Common Drug Review
Clinical Review Report

August 2015

Drug	omalizumab (Xolair) (150 mg and 300 mg subcutaneous injection)
Indication	Treatment of adults and adolescents (12 years of age and above) with chronic idiopathic urticaria who remain symptomatic despite H_1 antihistamine treatment
Listing request	Treatment of adults and adolescents (12 years of age and above) with persistent (disease duration ≥ 6 months) moderate to severe (UAS7 score ≥ 16 or DLQI ≥ 10) chronic idiopathic urticaria who remain symptomatic (presence of hives and/or associated itching) despite H1-antihistamine treatment.
Manufacturer	Novartis Pharmaceuticals Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in allergy and immunology who provided input on the conduct of the review and the interpretation of findings.

Through the CADTH Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
BOCF	baseline observation carried forward
CDR	CADTH Common Drug Review
CI	confidence interval
CIU	chronic idiopathic urticaria
CU-Q2oL	Chronic Urticaria Quality of Life Questionnaire
DLQI	Dermatology Life Quality Index
eDiary	electronic diary
EQ-5D	EuroQol 5-Dimensions Questionnaire
IgE	immunoglobulin E
LTRA	leukotriene receptor antagonist
MCID	minimal clinically important difference
OMA	omalizumab
SAE	serious adverse event
UAS	Urticaria Activity Score
UAS7	Urticaria Activity Score over seven days
WDAE	withdrawal due to adverse event
WISS	Weekly Itch Severity Score
WNHS	Weekly Number of Hives Score

EXECUTIVE SUMMARY

Introduction

Chronic idiopathic urticaria (CIU) is characterized by the presence of itchy hives, angioedema, or both, lasting for a period of six weeks or longer with no identifiable external cause.[1-4] The average duration of CIU is between one and five years, with a longer duration in more severe cases.[3] Although CIU can manifest at any age, the peak incidence rate is among individuals between 20 and 40 years of age.[1,3] The prevalence of CIU has been reported to be 0.5% to 1.0% in the overall population, with a twofold higher incidence in women than in men.[1,3,4] The pathogenesis of CIU is not completely understood, but may be associated with histamine release from cutaneous mast cells and blood basophils.[1]

International guidelines on the management of urticaria recommend non-sedating second-generation H_1 antihistamines such as cetirizine or loratadine as first-line treatment for adults and children with CIU.[5,6] For patients who do not achieve an adequate response, doses up to fourfold higher than approved doses are recommended. If symptoms persist, consideration of add-on therapy using omalizumab (OMA), cyclosporin A, or the leukotriene receptor antagonist (LTRA) montelukast is recommended. A short course of corticosteroids may be used to manage exacerbations.[5,6] The clinical expert consulted for this review indicated that H_2 antagonists (e.g., ranitidine) are also commonly prescribed for patients with inadequate response to H_1 antihistamines. The only Health Canada–approved drugs for the treatment of CIU are H_1 antihistamines and OMA.

OMA is a humanized, recombinant, monoclonal anti-immunoglobulin E (IgE) antibody that binds to IgE, thereby reducing IgE-induced mast cell and basophil degranulation and the release of histamine.[1] OMA is supplied as a lyophilized, sterile powder in a single-use vial designed to deliver a 150 mg dose for subcutaneous administration upon reconstitution. For CIU, OMA is administered subcutaneously every four weeks at a dose of 150 mg or 300 mg. The manufacturer has requested listing for the treatment of adults and adolescents (12 years of age and above) with persistent (disease duration greater than or equal to six months), moderate to severe (Urticaria Activity Score over seven days [UAS7] ≥ 16 or Dermatology Life Quality Index [DLQI] ≥ 10) CIU who remain symptomatic (presence of hives or associated itching) despite H_1 antihistamine treatment. OMA is also approved in Canada for the treatment of moderate to severe persistent asthma.

Indication Under Review
Treatment of adults and adolescents (12 years of age and above) with chronic idiopathic urticaria who remain symptomatic despite H_1 antihistamine treatment
Listing Criteria Requested by Sponsor
Treatment of adults and adolescents (12 years of age and above) with persistent (disease duration ≥ 6 months) moderate to severe (UAS7 score ≥ 16 or DLQI ≥ 10) chronic idiopathic urticaria who remain symptomatic (presence of hives and/or associated itching) despite H_1 antihistamine treatment. Response to treatment should be assessed 12 weeks following OMA initiation. For patients initiated on 150 mg every 4 weeks and who do not adequately respond by Week 12, consideration to increase the dose to 300 mg every 4 weeks should be given. Response to treatment should be reassessed 12 weeks thereafter.

The objective of this systematic review was to assess the beneficial and harmful effects of OMA for the treatment of CIU in adults and adolescents who remain symptomatic despite H_1 antihistamine treatment.

Results and Interpretation

Included Studies

The evidence for this review was derived from three phase 3, double-blind, multi-centre trials that compared three different doses of OMA (75 mg, 150 mg, and 300 mg, administered every four weeks) with placebo in a total of 978 adult and adolescent patients with H_1 antihistamine-refractive CIU. Because 75 mg is not an approved dose in Canada, data from the 75 mg dose groups were excluded from this report. ASTERIA I (N = 319) and GLACIAL (N = 336) had a treatment period of 24 weeks, and ASTERIA II (N = 323) of 12 weeks. All three trials had a 16-week treatment-free follow-up period.

The primary objective of ASTERIA I and ASTERIA II was to evaluate whether OMA was superior to placebo for improving the Weekly Itch Severity Score (WISS) after 12 weeks in patients with refractory CIU receiving concomitant standard-dose H_1 antihistamine therapy. The primary objective of GLACIAL was to evaluate the safety of OMA compared with placebo in patients with refractory CIU receiving up to four times the approved dose of H_1 antihistamines and either H_2 blockers or LTRAs, or both, as concomitant therapies. Other efficacy outcomes included UAS7 and Weekly Number of Hives Score (WNHS). Quality of life was assessed with the DLQI, the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) and the EuroQol 5-Dimensions Questionnaire (EQ-5D). End points were measured at 12 weeks, 24 weeks, and the end of the follow-up period. The main efficacy end points have previously been validated for use in CIU and were considered clinically relevant by the consulting clinical expert.

