometacine$2 or indomethacin$2 or indomethacine$2 or indomethacinum$2 or indomethegan$2 or indometicina$2 or indometin$2 or indomexum$2 or indomin$2 or indono$2 or indoptic$2 or indoptol$2 or indorektal$2 or indorem$2 or indos$2 or indosan$2 or indosima$2 or indosmos$2 or indotard$2 or indovis$2 or indoxen$2 or indoy$2 or indren$2 or indrenin$2 or indylon$2 or inflazon$2 or inmetsin$2 or inteban$2 or lauzit$2 or luiflex$2 or malival$2 or mcn r 1166 or mcn r1166 or metacen$2 or methacin$2 or methindol$2 or methindole$2 or methocaps$2 or metindol$2 or mezolin$2 or miometacen$2 or mk 615 or mk615 or mobilan$2 or novomethacin$2 or osmogit$2 or osmosin$2 or reumacid$2 or reusin$2 or rheumacid$2 or rheumacin$2 or salinac$2 or servimeta$2 or sidocin$2 or tannex$2 or taye$2 or tivorbex$2 or vi-gel$2 or vonum$2 or XXE1CET956 or 104614-77-9 or 113560-66-0 or 125770-88-9 or 28811-31-6 or 28811-32-7 or 53-86-1 or 58201-41-5 or 62509-41-5 or 70938-94-2 or 74252-25-8 or 7681-54-1 or 86947-68-4 or 88170-06-3).tw,kw,kf,ot,hw,rn. (144838)

81. hydroxychloroquine/ (51372)

82. (hydrochloroquine or chloroquinol$2 or dolquine$2 or ercoquin$2 or hydroxychlorochin$2 or oxychlorochin$2 or oxychloroquine$2 or plaquenil$2 or polirreumin$2 or quensyl$2 or sn 8137 or sn8137 or tlc 19 tlc19 or win 1258 or win1258 or 4QWG6N8QKH or 8Q2869CNVH or 118-42-3 or 747-36-4).tw,kw,kf,ot,hw,rn. (49476)

83. doxepin/ (11097)

84. (doxepin or adapin$2 or anten$2 or aponal$2 or co dox$2 or curatin$2 or deptran$2 or desidox$2 or doneurin$2 or doxal$2 or doxepia$2 or doxepine$2 or expadox$2 or expan$2 or gilex$2 or mareen$2 or p 3693a or p3693a or prudoxin$2 or quitaxon$2 or silenor$2 or sinequan$2 or sinquan$2 or sinquane$2 or xepin$2 or zonalon$2).tw,kw,kf,ot,hw,rn. (293597)

85. capsaicin/ (35049)

86. (capsaicin or abc-pflaster$2 or adlea$2 or algrx 4975 or algrx4975 or axsain$2 or biozone$2 or capsaicine$2 or capsicaine$2 or capsicum$2 or capsidol$2 or capsig$2 or captrix$2 or capzasin$2 or casacine$2 or cgs 200 or cgs200 or cntx 4975 or cntx4975 or dolenon$2 or dolorac$2 or gelcen$2 or katrum$2 or ngx 1998 or ngx1998 or ngx 4010 or ngx4010 or qutenza$2 or styptysat$2 or transacin$2 or zacin$2 or zostrix$2 or S07O44R1ZM or 404-86-4).tw,kw,kf,ot,hw,rn. (53632)

87. ephedrine/ (22533)

88. (ephedrine or biophedrin$2 or eciphin$2 or efedra$2 or efedrin$2 or efedrine$2 or efidrin$2 or eggophedrin$2 or ephadrosan$2 or ephalone$2 or ephedra$2 or ephedral$2 or ephedrin$2 or ephedrosan$2 or ephedrosst$2 or et 203 or et203 or fedrin$2 or i sedrin$2 or kratedyn$2 or mandrin$2 or neo fedrin$2 or primatene$2 or rezipres$2 or sanedrin$2 or sanedrine$2 or zephrol$2 or GN83C131XS or NLJ6390P1Z or U6X61U5ZEG or 299-42-3).tw,kw,kf,ot,hw,rn. (30351)

89. famotidine/ (12533)

90. (famotidine or agufam$2 or amfamox$2 or antodine$2 or apogastine$2 or ausfam$2 or beilande$2 or bestidine$2 or blocacid$2 or brolin$2 or cepal$2 or durater$2 or ep 335 or ep335 or facid$2 or fadin$2 or fadine$2 or fadul$2 or fafotin$2 or famoabz$2 or famoc$2 or famocid$2 or famodar$2 or famodil$2 of famodin$2 or famodine$2 or famogal$2 or gamogard$2 or gamogast$2 or famohexal$2 or famolta$2 or famonerton$2 or famopril$2 or famopsin$2 or famos$2 or famosan$2 or famosia$2 or famotal$2 or famotep$2 or famotin$2 or famotine$2 or famowal$2 or famox$2 or famoxal$2 or fanox$2 or fararidin$2 or farmotex$2 or farotin$2 or ferotine$2 or fibonel$2 or fluxid$2 or foxadul$2 or fudone$2 or fuweidin$2 or ganor$2 or gardin$2 or gaster$2 or gastren$2 or gastridin$2 or gastrion$2 or gastro$2 or gastrodomina$2 or gastroflux$2 or h2 bloc or incifam$2 or kemofam$2 or kimodin$2 or l 643341 or l643341 or mk 208 or mk208 or motiax$2 or motidine$2 or pecidine$2 or pepcid$2 or pepcidin$2 or pepcidina$2 or pepcidine$2 or pepdif$2 or pepdine$2 or pepdul$2 or pepfamin$2 or peptan$2 or pepticon$2 or peptifam$2 or pepzan$2 or purifam$2

or quamatel$2 or quamtel$2 or rapitab$2 or restadin$2 or rogasti$2 or sedanium$2 or stadin$2 or stomax$2 or supertidine$2 or tamin$2 or topcid$2 or ulcatif$2 or ulcefam$2 or ulcelac$2 or ulcenol$2 or ulcetrax$2 or ulcofam$2 or ulcusan$2 or ulfadin$2 or ulfagel$2 or ulfam$2 or ulfamid$2 or ulped$2 or voker$2 or weimok$2 or winiful$2 or wiretin$2 or yamarin$2 or ym 11170 or ym11170 or 5QZO15J2Z8 or 108885-67-2 or 76824-35-6).tw,kw,kf,ot,hw,rn. (112680)

91. montelukast/ (11626)