The included studies were generally of adequate design and assessed clinically relevant outcomes, but relatively high rates of major protocol violations and protocol issues were reported, including enrolment of patients not meeting inclusion and exclusion criteria. The impact of these limitations on the results of the trials is unclear. Baseline characteristics were generally reflective of patients with CIU in Canada according to the consulting clinical expert. However, the inclusion and exclusion criteria of GLACIAL were most aligned with common medical practice in Canada in terms of therapies tried (i.e., high-dose H_1 antihistamines, H_2 antagonists, and LTRAs) before progressing to OMA. A very low proportion of the included patients were adolescent or elderly, thereby limiting conclusions for these subpopulations.

Efficacy

In all three included trials, improvements in CIU symptoms as measured by UAS7 and its subcomponents WISS and WNHS were significantly greater in the OMA treatment groups compared with placebo. When compared with placebo at week 12, OMA 300 mg was associated with an improvement in UAS7 of −10.02 (95% confidence interval [CI], –13.17 to –6.86, $P < 0.0001$) points, in WISS of –4.52 (95% CI, –5.97 to −3.08, $P < 0.0001$) points and in WNHS of –5.90 (95% CI, –7.72 to –4.07, $P < 0.0001$) in the GLACIAL trial. These effects are likely to be clinically significant based on published minimal clinically important differences (MCIDs) for these outcomes. Responses were maintained at 24 weeks. In ASTERIA I and ASTERIA II, the efficacy results observed with OMA 300 mg were similar to or slightly larger than those observed in GLACIAL. The 150 mg dose in these trials failed to provide a clinically significant response on UAS7, WISS, or WNHS compared with placebo based on published MCID values for these outcomes, even though the observed differences were statistically significant at week 12. Moreover, the 150 mg dose was studied in ASTERIA I and ASTERIA II only, therefore the generalizability of the results to real-world practice in which patients are likely to have failed on high doses of H_1 antihistamines and one or more unapproved therapies is uncertain.

Other efficacy outcomes were quality of life measures such as DLQI, CU-Q2oL, and EQ-5D. In GLACIAL, OMA 300 mg appeared to be effective for improving quality of life as measured with DLQI (–4.67 [95% CI, –6.28 to –3.06] points, $P < 0.0001$) and CU-Q2oL (–13.4 [95% CI, –18.2 to –8.6] points, $P < 0.0001$) compared with placebo at week 12, and results were similar at week 24. Change from baseline in DLQI exceeded the MCID at both time points, whereas an MCID for CU-Q2oL was not identified in the literature. Results for EQ-5D did not show any statistically significant improvement with OMA at week 12 or 24; as this is a generic quality of life instrument that does not appear to have been validated for CIU, it is uncertain whether EQ-5D would be sufficiently sensitive to changes in CIU symptoms. Results for quality of life outcomes in the OMA 300 mg groups were similar in ASTERIA I and ASTERIA II. The results for DLQI and CU-Q2oL in the 150 mg dose groups were statistically significant versus placebo only in ASTERIA II.

Outcomes assessed after the 16-week treatment-free follow-up period showed that the majority of efficacy outcomes did not maintain statistically significant improvements compared with placebo.

Patient group input received by CADTH Common Drug Review (CDR) on this submission reflected anxiety, depression, shame regarding the appearance of affected skin, insomnia, and absenteeism from work as key concerns associated with CIU. Although not all of these outcomes were measured in the included trials, the observed benefits of OMA on CIU symptoms and quality of life can be expected to address these concerns of relevance to patients.

Harms

Patients in ASTERIA II had a lower incidence of adverse events (AEs) (from 40.5% to 47.7%) compared with patients in ASTERIA I (from 51.3% to 69.0%) or GLACIAL (63.9% and 65.1%), possibly due to the study's shorter duration. Compared with patients in the placebo groups, patients who received OMA were more likely to experience AEs across all trials. Patients randomized to the OMA 300 mg groups had a numerically higher (from 1% to 6% more) frequency of AEs than patients in the placebo groups. The most common AEs were nasopharyngitis (7.7%) and headache (6.6%). The only AE that appeared to be associated with OMA was headache. According to the clinical expert consulted on the review and patient input received by CDR, this AE is unlikely to significantly affect the tolerability of the treatment or result in treatment discontinuation.

Withdrawals due to adverse events (WDAEs) (1.1%) and serious adverse events (SAEs) (2.1%) did not occur more frequently in patients who received OMA than in patients who received placebo. The most frequent cause of WDAEs was urticaria (54.5% of all WDAEs). No deaths occurred during the trials. Based on published literature related to the use of OMA in asthma, safety warnings from regulatory agencies, and expert opinion, three notable harms were identified a priori for this review: arterial thrombotic events, anaphylaxis, and malignancies. The US FDA[7] noted that arterial thrombotic events were shown to be slightly elevated in patients who used OMA (incidence of 0.135% over five years) compared with placebo (incidence of 0.081% over five years). As with other biologic drugs, anaphylaxis may occur with OMA; approximately 0.2% of patients who use OMA experience this AE.[8] Long-term prospective data have not confirmed the suggestion from earlier studies of OMA in asthma that the drug may increase the risk of malignancy.[9] Arterial thrombotic events, anaphylaxis, and malignancies were rare in the included trials and none appeared to be related to the study drug.

Conclusions

The results of three double-blind, multi-centre, randomized, placebo-controlled trials suggest that 12 weeks of OMA 150 mg or 300 mg administered every four weeks statistically significantly improves UAS7 and its subcomponents (WISS and WNHS) compared with placebo in patients with CIU refractory to H_1 antihistamines. However, only OMA 300 mg every four weeks was associated with a statistically and clinically significant improvement in UAS7 of 10 points compared with placebo at 12 weeks, an improvement that was maintained at 24 weeks. Patients who received OMA 300 mg also demonstrated statistically and clinically significant improvements in quality of life measures such as DLQI and CU-Q2oL at 12 and 24 weeks compared with placebo. Upon discontinuation of OMA, treatment response was not sustained over time, such that differences between OMA and placebo were no longer statistically significant at 16 weeks after discontinuation. Due to the chronic nature of the condition, it is likely that many patients with CIU will require long-term therapy with OMA; however, there were no data regarding its efficacy upon re-treatment nor was there evidence to inform the optimal interval between courses of treatment. Patients receiving OMA 300 mg appeared more likely to experience adverse effects overall, and headaches in particular, than patients in the placebo groups, but the risks of other harm outcomes did not appear to differ across treatment groups.

TABLE 1: SUMMARY OF RESULTS

Outcome	ASTERIA I			ASTERIA II			GLACIAL	
	OMA (150 mg)	OMA (300 mg)	PBO	OMA (150 mg)	OMA (300 mg)	PBO	OMA (300 mg)	PBO
Change From Baseline in UAS7 at Week 12								
Baseline (SD)	30.26 (7.26)	31.32 (5.79)	31.10 (6.67)	31.35 (6.99)	29.47 (6.90)	31.04 (6.58)	31.17 (6.57)	30.24 (6.66)
Mean value at week 12 (SD)	15.83 (13.78)	10.57 (12.28)	23.09 (12.55)	13.47 (12.64)	7.74 (11.14)	20.69 (12.64)	12.16 (13.77)	21.74 (11.55)
Change from baseline, mean (SD)	–14.44 (12.95)	–20.75 (12.17)	–8.01 (11.47)	–17.89 (13.23)	–21.74 (12.78)	–10.36 (11.61)	–19.01 (13.15)	–8.50 (11.71)
Difference vs. PBO, LSM (95% CI)[a]	–6.54 (–10.33 to –2.75)	–12.80 (–16.44 to –9.16)	–	–7.69 (–11.49 to –3.88)	–12.40 (–16.13 to –8.66)	–	–10.02 (–13.17 to –6.86)	–
P value vs. PBO[b]	0.0008	< 0.0001	–	0.0001	< 0.0001	–	< 0.0001	–
Change From Baseline in WISS at Week 12								
Baseline (SD)	14.09 (3.77)	14.20 (3.31)	14.37 (3.48)	14.23 (4.14)	13.66 (3.53)	14.02 (3.45)	14.05 (3.61)	13.82 (3.63)
Mean value at week 12 (SD)	7.44 (6.59)	4.80 (5.55)	10.73 (5.99)	6.09 (5.94)	3.89 (5.30)	8.88 (5.83)	5.50 (6.32)	9.81 (5.41)
Change from baseline, mean (SD)	–6.66 (6.28)	–9.40 (5.73)	–3.63 (5.22)	–8.14 (6.44)	–9.77 (5.95)	–5.14 (5.58)	–8.55 (6.01)	–4.01 (5.87)
Difference vs. PBO, LSM (95% CI)[c]	–2.95 (–4.72 to –1.18)	–5.80 (–7.49 to –4.10)	–	–3.04 (–4.85 to –1.24)	–4.81 (–6.49 to –3.13)	–	–4.52 (–5.97 to –3.08)	–
P value vs. PBO	0.0012	< 0.0001	–	0.0011	< 0.0001	–	< 0.0001	–
Change From Baseline in WNHS at Week 12								
Baseline (SD)	16.17 (4.61)	17.12 (3.82)	16.73 (4.42)	17.13 (4.14)	15.82 (4.62)	17.03 (4.20)	17.12 (4.20)	16.42 (4.59)
Mean value at week 12 (SD)	8.39 (7.59)	5.77 (7.17)	12.36 (7.22)	7.38 (7.32)	3.85 (6.35)	11.80 (7.45)	6.66 (7.89)	11.93 (6.89)
Change from baseline, mean (SD)	–7.78 (7.08)	–11.35 (7.25)	–4.37 (6.60)	–9.75 (7.28)	–11.97 (7.58)	–5.22 (6.56)	–10.46 (7.74)	–4.49 (6.33)
Difference vs. PBO, LSM (95% CI)[d]	–3.44 (–5.57 to –1.32)	–6.93 (–9.10 to –4.76)	–	–4.51 (–6.65 to –2.36)	–7.09 (–9.26 to –4.93)	–	–5.90 (–7.72 to –4.07)	–
P value vs. PBO	0.0017	< 0.0001	–	< 0.0001	< 0.0001	–	< 0.0001	–
Withdrawals								
Total, n/N (%)	16/80 (20.0)	12/81 (14.8)	15/80 (18.8)	9/83 (10.8)	12/79 (15.2)	5/79 (6.3)	28/252 (11.1)	18/84 (21.4)
Harms								
SAEs, n/N (%)	3/87 (3.4%)	0	4/80 (5.0%)	0	2/79 (2.5%)	2/79 (2.5%)	7/252 (2.8%)	3/83 (3.6%)
WDAEs, n/N (%)	2/87 (2.3%)	1/81 (1.2%)	2/80 (2.5%)	1/88 (1.1%)	0	1/79 (1.3%)	3/252 (1.2%)	1/83 (1.2%)

Outcome	ASTERIA I			ASTERIA II			GLACIAL	
	OMA (150 mg)	OMA (300 mg)	PBO	OMA (150 mg)	OMA (300 mg)	PBO	OMA (300 mg)	PBO
Notable Harms								
Arterial thrombotic events	1/87 (1.1%)	0	0	0	0	0	0	1/83 (1.2%)
Anaphylaxis	0	1/81 (1.2%)	0	0	0	0	0	0
Malignancies	0	0	1/80 (1.3)	0	1/79 (1.3%)	0	0	0

AE = adverse event; ANCOVA = analysis of covariance; CI = confidence interval; LSM = least squares mean; OMA = omalizumab; PBO = placebo; SAE = serious adverse event; SD = standard deviation; UAS7 = Urticaria Activity Score over seven days; vs. = versus; WDAE = withdrawal due to adverse event; WISS = Weekly Itch Severity Score; WNHS = Weekly Number of Hives Score.