92. (montelukast or actamone$2 or airathon$2 or aircast$2 or airing$2 or alvokast$2 or apilone$2 or ascafi$2 or ascolin$2 or asmenol$2 or asprevent$2 or astecon$2 or asthator$2 or asthmasan$2 or asthmont$2 or astmirex$2 or astmodil$2 or atentus$2 or atlabiclo$2 or belokast$2 or brolyt$2 or castispir$2 or chesmon$2 or deprive$2 or elukan$2 or elunkast$2 or eonic$2 or ephyra$2 or filkast$2 or fulmont$2 or imvlo$2 or ispyrra$2 or jepafex$2 or kipres$2 or l 706631 or l706631 or lanair$2 or leukast$2 or lukair$2 or lukanof$2 or lukas aiwa$2 or lukasm$2 or lukastang$2 or lukavent$2 or melarth$2 or metigreunul$2 or milukante$2 or mintalos$2 or miralust$2 or “mk 0476” or mk 476 or mk0476 or modrian$2 or modulair$2 or mofenstra$2 or mokast$2 or molucar$2 or monalux$2 or monart$2 or monast$2 or moncas$2 or mondeo$2 or monkasta$2 or monlast$2 or monlucare$2 or monspes$2 or monstonol$2 or montair$2 or montast$2 or montecell$2 or montecon$2 or montefar$2 or montegen$2 or montek$2 or montelair$2 or montelak$2 or montelar$2 or montelex$2 or montelax$2 or montelubronch$2 or montelucaste$2 or montelukast$2 or montelukaste$2 or montelukastteva$2 or montelukastum$2 or montelukasturn$2 or montelux$2 or montemyl$2 or montep$2 or monterast$2 or monteresp$2 or montespir$2 or montewin$2 or montexal$2 or monthan$2 or montol$2 or montul$2 or montus$2 or moolpas$2 or nal 6336 or nal6336 or orilukast$2 or otelus$2 or pentafeno$2 or perasm$2 or pluralais$2 or pneumo-kast$2 or promonta$2 or rasec$2 or relukas$2 or respilukas$2 or romilast$2 or saslong$2 or singodem$2 or singulair$2 or singulergy$2 or solok$2 or spirokast$2 or spiromon$2 or stangen$2 or surfair$2 or symlukast$2 or telelux$2 or telukast$2 or teluki$2 or tevalukast$2 or thordel$2 or valnuen$2 or velukast$2 or xaira$2 or yekast$2 or zakomoxit$2 or MHM278SD3E or U1O3J18SFL or 158966-92-8). tw,kw,kf,ot,hw,rn. (98508)

93. zafirlukast/ (2764)

94. (zafirlukast or accolate$2 or accoleit$2 or aeronix$2 or ici 204219 or ici204219 or olmoran$2 or respix$2 or vanticon$2 or zafirst$2 or zuvair$2 or XZ629S5L50 or 107753-78-6). tw,kw,kf,ot,hw,rn. (3687)

95. nizatidine/ (2709)

96. (nizatidine or acinon$2 or actidine$2 or antizid$2 or axadine$2 or axid$2 or calmaxid$2 or cronizat$2 or distaxid$2 or dixtasid$2 or gastrax$2 or jadin$2 or ly 139037 or ly139037 or nacid$2 or naxidine$2 or nixaxid$2 or nizax$2 or panaxid$2 or tazac$2 or tinza$2 or ulxit$2 or zanitidine$2 or zanitin$2 or zanizal$2 or zatidine$2 or zinga$2 or zl 101 or zl101 or P41PML4GHR or 76963-41-2). tw,kw,kf,ot,hw,rn. (10794)

97. ranitidine/ (33927)
98. (ranitidine or achedos$2 or acidex$2 or aciloc$2 or acloral$2 or acran$2 or ah 19065 or ah19065 or aldin$2 or alquen$2 or anistal$2 or antagonin$2 or ardoral$2 or atural$2 or ausran$2 or avintac$2 or axoban$2 or azantac$2 or baroxal$2 or biotidin$2 or consec$2 or coralen$2 or cygran$2 or d 14951 or d14951 or duractin$2 or eltidine$2 or eu-ran$2 or ezopta$2 or galidrin$2 or gastran$2 or gastrial$2 or gastridina$2 or gastrosedol$2 or hexer$2 or histac$2 or histak$2 or hyzan$2 or incid$2 or istomar$2 or iqfadina$2 or kemoranin$2 or kiradin$2 or logast$2 or lumaren$2 or lydin$2 or mauran$2 or microtid$2 or midaven$2 or nadine$2 or neoceptin$2 or pilorex$2 or ponaltin$2 or ptinolin$2 or quantor$2 or quicran$2 or r-loc$2 or radinat$2 or radine$2 or rafitaz$2 or ranacid$2 or rancet$2 or randin$2 or “rani 2” or ranial$2 or raniben$2 or ranibloc$2 or ranicalm$2 or ranidil$2 or ranidine$2 or ranidura$2 or ranigast$2 or ranihexal$2 or ranimex$2 or ranin$2 or raniogas$2 or raniplex$2 or ranisan$2 or ranisen$2 or ranitab$2 or ranital$2 or ranitax$2 or raniter$2 or ranitidin$2 or ranitidina$2 or ranitil$2 or ranitin$2 or ranitine$2 or ranolta$2 or rantac$2 or rantacid$2 or rantin$2 or ranuber$2 or ranzac$2 or ratic$2 or raticina$2 or raxide$2 or retamin$2 or rolan$2 or rosimol$2 or sampep$2 or simetac$2 or sostril$2 or tanidina$2 or taural$2 or terodul$2 or toriol$2 or ulcaid$2 or ulceran$2 or ulcex$2 or ulcin$2 or ulcocur$2 or ulsal$2 or ultak$2 or ultidine$2 or urantac$2 or verlost$2 or vesyca$2 or vizerul$2 or weichilin$2 or weidos$2 or xanidine$2 or zantab$2 or zantac$2 or zantadin$2 or zantic$2 or zinetac$2 or 884KT10YB7 or BK76465IHM or 66357-35-5 or 66357-59-3).tw,kw,kf,ot,hw,rn. (53624)
99. or/56-98 [OMALIZUMAB + OTHER DRUGS OF INTEREST] (1736609)
100. chronic urticaria/ (7634)
101. chronic spontaneous urticaria/ (1316)
102. urticaria/ and exp chronic disease/ (3973)
103. ((idiopathic* or spontaneous*) adj2 urticaria*).tw,kw,kf. (7343)
104. (CIU adj1 CSU).tw,kw,kf. (209)
105. ((CIU or CSU) adj6 urticaria*).tw,kw,kf. (3481)
106. ((autoimmun* or auto-immun*) adj2 urticaria*).tw,kw,kf. (787)
107. or/100-106 [CHRONIC SPONTANEOUS URTICARIA] (14378)
108. 99 and 107 [OMALIZUMAB + OTHER DRUGS - CHRONIC SPONTANEOUS URTICARIA] (6072)
109. (exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/) not (exp human/ or exp human experimentation/ or exp human experiment/) (13126910)
110. 108 not 109 [ANIMAL-ONLY REMOVED] (6029)