[a] The LSM was estimated using an ANCOVA model. The strata or covariates are baseline UAS7 (less than median versus greater than or equal to median) and baseline weight (< 80 kg versus ≥ 80 kg).

[b] *P* value is derived from ANCOVA t-test.

[c] The LSMs were estimated using an ANCOVA model. The strata are baseline WISS (< 13, ≥ 13) and baseline weight (< 80 kg versus ≥ 80 kg).

[d] The LSM was estimated using an ANCOVA model. The strata are baseline WNHS (less than median versus greater than or equal to median) and baseline weight (< 80 kg versus ≥ 80 kg).

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Chronic idiopathic urticaria (CIU), also referred to as chronic spontaneous urticaria, is characterized by the presence of itchy hives, angioedema, or both, lasting for a period of six weeks or longer with no identifiable external cause.[1-4] The average duration of CIU is between one and five years, with a longer duration in more severe cases, cases with concurrent angioedema, cases in combination with physical urticaria, or cases with a positive autologous serum skin test.[3] Although CIU can manifest at any age, the peak incidence rate is among individuals between 20 and 40 years of age.[1,3] The prevalence of CIU has been reported to be 0.5% to 1.0% in the overall population, with a twofold higher incidence in women than in men.[1,3,4] Available data suggest that 33% to 67% of patients with CIU exhibit both hives and angioedema, 29% to 65% exhibit only hives, and 1 to 13% exhibit only angioedema.[3]

The pathogenesis of CIU is not completely understood but may be associated with histamine release from cutaneous mast cells and blood basophils.[1] Approximately one-third of patients will test positive on the autologous serum skin test, indicating the presence of autoantibodies or histamine-releasing factors, and some patients test positive for autoantibodies to the immunoglobulin E (IgE) receptor or IgE in the basophil histamine-release assay, or both.[1]

1.2 Standards of Therapy

The goal of CIU management is to achieve complete symptom control of hives. The first approach is to identify and eliminate underlying causes or eliciting triggers, and the second is pharmacotherapy aimed at providing symptom relief.[3,6,10]

Identifying and eliminating the underlying cause is the most desirable option, but this may not be applicable in many cases of CIU.[3] Studies have reported successful identification of possible underlying causes of CIU in 0% to 43% of patients.[3] Identifying underlying causes often requires a broad spectrum of investigative procedures from specialized centres.[3]

Pharmacological treatments aim to reduce the effect of mast cell mediators such as histamine, platelet-activating factor, and others on target organs. International guidelines on the management of urticaria were developed by a joint initiative of the Dermatology Section of the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization with participating delegates from 21 national and international societies.[5,6] The Allergy 2014 guidelines recommend non-sedating second-generation H_1 antihistamines as first-line treatment of CIU for adults and children. Older first-generation antihistamines have anticholinergic sedative effects that make them unsuitable for use both in adults and, especially, in children. For patients not responding adequately to the recommended dose of second-generation H_1 antihistamines after two weeks, the dose can be increased up to fourfold. If symptoms persist after one to four further weeks of treatment at a fourfold dose of second-generation H_1 antihistamines, add-on therapy using omalizumab (OMA), cyclosporin A, or the leukotriene receptor antagonist (LTRA) montelukast should be considered. The clinical expert consulted for this review indicated that H_2 antagonists (e.g., ranitidine) are also commonly prescribed for patients with inadequate response to H_1 antihistamines, although the aforementioned international guidelines do not recommend their use.[5,6] A short course of corticosteroids up to a maximum of 10 days may be used to manage exacerbations, but long-term use of systemic corticosteroids is not recommended.

Approximately 50% of CIU patients will continue to experience symptoms despite treatment with standard doses of H_1 antihistamines.[3] Although higher doses are often used, side effects such as drowsiness may limit the ability to reach sufficient doses to achieve full resolution of hives.

The only Health Canada–approved drugs for the treatment of CIU are H_1 antihistamines (i.e., cetirizine, loratadine, desloratadine, and fexofenadine) and OMA.

1.3 Drug

OMA is a humanized, recombinant, immunoglobulin G, anti-IgE monoclonal antibody that binds to IgE and prevents it from binding to its high-affinity receptor on mast cells and basophils, thereby reducing IgE-induced mast cell and basophil degranulation and the release of histamine.[1] For CIU, OMA is administered subcutaneously by a health care provider every four weeks at a dose of 150 mg or 300 mg. OMA is available as a lyophilized, sterile powder in a single-use 5 mL vial designed to deliver 150 mg of OMA for subcutaneous administration upon reconstitution with 1.4 mL sterile water for injection.

OMA was previously reviewed by the Canadian Expert Drug Advisory Committee (CEDAC, now the Canadian Drug Expert Committee [CDEC]) in March 2006 for the treatment of moderate to severe persistent asthma in adults and adolescents aged 12 years or older whose symptoms are inadequately controlled with inhaled corticosteroids, and received a recommendation of "do not list."[11]

Indication under review
Treatment of adults and adolescents (12 years of age and above) with chronic idiopathic urticaria who remain symptomatic despite H_1 antihistamine treatment
Listing criteria requested by sponsor
Treatment of adults and adolescents (12 years of age and above) with persistent (disease duration ≥ 6 months) moderate to severe (UAS7 score ≥ 16 or DLQI ≥ 10) chronic idiopathic urticaria who remain symptomatic (presence of hives and/or associated itching) despite H_1 antihistamine treatment. Response to treatment should be assessed 12 weeks following OMA initiation. For patients initiated on 150 mg every 4 weeks and who do not adequately respond by Week 12, consideration to increase the dose to 300 mg every 4 weeks should be given. Response to treatment should be reassessed 12 weeks thereafter.

TABLE 2: KEY CHARACTERISTICS OF OMALIZUMAB AND SECOND-GENERATION H_1 ANTIHISTAMINES

	Omalizumab	Second-Generation H_1 antihistamines
Mechanism of Action	Omalizumab is a recombinant DNA-derived humanized monoclonal antibody that selectively binds to human IgE. It prevents binding of IgE to the high-affinity IgE receptor, FcεRI, thereby reducing the amount of free IgE that is available to trigger the allergic–inflammatory cascade.	H_1 antihistamines are histamine H_1 receptor reverse agonists. Second-generation H_1 antihistamines (cetirizine, loratadine, desloratadine and fexofenadine) act via selective inhibition of peripheral H_1 receptors.

	Omalizumab	Second-Generation H_1 antihistamines
Indication[a]	Treatment of patients with CIU who remain symptomatic despite H_1 antihistamine treatment	• Cetirizine is indicated for the fast relief of CIU (e.g., pruritus and hives). • Loratadine is indicated for the relief of symptoms and signs of chronic urticaria and other allergic dermatologic disorders. • Desloratadine is indicated for the rapid relief of symptoms associated with CIU, such as pruritus and hives. • Fexofenadine is indicated for the relief of symptoms associated with CIU in adults and children 12 years of age and older.
Route of Administration	Subcutaneous injection	Oral tablets
Recommended Dose[b]	150 mg and 300 mg, every 4 weeks	Cetirizine: 5 mg to 20 mg daily Loratadine: 10 mg daily Desloratadine: 5 mg daily Fexofenadine: 120 mg daily
Serious Side Effects and Safety Issues	Anaphylaxis has been reported to occur after administration of omalizumab.	Contraindicated in patients with a known hypersensitivity
Other	–	One of the most common side effects is somnolence.

CIU = chronic idiopathic urticaria; FcεRI = fragment crystallizable epsilon receptor I; IgE = immunoglobulin E.
[a] Health Canada indication.
[b] Second-generation antihistamines are also used in practice at up to four times the approved dose.
Source: Product monographs for OMA,[8] cetirizine,[12] loratadine,[13] desloratadine,[14] and fexofenadine.[15]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of OMA (150 mg or 300 mg subcutaneous injection every four weeks) for the treatment of CIU in adults and adolescents (12 years of age and above) who remain symptomatic despite H_1 antihistamine treatment.

2.2 Methods

All trials considered pivotal by Health Canada for the CIU indication of OMA were included in the systematic review. Other studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult and adolescent patients with CIU who remain symptomatic despite H_1 antihistamine treatment
Intervention	Omalizumab 150 mg or 300 mg SC injection every four weeks with H_1 antihistamines as background therapy
Comparators	• Placebo • Montelukast[a] • H_2 antagonists[a] • Cyclosporine[a] • Doxepin[a] • Hydroxychloroquine[a] • Prednisone[a] • All with H_1 antihistamines as background therapy
Outcomes	**Key efficacy outcomes** • UAS7 • WISS • WNHS • Urticaria control test • Quality of life **Harms outcomes** • AEs • SAEs • WDAEs • Mortality • Notable harms: ATEs, anaphylaxis, malignancies
Study Design	Published and unpublished phase 3 RCTs

AE = adverse event; ATEs = arterial thrombotic events; CIU = chronic idiopathic urticaria; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; UAS7 = Urticaria Activity Score over seven days; WDAE = withdrawal due to adverse event; WISS = Weekly Itch Severity Score; WNHS = Weekly Number of Hives Score.

[a] Not approved for the treatment of CIU in Canada, but used in clinical practice according to the clinical expert consulted for this review.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Xolair (omalizumab) and chronic idiopathic urticaria.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on December 1, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on April 8, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Databases (free), Internet Search, and Open Access Journals. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

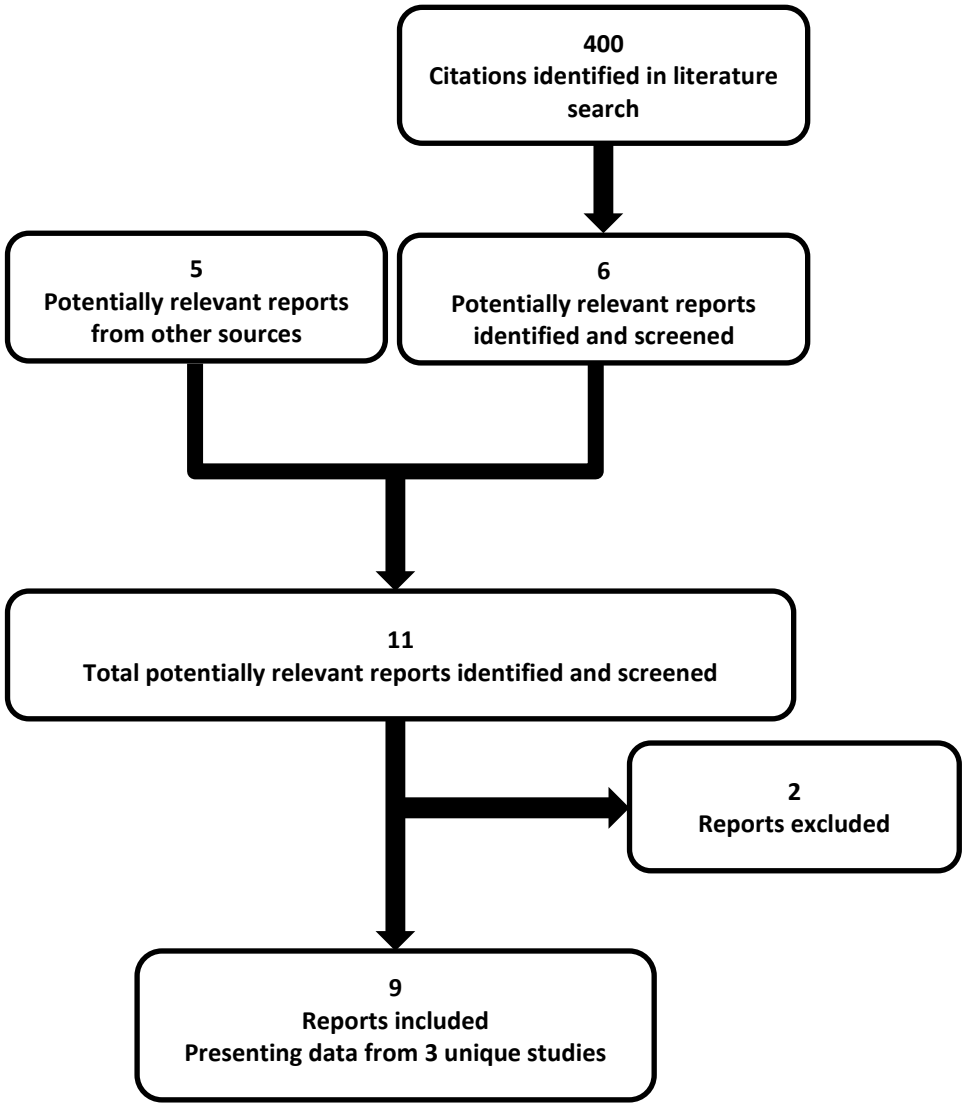
Two clinical reviewers for CADTH Common Drug Review (CDR) independently selected studies for inclusion in the review based on titles and abstracts according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in Appendix 3: Excluded Studies.