111. editorial.pt. (1416866)

112. 110 not 111 [OPINION PIECES REMOVED] (5936)

113. (juvenile/ or exp adolescent/ or exp child/) not (adult/ or exp aged/ or middle aged/ or young adult/) (4510810)

114. 112 not 113 [UNDER-18 POPULATION REMOVED] (5588)

115. limit 114 to yr="2005-current" [DATE LIMIT APPLIED] (4632)

116. 115 use emczd [EMBASE RECORDS] (3199)

117. Omalizumab/ (13780)

118. (omalizumab or ct-p39 or ctp39 or fb 317 or fb317 or gbr 310 or gbr310 or hu 901 or hu901 or ige 25 or ige25 or "ige 025" or ige025 or olizumab$2 or rg 3648 or rg3648 or rhumab 25 or rhumab e25 or "sti 004" or sti004 or "syn 008" or syn008 or xolair$2 or 2p471x1z11 or 242138-07-4).ti,ab,kw. (11153)

119. ((anti-IgE or antiIgE) adj4 (antibod* or anti-bod*)).ti,ab,kw. (3339)

120. Loratadine/ (8677)

121. (loratadine or aerotina$2 or alavert$2 or alerfast$2 or alernitis$2 or alerpriv$2 or alertadin$2 or alertrin$2 or allerta$2 or allertyn$2 or allohex$2 or ambrace$2 or analergal$2 or anhissen$2 or anlos$ or ardin$2 or biloina$2 or bonalerg$2 or caradine$2 or carin$2 or civeran$2 or clalodine$2 or claratyne$2 or clarid$2 or clarium$2 or claritin$2 or claritine$2 or clarityn$2 or clarityne$2 or cronitin$2 or cronopen$2 or curyken$2 or demazin$2 or ezasmin$2 or ezede$2 or finska$2 or frenaler$2 or fristamin$2 or genadine$2 or halodin$2 or hislorex$2 or histalor$2 or histaloran$2 or j-tadine$2 or klarihist$2 or klinset$2 or laredine$2 or lergia$2 or lertamine$2 or lesidas$2 or lindine$2 or lisino$2 or lobeta$2 or lodain$2 or lora-lich$2 or lora-tabs$2 or lorabasics$2 or loracert$2 or loraclar$2 or loraderm$2 or loradex$2 or loradif$2 or loradin$2 or lorahist$2 or loralerg$2 or lorano$2 or loranox$2 or lorantis$2 or lorapaed$2 or lorastine$2 or loratadura$2 or loratan$2 or loratazine$2 or loratidin$2 or loratidine$2 or loraton$2 or loratrim$2 or loratyne$2 or loraver$2 or loraxin$2 or loreen$2 or lorfast$2 or lorihis$2 or lorin$2 or lorita$2 or loritine$2 or lotadine$2 or lotarin$2 or lowadina$2 or mosedin$2 or noratin$2 or notamin$2 or nularef$2 or onemin$2 or optimin$2 or polaratyne$2 or proactin$2 or pylor$2 or restamine$2 or ridamin$2 or rihest$2 or rinityn$2 or rityne$2 or roletra$2 or rotifar$2 or sanelor$2 or sch-2985 or sch2985 or sch 29851 or sch29851 or sensibit$2 or sohotin$2 or tadine$2 or tidilor$2 or tirlor$2 or toradine$2 or velodan$2 or versal$2 or voratadine$2 or zeos$2 or 7AJO3BO7QN or 79794-75-5).ti,ab,kw. (316570)

122. (fexofenadine or allegra$2 or allegratab$2 or almerg$2 or fexallegra$2 or fexofenadin$2 or fexofenadine$2 or "m 016455" or m016455 or mdl 16455 or mdl16455 or mdl 16455a or mdl16455a or telfast$2 or treathay$2 or E6582LOH6V or 138452-21-8).ti,ab,kw. (3464)

123. (desloratadine or aerius$2 or alerdin$2 or aleric$2 or allex$2 or aviant$2 or azomyr$2 or claramax$2 or clarinex$2 or dasselta$2 or decarbethoxyloratadine$2 or denosin$2 or desalergo$2 or desalex$2 or descarboethoxyloratadine$2 or deslor$2 or escontral$2 or mk 4117 or mk4117 or neoclaritine$2 or neoclarityn$2 or opulis$2 or sch 34117 or sch34117 or sinalerg$2 or supraler$2 or FVF865388R or 100643-72-9 or 100643-71-8).ti,ab,kw. (2420)

124. Cetirizine/ (11114)

125. (cetirizine or ac 170 or ac170 or acidrine$2 or actifed allergie$2 or adezio$2 or agelmin$2 or alairgix$2 or alercet$2 or alerid$2 or alerlisin$2 or alertop$2 or alerviden$2 or aletir$2 or alled$2 or aller tec$2 or allertec$2 or alltec$2 or alzytec$2 or benaday$2 or benadryl$2 or betarhin$2 or cabal$2 or cerazine$2 or cerini$2 or cerotec$2 or cesta$2 or cetalerg$2 or ceterifug$2 or cethis$2 or ceti tab$2 or ceti-puren$2 or cetilich$2 or cetiderm$2 or cetidura$2 or cetil von ct $2 or cetimin$2 or cetin$2 or cetirigamma$2 or cetirax$2 or cetirin$2 or cetirizin$2 or cetirizina$2 or cetirizinum$2 or cetirlan$2 or cetizin$2 or cetrimed$2 or cetrine$2 or cetrizet$2 or cetrizin$2 or cetryn$2 or cetymin$2 or cistmine$2 or deallergy$2 or drill allergie$2 or falergi$2 or finallerg$2 or formistin$2 or generit$2 or histazine$2 or histica$2 or humex$2 or incidal-od$2 or jdp 205 or jdp205 or jdp 207 or jdp207 or lergium$2 or livoreactine$2 or nosemin$2 or nosmin$2 or ot 1001 or ot1001 or ozen$2 or “p 071” or p071 or piriteze allergy$2 or pollenase$2 or pollenshield$2 or prixlae$2 or quzyttir$2 or qzytir$2 or raingen$2 or razene$2 or reactine$2 or rhizin$2 or risima$2 or ritecam$2 or ryvel$2 or ryzen$2 or sancotec$2 or selitex$2 or setizin$2 or setir$2 or simtec$2 or sutac$2 or symitec$2 or terizin$2 or terizine$2 or vick-zyrt$2 or virlix$2 or voltric$2 or xarlin$2 or zenriz$2 or zensil$2 or zeran$2 or zertine$2 or zerviate$2 or zetir$2 or zicet$2 or zinex$2 or ziptek$2 or ziralton$2 or zirtec$2 or zirtek$2 or zirtin$2 or zyllergy$2 or zymed$2 or zyrac$2 or zyrazine$2 or zyrcon$2 or zyrlex$2 or zyrtec$2 of zyrtecset$2 or zyrtek$2 or YO7261ME24 or 64O047KTOA or 83881-51-0 or 83881-52-1). ti,ab,kw. (22028)

126. (levocetirizine or allerwet$2 or cetirmar$2 or levocetira$2 or levocetirizina$2 or levrix$2 or muntel$2 or novocetrin$2 or rinozal$2 or sopras$2 or vozet$2 or xarlin$2 or xazal$2 or xozal$2 or xusal$2 or xyzal$2 or xyzall$2 or 6U5EA9RT2O or SOD6A38AGA or W69HSF2416 or 130018-77-8 or 130018-77-8).ti,ab,kw. (1680)

127. exp Diphenhydramine/ (31209)

128. (diphenhydramine or alledryl$2 or allerdryl$2 or allergina$2 or amidryl$2 or antistominum$2 or antomin$2 or bagodryl$2 or banaril$2 or baramine$2 or beldin$2 or belix$2 or benachlor$2 or benadril$2 or benadrin$2 or benadryl$2 or benadyl$2 or benapon$2 or benhydramin$2 or benocten$2 or benodin$2 or benodine$2 or benylan$2 or benylin$2 or benzantine$2 or benzhydramine$2 or benzhydril$2 or betramin$2 or broncho d$2 or caladryl$2 or carphenamine$2 or carphenex$2 or cathejell$2 or compoz$2 or dabylen$2 or debendrin$2 or dermistina$2 or dermodrin$2 or desentol$2 or diabenyl$2 or diabylen$2 or dibadorm$2 or dibendrin$2 or dibenil$2 or dibondrin$2 or dibrondrin$2 or difedryl$2 or difenhydramin$2 or difenhydramine$2 or dihidral$2 or dimedrol$2 or

dimedryl$2 or dimidril$2 or dimiril$2 or diphantine$2 or diphedryl$2 or diphen$2 or diphenacen$2 or diphendramine$2 or diphenhydramide$2 or diphenhydramin$2 or diphenydramine$2 or diphenylhydramin$2 or diphenylhydramine$2 or dobacen$2 or dormin$2 or dryhistan$2 or drylistan$2 or dylamon$2 or dytan$2 or emesan$2 or histaxin$2 or histergan$2 or hyadrine$2 or hydramine$2 or hyrexin$2 or ibiodral$2 or medidryl$2 or mephadryl$2 or nausen$2 or neosynodorm$2 or novamina$2 or nytol quickgels$2 or pm 255 or pm255 or probedryl$2 or q-dryl$2 or reisegold$2 or resmin$2 or restamin$2 or sediat$2 or sedryl$2 or silphen$2 or sleepeze$2 or sominex$2 or syntedril$2 or trux-adryl$2 or tzoali$2 or unisom sleepgels$2 or valdrene$2 or valu-dryl$2 or venasmin$2 or vertirosan$2 or “vicks formula 44” or vilbin$2 or wehdryl$2 or ziradryl$2 or 8GTS82S83M or 4OD433S209 or TC2D6JAD40 or 147-24-0 or 58-73-1 or 88637-37-0).ti,ab,kw. (86385)

129. Hydroxyzine/ (12113)

130. (hydroxyzine or abacus$2 or “ah3 n” or antizine$2 or arcanax$2 or atarax$2 or ataraxone$2 or aterax$2 or attarax$2 or bestalin$2 or bobsule$2 or centilax$2 or cerax$2 or darax$2 or disron$2 or dormirex$2 or durrax$2 or efidac$2 or hiderax$2 or hizin$2 or hydroxizine$2 o r hyzine$2 or idroxizina$2 or iremofar$2 or iterax$2 or novohydroxyzin$2 or orgatrax$2 or otarex$2 or paxistil$2 or phymorax$2 or postarax$2 or prurid$2 or qualidrozine$2 or quiess$2 or “r-rax” or “tran q” or trandozine$2 or tranquijust$2 or ucb 4492 or ucb4492 or ucerax$2 or unamine$2 or vistacot$2 or vistaject$2 or vistaril$2 or 30S50YM8OG or 76755771U3 or M20215MUFR or 10246-75-0 or 2192-20-3 or 68-88-2).ti,ab,kw. (5011)

131. Methotrexate/ (257024)

132. (methotrexate or “a methopterine” or abitextrate$2 or abitrexate$2 or “adx 2191” or adx2191 or amethopterin$2 or amethopterine$2 or ametopterine$2 or antifolan$2 or biotrexate$2 or brimexate$2 or canceren$2 or cl 14377 or cl14377 or emt 25299 or emt25299 or emtexate$2 or emthexat$2 or emthexate$2 or emtrexate$2 or enthexate$2 or farmitrexat$2 or farmitrexate$2 or farmotrex$2 or folex$2 or ifamet$2 or imeth$2 or intradose MTX or jylamvo$2 or lantarel$2 or ledertrexate$2 or lumexon$2 or maxtrex$2 or metatrexan$2 or metex$2 or methoblastin$2 or methohexate$2 or methotrate$2 or methotrexat$2 or methotrexate$2 or methotrexato$2 or methoxtrexate$2 or methrotrexate$2 or methylaminopterin$2 or methylaminopterine$2 or meticil$2 or metoject$2 or metothrexate$2 or metotrexat$2 or metotrexate$2 or metotrexin$2 or metrex$2 or metrotex$2 or mexate$2 or mpi 2505 or mpi2505 or mpi 5004 or mpi5004 or neotrexate$2 or nordimet$2 or novatrex$2 or nsc 740 or nsc740 or otrexup$2 or r 9985 or r9985 or rasuvo$2 or reditrex$2 or reumatrex$2 or rheumatrex$2 or texate$2 or texorate$2 or tremetex$2 or trexall$2 or trexeron$2 or wr 19039 or wr19039 or xaken$2 or xatmep$2 or zexate$2 or zlatal$2 or YL5FZ2Y5U1 or 3IG1E710ZN or 133073-73-1 or 15475-56-6 or 51865-79-3 or 59-05-2 or 60388-53-6 or 86669-44-5).ti,ab,kw. (143409)