3. RESULTS

3.1 Findings From the Literature

A total of three studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 2 and described in Section 3.2. A list of excluded studies is presented in Appendix 3: Excluded Studies.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



QUOROM = Quality of Reporting of Meta-analyses.

TABLE 4: DETAILS OF INCLUDED STUDIES

		ASTERIA I	ASTERIA II	GLACIAL
DESIGNS AND POPULATIONS	**Study Design**	Multi-centre double-blind placebo-controlled RCT	Multi-centre double-blind placebo-controlled RCT	Multi-centre double-blind placebo-controlled RCT
	Locations	53 centres in 8 countries: 35 centres in United States, the rest in Europe	55 centres in 8 countries: 34 centres in United States, the rest in Europe	65 centres in 7 countries: 39 in United States, 16 in Europe, 8 in Oceania, and 2 in Singapore
	Randomized (N)	319	323	336
	Inclusion Criteria	Aged 12 to 75 years, diagnosed with CIU for ≥ 6 months, remained symptomatic for ≥ 8 consecutive weeks despite standard-dose H_1 antihistamine treatment, UAS7 ≥ 16 for at least 4 out of 7 days, WISS ≥ 8 for the 7 days prior to randomization, in-clinic UAS ≥ 4 on at least one screening visit		Aged 12 to 75 years, diagnosed with CIU for ≥ 6 months, remained symptomatic for > 6 consecutive weeks despite using H_1 antihistamine (up to four times the approved dosage) and H_2 blockers or LTRAs, or both, UAS7 ≥ 16 for at least 4 out of 7 days, WISS ≥ 8 for the 7 days prior to randomization, in-clinic UAS ≥ 4 on at least one screening visit
	Exclusion Criteria	Previous treatment with OMA (within a year), H_2 blockers (within a week), LTRA (within a week); greater than approved dose of H_1 antihistamines (within 3 days); regular doses of doxepin (within 14 days); routine doses of corticosteroids, hydroxychloroquine, methotrexate, cyclosporine, or cyclophosphamide (within 30 days); weight < 20 kg; clearly defined underlying etiology for chronic urticaria; evidence of parasitic infection; other skin disease associated with itch		Previous treatment with OMA (within a year); regular doses of doxepin (within 14 days); routine doses of corticosteroids, hydroxychloroquine, methotrexate, cyclosporine, or cyclophosphamide (within 30 days); weight < 20 kg; clearly defined underlying etiology for chronic urticaria; evidence of parasitic infection; other skin disease associated with itch
DRUGS	**Intervention(s)**	OMA 75 mg (n = 78) OMA 150 mg (n = 80) OMA 300 mg (n = 81) every 4 weeks by subcutaneous injection	OMA 75 mg (n = 82) OMA 150 mg (n = 83) OMA 300 mg (n = 79) every 4 weeks by subcutaneous injection	OMA 300 mg (n = 252) every 4 weeks by subcutaneous injection
	Comparator(s)	Placebo (n = 80) every 4 weeks by subcutaneous injection	Placebo (n = 79) every 4 weeks by subcutaneous injection	Placebo (n = 84) every 4 weeks by subcutaneous injection
DURATION	**Phase**			
	Run-in	14 days	14 days	14 days
	Double-blind	24 weeks	12 weeks	24 weeks

		ASTERIA I	ASTERIA II	GLACIAL
	Follow-up	16 weeks	16 weeks	16 weeks
OUTCOMES	**Primary End Point**	Change from baseline in WISS at week 12	Change from baseline in WISS at week 12	Safety outcomes: AEs, laboratory test results, vital signs and antibodies to omalizumab
	Other End Points	**Secondary** • Change from baseline in UAS7 at week 12 • Change from baseline in WNHS at week 12 • Time to MCID[a] response in WISS by week 12 • Proportion of patients with UAS7 ≤ 6 at week 12 • Proportion of WISS MCID responders at week 12 • Change from baseline in DLQI at week 12 • Proportion of complete responders (UAS7 = 0) at week 12 **Exploratory outcomes** • UAS7 (weeks 12, 24, 40), WISS (week 24), WNHS (week 24), DLQI (weeks 24, 40), CU-Q2oL (weeks 12, 24), and EQ-5D (weeks 12, 40)	**Secondary** • Change from baseline in UAS7 at week 12 • Change from baseline in WNHS at week 12 • Time to MCID response in WISS by week 12 • Proportion of patients with UAS7 ≤ 6 at week 12 • Proportion of WISS MCID responders at week 12 • Change from baseline in DLQI at week 12 **Exploratory outcomes** • UAS7 (weeks 12, 28), DLQI (week 28), CU-Q2oL (weeks 12, 28), and EQ-5D (weeks 12, 28)	**Key efficacy end point** • Change from baseline in WISS at week 12 **Other efficacy end points** • Change from baseline in UAS7 at week 12 • Change from baseline in WNHS at week 12 • Time to MCID response in WISS by week 12 • Proportion of patients with UAS7 ≤ 6 at week 12 • Proportion of WISS MCID responders at week 12 • Change from baseline in DLQI at week 12 • Proportion of complete responders (UAS7 = 0) at week 12 **Exploratory outcomes** • UAS7 (weeks 12, 24), WISS (week 24), WNHS (week 24), CU-Q2oL (week 12), and EQ-5D (week 12)
NOTES	**Publications**	Saini et al. 2014[16]	Maurer et al. 2013[17]	Kaplan et al. 2013[18]

AE = adverse event; CIU = chronic idiopathic urticaria; CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimenions Questionnaire; LTRA = leukotriene receptor antagonist; MCID = minimal clinically important difference; OMA = omalizumab; RCT = randomized controlled trial; UAS = Urticaria Activity Score; UAS7 = Urticaria Activity Score over seven days; WISS = Weekly Itch Severity Score; WNHS = Weekly Number of Hives Score.

[a] The MCID used by the manufacturer for WISS was ≥ 5 points.

Note: Five additional reports were included: the manufacturer's submission;[19] Clinical Study Reports for ASTERIA I,[20] ASTERIA II,[21] and GLACIAL;[22] and the Health Canada report.[23]

Source: Clinical Study Reports for ASTERIA I,[20] ASTERIA II,[21] and GLACIAL.[22]

3.2 Included Studies

3.2.1 Description of studies

All three included studies were pivotal trials: ASTERIA I, ASTERIA II, and GLACIAL (Table 4).

ASTERIA I and ASTERIA II were phase 3, multi-centre, randomized, double-blind studies that compared three doses of OMA (75 mg, 150 mg, and 300 mg) with placebo. The primary objective of ASTERIA I and ASTERIA II was to evaluate whether OMA was superior to placebo for improving the Weekly Itch Severity Score (WISS) after 12 weeks in adult and adolescent patients with refractory CIU receiving concomitant standard-dose H_1 antihistamine therapy. The main difference between ASTERIA I and ASTERIA II was that the treatment period was 24 weeks in duration in ASTERIA I and 12 weeks in ASTERIA II. Both trials had a 16-week follow-up period thereafter. Study designs are presented in Figure 5 and Figure 6 (Appendix 4). Patients in ASTERIA I (N = 319) and ASTERIA II (N = 323) were randomized to three OMA treatment groups (75 mg, 150 mg, and 300 mg doses) and one placebo treatment group at a ratio of 1:1:1:1. A hierarchical dynamic randomization scheme stratified for overall balance, baseline WISS (< 13 versus ≥ 13), body weight (< 80 kg versus ≥ 80 kg), and study centre was used. Treatment was assigned using an interactive voice and web response system. All patients and study personnel were blinded to treatment assignment. Patients were given the first dose of study medication at day 1 and were re-treated every four weeks. Monitoring for efficacy and safety occurred at each visit and twice daily with an electronic diary (eDiary) portable device.

GLACIAL was a phase 3, multi-centre, randomized, double-blind study that compared OMA 300 mg with placebo. The primary objective of GLACIAL was to evaluate the safety of OMA compared with placebo in adult and adolescent patients with refractory CIU receiving concomitant therapy including H_1 antihistamines at up to four times the approved dose and either H_2 blockers or LTRAs, or both. The treatment period lasted for 24 weeks followed by a 16-week follow-up period. The study design is presented in Figure 7 (Appendix 4). Patients in GLACIAL (N = 336) were randomized to OMA 300 mg or placebo in a ratio of 3:1. The methods for treatment assignment and the hierarchical randomization scheme were similar to those in ASTERIA I and ASTERIA II. Patients were dosed and monitored in the same manner as in ASTERIA I and ASTERIA II.

Only the 150 mg and the 300 mg doses of OMA are approved for treatment of CIU in Canada. Therefore, the data for the 75 mg OMA treatment group are not reported in this review.

3.2.2 Populations

a) Inclusion and exclusion criteria

Inclusion and exclusion criteria for ASTERIA I and ASTERIA II were the same: eligible patients were between 12 and 75 years of age, had been diagnosed with CIU for more than six months, and had been symptomatic for more than eight weeks despite standard-dose H_1 antihistamine treatment. Patients also had to reach a specific threshold for Urticaria Activity Score over seven days (UAS7) (≥ 16) and WISS (≥ 8) during the screening period.

GLACIAL included patients aged 12 to 75 years who had been diagnosed with CIU for more than six months and who had remained symptomatic for more than six weeks despite using H_1 antihistamines (including doses up to four times the approved dosage level) and either H_2 blockers or LTRAs, or both. Patients had to reach the same thresholds for UAS7 and WISS during the screening period as in the ASTERIA trials.

b) Baseline characteristics

Baseline characteristics of patients enrolled in ASTERIA I, ASTERIA II, and GLACIAL are summarized in Table 5, Table 6, and Table 7, respectively. In all trials, most demographic and baseline characteristics were similar across treatment groups. Some differences were noted between groups: a higher proportion of males in the placebo group of ASTERIA I, ASTERIA II, and GLACIAL; a lower duration (by

greater than or equal to one year) of disease in the 300 mg groups of all trials; and a higher proportion of Caucasians in the 300 mg treatment group of ASTERIA I. However, none of the observed differences was considered to be clinically relevant by the consulting clinical expert.