133. Colchicine/ (55988)

134. (colchicine or aqua colchin$2 or colchichine$2 or colchicin$2 or colchicina$2 or colchicinum$2 or colchicum$2 or colchily$2 or colchimedio$2 or colchineos$2 or colchiquim$2 or colchisol$2 or colchysat$2 or colcin$2 or colcine$2 or colcrys$2 or colctab$2 or colgout$2 or colrefuz$2 or colsaloid$2 or colstat$2 or condylon$2 or gloperba$2 or goutichine$2 or goutnil$2 or kolkicin$2 or kolkisin$2 or mitigare$2 or "mpc 004" or mpc004 or myinfla$2 or tolchicine$2 or SML2Y3J35T or 54192-66-4 or 64-86-8 or 75520-89-7).ti,ab,kw. (44002)

135. Dapsone/ (26723)

136. (dapsone or aczone$2 or atrisone$2 or avlosulfan$2 or avlosulfon$2 or avlosulfone$2 or bn 2405 or bn2405 or croysulfone$2 or dapsoderm$2 or dapson$2 or dapsona$2 or diamino diphenyl sulfone$2 or diaminodiphenyl sulfone$2 or diaminodiphenylosulfone$2 or diaminodiphenylsulfon$2 or diaminodiphenylsulfone$2 or diammodiphenylsulfone$2 or diaphenyl sulfone$2 or diaphenylsulfon$2 or diaphenylsulfone$2 or diaphenylsulphone$2 or diphenason$2 or diphenasone$2 or diphone$2 or disulone$2 or dopsan$2 or dumitone$2 or eporal$2 or f 1358 or f1358 or lepravir$2 or novasulfon$2 or novophone$2 or servidapson$2 or servidapsone$2 or sulfadione$2 or sulfadoine$2 or sulfona$2 or sulfone mere$2 or udolac$2 or 8W5C518302 or 80-08-0).ti,ab,kw. (46205)

137. Indomethacin/ (112669)

138. (indomethacin or algiflam$2 or algometacin$2 or amuno$2 or antalgin dialicels$2 or areumatin$2 or argilex$2 or arthrexin$2 or articulen$2 or artracin$2 or artrilona$2 or artrinovo$2 or artrocid$2 or asimet$2 or benocid$2 or betacin$2 or bonidon$2 or boutycin$2 or catlep$2 or chrono indocid$2 or chronoindocid$2 or confortid$2 or docin$2 or dolazal$2 or dolazol$2 or dolcidium$2 or dometin$2 or durametacin$2 or elmego spray$2 or elmetacin$2 or endometacin$2 or flamaret$2 or flexin continus$2 or grindocin$2 or helvecin$2 or idicin$2 or im-75 or imbrilon$2 or imet$2 or inacid$2 or indacin$2 or indaflex$2 or indalgin$2 or inderapollon$2 or indicin$2 or indo phlogont$2 or indo-lemmon$2 or indo-tablinen$2 or indocap$2 or indocid$2 or indocin$2 or indocolir$2 or indocollyre$2 or indogesic$2 or indolag$2 or indolar$2 or indolemmon$2 or indomecin$2 or indomed$2 or indomee$2 or indomelan$2 or indomelol$2 or indomet$2 or indometacin$2 or indometacine$2 or indomethacin$2 or indomethacine$2 or indomethacinum$2 or indomethegan$2 or indometicina$2 or indometin$2 or indomexum$2 or indomin$2 or indono$2 or indoptic$2 or indoptol$2 or indorektal$2 or indorem$2 or indos$2 or indosan$2 or indosima$2 or indosmos$2 or indotard$2 or indovis$2 or indoxen$2 or indoy$2 or indren$2 or indrenin$2 or indylon$2 or inflazon$2 or inmetsin$2 or inteban$2 or lauzit$2 or luiflex$2 or malival$2 or mcn r 1166 or mcn r1166 or metacen$2 or methacin$2 or methindol$2 or methindole$2 or methocaps$2 or metindol$2 or mezolin$2 or miometacen$2 or mk 615 or mk615 or mobilan$2 or novomethacin$2 or osmogit$2 or osmosin$2 or reumacid$2 or reusin$2 or rheumacid$2 or rheumacin$2 or salinac$2 or servimeta$2 or sidocin$2 or tannex$2 or taye$2 or tivorbex$2 or vi-gel$2 or vonum$2 or XXE1CET956 or 104614-77-9 or 113560-66-0 or 125770-88-9 or 28811-31-6 or 28811-32-7 or 53-86-1 or 58201-41-5 or 62509-41-5 or 70938-94-2 or 74252-25-8 or 7681-54-1 or 86947-68-4 or 88170-06-3).ti,ab,kw. (94780)

139. Hydroxychloroquine/ (51372)

140. (hydrochloroquine or chloroquinol$2 or dolquine$2 or ercoquin$2 or hydroxychlorochin$2 or oxychlorochin$2 or oxychloroquine$2 or plaquenil$2 or polirreumin$2 or quensyl$2 or sn 8137 or sn8137 or tlc 19 tlc19 or win 1258 or win1258 or 4QWG6N8QKH or 8Q2869CNVH or 118-42-3 or 747-36-4).ti,ab,kw. (1336)

141. Doxepin/ (11097)

142. (doxepin or adapin$2 or anten$2 or aponal$2 or co dox$2 or curatin$2 or deptran$2 or desidox$2 or doneurin$2 or doxal$2 or doxepia$2 or doxepine$2 or expadox$2 or expan$2 or gilex$2 or mareen$2 or p 3693a or p3693a or prudoxin$2 or quitaxon$2 or silenor$2 or sinequan$2 or sinquan$2 or sinquane$2 or xepin$2 or zonalon$2).ti,ab,kw. (280249)

143. Capsaicin/ (35049)

144. (capsaicin or abc-pflaster$2 or adlea$2 or algrx 4975 or algrx4975 or axsain$2 or biozone$2 or capsaicine$2 or capsicaine$2 or capsicum$2 or capsidol$2 or capsig$2 or captrix$2 or capzasin$2 or casacine$2 or cgs 200 or cgs200 or cntx 4975 or cntx4975 or dolenon$2 or dolorac$2 or gelcen$2 or katrum$2 or ngx 1998 or ngx1998 or ngx 4010 or ngx4010 or qutenza$2 or styptysat$2 or transacin$2 or zacin$2 or zostrix$2 or S07O44R1ZM or 404-86-4).ti,ab,kw. (42824)

145. Ephedrine/ (22533)

146. (ephedrine or biophedrin$2 or eciphin$2 or efedra$2 or efedrin$2 or efedrine$2 or efidrin$2 or eggophedrin$2 or ephadrosan$2 or ephalone$2 or ephedra$2 or ephedral$2 or ephedrin$2 or ephedrosan$2 or ephedrosst$2 or et 203 or et203 or fedrin$2 or i sedrin$2 or kratedyn$2 or mandrin$2 or neo fedrin$2 or primatene$2 or rezipres$2 or sanedrin$2 or sanedrine$2 or zephrol$2 or GN83C131XS or NLJ6390P1Z or U6X61U5ZEG or 299-42-3).ti,ab,kw. (15672)

147. Famotidine/ (12533)

148. (famotidine or agufam$2 or amfamox$2 or antodine$2 or apogastine$2 or ausfam$2 or beilande$2 or bestidine$2 or blocacid$2 or brolin$2 or cepal$2 or durater$2 or ep 335 or ep335 or facid$2 or fadin$2 or fadine$2 or fadul$2 or fafotin$2 or famoabz$2 or famoc$2 or famocid$2 or famodar$2 or famodil$2 of famodin$2 or famodine$2 or famogal$2 or gamogard$2 or gamogast$2 or famohexal$2 or famolta$2 or famonerton$2 or famopril$2 or famopsin$2 or famos$2 or famosan$2 or famosia$2 or famotal$2 or famotep$2 or famotin$2 or famotine$2 or famowal$2 or famox$2 or famoxal$2 or fanox$2 or fararidin$2 or farmotex$2 or farotin$2 or ferotine$2 or fibonel$2 or fluxid$2 or foxadul$2 or fudone$2 or fuweidin$2 or ganor$2 or gardin$2 or gaster$2 or gastren$2 or gastridin$2 or gastrion$2 or gastro$2 or gastrodomina$2 or gastroflux$2 or h2 bloc or incifam$2 or kemofam$2 or kimodin$2 or l 643341 or l643341 or mk 208 or mk208 or motiax$2 or motidine$2 or pecidine$2 or pepcid$2 or pepcidin$2 or pepcidina$2 or pepcidine$2 or pepdif$2 or pepdine$2 or pepdul$2 or pepfamin$2 or peptan$2 or pepticon$2 or peptifam$2 or pepzan$2 or purifam$2

or quamatel$2 or quamtel$2 or rapitab$2 or restadin$2 or rogasti$2 or sedanium$2 or stadin$2 or stomax$2 or supertidine$2 or tamin$2 or topcid$2 or ulcatif$2 or ulcefam$2 or ulcelac$2 or ulcenol$2 or ulcetrax$2 or ulcofam$2 or ulcusan$2 or ulfadin$2 or ulfagel$2 or ulfam$2 or ulfamid$2 or ulped$2 or voker$2 or weimok$2 or winiful$2 or wiretin$2 or yamarin$2 or ym 11170 or ym11170 or 5QZO15J2Z8 or 108885-67-2 or 76824-35-6).ti,ab,kw. (96664)

149. (montelukast or actamone$2 or airathon$2 or aircast$2 or airing$2 or alvokast$2 or apilone$2 or ascafi$2 or ascolin$2 or asmenol$2 or asprevent$2 or astecon$2 or asthator$2 or asthmasan$2 or asthmont$2 or astmirex$2 or astmodil$2 or atentus$2 or atlabiclo$2 or belokast$2 or brolyt$2 or castispir$2 or chesmon$2 or deprive$2 or elukan$2 or elunkast$2 or eonic$2 or ephyra$2 or filkast$2 or fulmont$2 or imvlo$2 or ispyrra$2 or jepafex$2 or kipres$2 or l 706631 or l706631 or lanair$2 or leukast$2 or lukair$2 or lukanof$2 or lukas aiwa$2 or lukasm$2 or lukastang$2 or lukavent$2 or melarth$2 or metigreunul$2 or milukante$2 or mintalos$2 or miralust$2 or “mk 0476” or mk 476 or mk0476 or modrian$2 or modulair$2 or mofenstra$2 or mokast$2 or molucar$2 or monalux$2 or monart$2 or monast$2 or moncas$2 or mondeo$2 or monkasta$2 or monlast$2 or monlucare$2 or monspes$2 or monstonol$2 or montair$2 or montast$2 or montecell$2 or montecon$2 or montefar$2 or montegen$2 or montek$2 or montelair$2 or montelak$2 or montelar$2 or montelex$2 or montelax$2 or montelubronch$2 or montelucaste$2 or montelukast$2 or montelukaste$2 or montelukastteva$2 or montelukastum$2 or montelukasturn$2 or montelux$2 or montemyl$2 or montep$2 or monterast$2 or monteresp$2 or montespir$2 or montewin$2 or montexal$2 or monthan$2 or montol$2 or montul$2 or montus$2 or moolpas$2 or nal 6336 or nal6336 or orilukast$2 or otelus$2 or pentafeno$2 or perasm$2 or pluralais$2 or pneumo-kast$2 or promonta$2 or rasec$2 or relukas$2 or respilukas$2 or romilast$2 or saslong$2 or singodem$2 or singulair$2 or singulergy$2 or solok$2 or spirokast$2 or spiromon$2 or stangen$2 or surfair$2 or symlukast$2 or telelux$2 or telukast$2 or teluki$2 or tevalukast$2 or thordel$2 or valnuen$2 or velukast$2 or xaira$2 or yekast$2 or zakomoxit$2 or MHM278SD3E or U1O3J18SFL or 158966-92-8).ti,ab,kw. (90881)

150. (zafirlukast or accolate$2 or accoleit$2 or aeronix$2 or ici 204219 or ici204219 or olmoran$2 or respix$2 or vanticon$2 or zafirst$2 or zuvair$2 or XZ629S5L50 or 107753-78-6).ti,ab,kw. (1371)

151. Nizatidine/ (2709)

152. (nizatidine or acinon$2 or actidine$2 or antizid$2 or axadine$2 or axid$2 or calmaxid$2 or cronizat$2 or distaxid$2 or dixtasid$2 or gastrax$2 or jadin$2 or ly 139037 or ly139037 or nacid$2 or naxidine$2 or nixaxid$2 or nizax$2 or panaxid$2 or tazac$2 or tinza$2 or ulxit$2 or zanitidine$2 or zanitin$2 or zanizal$2 or zatidine$2 or zinga$2 or zl 101 or zl101 or P41PML4GHR or 76963-41-2).ti,ab,kw. (3319)

153. Ranitidine/ (33927)

154. (ranitidine or achedos$2 or acidex$2 or aciloc$2 or acloral$2 or acran$2 or ah 19065 or ah19065 or aldin$2 or alquen$2 or anistal$2 or antagonin$2 or ardoral$2 or atural$2 or ausran$2 or avintac$2 or axoban$2 or azantac$2 or baroxal$2 or biotidin$2 or consec$2 or coralen$2 or cygran$2 or d 14951 or d14951 or duractin$2 or eltidine$2 or eu-ran$2 or ezopta$2 or galidrin$2 or gastran$2

or gastrial$2 or gastridina$2 or gastrosedol$2 or hexer$2 or histac$2 or histak$2 or hyzan$2 or incid$2 or istomar$2 or iqfadina$2 or kemoranin$2 or kiradin$2 or logast$2 or lumaren$2 or lydin$2 or mauran$2 or microtid$2 or midaven$2 or nadine$2 or neoceptin$2 or pilorex$2 or ponaltin$2 or ptinolin$2 or quantor$2 or quicran$2 or r-loc$2 or radinat$2 or radine$2 or rafitaz$2 or ranacid$2 or rancet$2 or randin$2 or “rani 2” or ranial$2 or raniben$2 or ranibloc$2 or ranicalm$2 or ranidil$2 or ranidine$2 or ranidura$2 or ranigast$2 or ranihexal$2 or ranimex$2 or ranin$2 or raniogas$2 or raniplex$2 or ranisan$2 or ranisen$2 or ranitab$2 or ranital$2 or ranitax$2 or raniter$2 or ranitidin$2 or ranitidina$2 or ranitil$2 or ranitin$2 or ranitine$2 or ranolta$2 or rantac$2 or rantacid$2 or rantin$2 or ranuber$2 or ranzac$2 or ratic$2 or raticina$2 or raxide$2 or retamin$2 or rolan$2 or rosimol$2 or sampep$2 or simetac$2 or sostril$2 or tanidina$2 or taural$2 or terodul$2 or toriol$2 or ulcaid$2 or ulceran$2 or ulcex$2 or ulcin$2 or ulcocur$2 or ulsal$2 or ultak$2 or ultidine$2 or urantac$2 or verlost$2 or vesyca$2 or vizerul$2 or weichilin$2 or weidos$2 or xanidine$2 or zantab$2 or zantac$2 or zantadin$2 or zantic$2 or zinetac$2 or 884KT10YB7 or BK76465IHM or 66357-35-5 or 66357-59-3).ti,ab,kw. (31752)

155. or/117-154 [OMALIZUMAB + OTHER DRUGS OF INTEREST] (1644882)
156. Chronic Urticaria/ (7634)
157. Urticaria/ and Chronic Disease/ (3753)
158. ((idiopathic* or spontaneous*) adj2 urticaria*).ti,ab,kw. (7223)
159. (CIU adj1 CSU).ti,ab,kw. (209)
160. ((CIU or CSU) adj6 urticaria*).ti,ab,kw. (3460)
161. ((autoimmun* or auto-immun*) adj2 urticaria*).ti,ab,kw. (756)
162. or/156-161 [CHRONIC SPONTANEOUS URTICARIA] (14136)
163. 155 and 162 [OMALIZUMAB + OTHER DRUGS - CHRONIC SPONTANEOUS URTICARIA] (5850)
164. (exp Child/ or exp Infant/) not (exp Adult/ or Adolescent/) (3594454)
165. 163 not 164 [UNDER-18 POPULATION ONLY REMOVED] (5641)
166. limit 165 to yr=”2005-current” [DATE LIMIT APPLIED] (4709)
167. 166 use coch,cctr [CLIB RECORDS] (362)
168. 55 or 116 or 167 [ALL DATABASES] (4651)
169. remove duplicates from 168 (3341) [TOTAL UNIQUE RECORDS]
170. 169 use medall [MEDLINE UNIQUE RECORDS] (1075)
171. 169 use emczd [EMBASE UNIQUE RECORDS] (2134)

172. 169 use cctr [CENTRAL UNIQUE RECORDS] (131)

173. 169 use coch [CDSR UNIQUE RECORDS] (1)

Appendix 2: List of Included Studies

Note that this appendix has not been copy-edited.

Table 27: Included Records by Unique Study

Author (study name); primary citation; NCT	Companion record(s)
Randomized controlled trials (n = 2)	
Maurer, 2018 (XTEND-CIU) Maurer M, Kaplan A, Rosén K, Holden M, Iqbal A, Trzaskoma BL, Yang M, Casale TB. The XTEND-CIU study: long-term use of omalizumab in chronic idiopathic urticaria. Journal of Allergy and Clinical Immunology. 2018 Mar 1;141(3):1138 to 9. NCT02392624	Genentech, Inc. NCT02392624, A Study of the Efficacy and Safety of Omalizumab Through 48 Weeks in Participants With Chronic Idiopathic Urticaria
	Casale TB, Win PH, Bernstein JA, Rosén K, Holden M, Iqbal A, Trzaskoma BL, Yang M, Antonova EN, Murphy T, Scarupa MD. Omalizumab response in patients with chronic idiopathic urticaria: insights from the XTEND-CIU study. Journal of the American Academy of Dermatology. 2018 Apr 1;78(4):793 to 5.
	Casale TB, Murphy TR, Holden M, Rajput Y, Yoo B, Bernstein JA. Impact of omalizumab on patient-reported outcomes in chronic idiopathic urticaria: Results from a randomized study (XTEND-CIU). The Journal of Allergy and Clinical Immunology: In Practice. 2019 Sep 1;7(7):2487 to 90.
	Bernstein, J.; Antonova, E.; Trzaskoma, B.; Holden, M.; Kaplan, A. Changes in symptom control, work productivity and activity impairment, and anxiety symptoms in chronic idiopathic urticaria patients after 24-week treatment with omalizumab, 2017, Journal of Managed Care and Specialty Pharmacy 23 (3-A SUPPL.), S77
	Casale, T. B.; Scarupa, M. D.; Holden, M.; Trzaskoma, B. L.; Antonova, E.; Win, P. H, Study design, baseline and open-label results from XTEND-CIU: A phase IV, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of omalizumab through 48 weeks in patients with chronic idiopathic urticaria, 2017, Journal of Allergy and Clinical Immunology, 139(2 Supplement 1), AB271
	Casale, T. B.; Bernstein, J. A.; Holden, M.; Trzaskoma, B.; Iqbal, A.; Murphy, T., Exploring demographic and clinical differences among omalizumab responders and non-responders: interim results from a 48-week, phase IV study of omalizumab in chronic idiopathic/spontaneous urticaria,, 2017, Allergy, 72, 96 to 97
	Sofen, H.; Kaplan, A.; Holden, M.; Trzaskoma, B.; Murphy, T.; Antonova, E, Changes in dermatology quality of life, sleep, and symptoms during the 24-week open-label period of XTEND-CIU: a phase IV, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of omalizumab through 48 weeks, 2017, Journal of the American Academy of Dermatology, Vol.76, 6, AB65-p

Author (study name); primary citation; NCT	Companion record(s)
	Kaplan, A. P.; Casale, T. B.; Bernstein, J. A.; Holden, M.; Iqbal, A.; Trzaskoma, B. L.; Maurer, M.,The urticaria control test as a tool for monitoring chronic idiopathic/spontaneous urticaria treatment: Results from XTEND-CIU, a 48-week, randomized, placebo-controlled study, 2018, Journal of Allergy and Clinical Immunology, 141(2 Supplement 1), AB54
	Maurer, M.; Rajput, Y.; Thomas, C.; Holden, M.; Yoo, B., Sustained improvement in work productivity and activity impairment in chronic sponta neous urticaria (CSU) patients with omalizumab: Results from XTEND-CIU, 2018, Value in Health, 21(Supplement 1), S243
	Casale, T. B.; Murphy, T. R.; Holden, M.; Le, J. A.; Rajput, Y.; Trzaskoma, B. L.; Bernstein, J. A., Impact of omalizumab on patient reported outcomes in chronic idiopathic urticaria: Results From XTEND-CIU, A 48-Week, randomized, placebo-controlled study, 2018, Journal of Allergy and Clinical Immunology, 141(2 Supplement 1), AB405
	Kaplan, A. P.; Murphy, T. R.; Holden, M.; Iqbal, A.; Yoo, B.; Bernstein, J. A., Impact of Omalizumab Treatment Withdrawal After 24 and 48 Weeks in Patients with Chronic Idiopathic Urticaria: Results From the XTEND-CIU Study, 2019, Journal of Allergy and Clinical Immunology, 143(2 Supplement), AB209
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CIU = chronic idiopathic urticaria; CSU = chronic spontaneous urticaria; NCT = National Clinical Trial.

Appendix 3: Description of Outcome Measures

Note that this appendix has not been copy-edited.

Table 28: Details for Reported Outcome Measures

Outcome measure	Scoring	Interpretation
Urticaria Activity Score (UAS7) or UAS, and subcomponents WISS and WNHS	UAS7 is a simple scoring system to evaluate the extent of urticaria signs and symptoms. It is based on scoring the wheals and itch separately on a scale of 0 to 3 over 7 days. The final weekly score is calculated by adding together the daily scores, which can range from 0 to 6, for 7 days. The maximum final score is 42. A lower UAS7 score Indicates a reduction in CIU symptoms.	Higher scores indicate greater disease activity. A lower UAS7 score indicates a reduction in CIU symptoms. MCID: UAS7: 9.5 to 10.5 points[66] WISS: 4.5 to 5.0 points WNHS: 5.0 to 5.5 points
Chronic Urticaria Quality of Life (CU-Q2oL)[67]	The Chronic Urticaria Quality of Life questionnaire is an instrument specifically developed to assess quality of life in patients with CIU. It is a self-administered questionnaire where patients indicate how much they have been troubled by each noted problem (e.g., sleep, symptoms, work, mood). The CU-Q2oL questionnaire comprises 23 items categorized into 6 domains: pruritus (2 items), impact on daily activities (6), sleep problems (5), limitations (3), look (5), and swelling (2). For each item, patients are asked to choose between 5 response values (scored 0 to 4) indicating the intensity of each item in the last 2 weeks. A total summed score across all items is calculated and transformed into scores ranging from 0 to 100, with a score of 100 indicating the worst HRQoL impairment.	Higher scores indicate greater disease-related impairment. A lower CU-Q2oL score indicates an improvement in QoL. MCID: 15.0 points[a,68]
Dermatology Life Quality Index (DLQI)	The DLQI is a dermatology-specific 10-item QoL instrument. The questionnaire assesses 6 different aspects that may affect QoL: symptoms and feelings, daily activities, leisure activities, work or school, personal relationships, and treatment. Higher scores indicate a greater impairment in QoL.	Higher scores on the DLQI indicate a greater impairment in QoL. A lower DLQI score indicates an improvement in QoL. MCID: 4 points[69-71]
UCT	A 4-item disease-specific instrument with a recall period of 4 weeks intended to assess disease control in patients with chronic urticaria (spontaneous and inducible). A score of 16 indicates complete disease control. A score of < 12 on the UCT identifies patients with poorly controlled chronic urticaria (CU), and a score of ≥ 12 identifies those with well-controlled symptoms.	Higher score indicates better disease control. MCID: 3 points[72,73] An improvement in 3 points is a minimal response, and an improvement of ≥ 6 points is a marked response.

CIU = chronic idiopathic urticaria; CU-Q2oL = Chronic Urticaria Quality of Life questionnaire; DLQI = Dermatology Life Quality Index; HRQoL = health-related quality of life; MCID = minimal clinically important difference; QoL = quality of life; UAS7 = 7-Day Urticaria Activity Score; UCT = Urticaria/Angioedema Control Test; WHNS = Weekly Number of Hives Score; WISS = Weekly Itch Severity Score.

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