The mean age of randomized participants across treatment groups in the included trials ranged from 40.4 years to 44.3 years. Female patients represented 65.0% to 80.0% of the trial populations. Caucasians represented 78.8% to 91.4% of enrolled patients. Body mass index ranged from 28.7 kg/m^2 to 31.0 kg/m^2. Included patients had CIU for a mean of 6.2 years to 8.8 years. For baseline disease characteristics, mean in-clinic Urticaria Activity Score (UAS) ranged from 5.2 points to 5.3 points, mean UAS7 from 29.5 points to 31.4 points, mean WISS from 13.7 points to 14.4 points, and mean Weekly Number of Hives Score (WNHS) from 15.8 points to 17.1 points.

TABLE 5: SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS — ASTERIA I

	ASTERIA I		
	OMA 150 mg (N = 80)	OMA 300 mg (N = 81)	PBO (N = 80)
Age (Years)			
Mean (SD)	41.1 (14.0)	42.4 (13.2)	40.4 (15.6)
Range	12 to 68	14 to 72	13 to 74
Sex			
Male, N (%)	16 (20.0%)	21 (25.9%)	28 (35.0%)
Female, N (%)	64 (80.0%)	60 (74.1%)	52 (65.0%)
Race, N (%)			
Native American	1 (1.3%)	1 (1.2%)	0
Asian	6 (7.5%)	1 (1.2%)	3 (3.8%)
Black	9 (11.3%)	5 (6.2%)	10 (12.5%)
White	63 (78.8%)	74 (91.4%)	64 (80.0%)
Not available	1 (1.3%)	0	3 (3.8%)
BMI (kg/m^2)			
Mean (SD)	29.8 (7.7)	29.3 (6.9)	28.7 (6.2)
Duration of CIU (Years)			
Mean (SD)	7.6 (9.2)	6.2 (8.0)	7.0 (9.7)
In-Clinic UAS			
Mean (SD)	5.3 (0.7)	5.3 (0.8)	5.3 (0.8)
UAS7			
Mean (SD)	30.3 (7.3)	31.3 (5.8)	31.1 (6.7)
WISS			
Mean (SD)	14.1 (3.8)	14.2 (3.3)	14.4 (3.5)
WNHS			
Mean (SD)	16.2 (4.6)	17.1 (3.8)	16.7 (4.4)

BMI = body mass index; CIU = chronic idiopathic urticaria; OMA = omalizumab; PBO = placebo; SD = standard deviation; UAS = Urticaria Activity Score; UAS7 = Urticaria Activity Score over seven days; WISS = Weekly Itch Severity Score; WNHS = Weekly Number of Hives Score.
Source: Clinical Study Report for ASTERIA I.[20]

TABLE 6: SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS — ASTERIA II

	ASTERIA II		
	OMA 150 mg (N = 82)	OMA 300 mg (N = 79)	PBO (N = 79)
Age (Years)			
Mean (SD)	43.0 (13.2)	44.3 (13.7)	43.1 (12.5)
Range	14 to 72	15 to 75	17 to 73
Sex			
Male, N (%)	17 (20.7%)	16 (20.3%)	24 (30.4%)
Female, N (%)	65 (79.3%)	63 (79.7%)	55 (69.6%)
Race, N (%)			
Native American	1 (1.2%)	0	0
Asian	1 (1.2%)	2 (2.5%)	2 (2.5%)
Black	5 (6.1%)	7 (8.9%)	4 (5.1%)
White	70 (85.4%)	68 (86.1%)	70 (88.6%)
Other	2 (2.4%)	1 (1.3%)	1 (1.3%)
Not available	3 (3.7%)	1 (1.3%)	2 (2.5%)
BMI (kg/m^2)			
Mean (SD)	30.0 (7.3)	29.0 (6.3)	30.0 (7.7)
Duration of CIU (Years)			
Mean (SD)	7.2 (8.9)	6.1 (7.3)	7.2 (10.7)
In-Clinic UAS			
Mean (SD)	5.3 (0.7)	5.3 (0.7)	5.3 (0.7)
UAS7			
Mean (SD)	31.4 (7.0)	29.5 (6.9)	31.0 (6.6)
WISS			
Mean (SD)	14.2 (4.1)	13.7 (3.5)	14.0 (3.4)
WNHS			
Mean (SD)	17.1 (4.1)	15.8 (4.6)	17.0 (4.2)

BMI = body mass index; CIU = chronic idiopathic urticaria; OMA = omalizumab; PBO = placebo; SD = standard deviation; UAS = Urticaria Activity Score; UAS7 = Urticaria Activity Score over seven days; WISS = Weekly Itch Severity Score; WNHS = Weekly Number of Hives Score.
Source: Clinical Study Report for ASTERIA II.[21]

TABLE 7: SUMMARY OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS — GLACIAL

	GLACIAL	
	OMA 300 mg (N = 252)	PBO (N = 83)
Age (Years)		
Mean (SD)	42.7 (13.9)	44.3 (14.7)
Range	14 to 75	14 to 73
Sex		
Male, N (%)	66 (26.2%)	28 (33.7%)
Female, N (%)	186 (73.8%)	55 (66.3%)

	GLACIAL	
	OMA 300 mg (N = 252)	PBO (N = 83)
Race, N (%)		
Native American	1 (0.4%)	0
Asian	8 (3.2%)	1 (1.2%)
Black	15 (6.0%)	6 (7.2%)
White	223 (88.5%)	75 (90.4%)
Other	1 (0.4%)	1 (1.2%)
Not available	4 (1.6%)	0
BMI (kg/m^2)		
Mean (SD)	29.4 (7.1)	31.0 (9.6)
Duration of CIU (Years)		
Mean (SD)	7.0 (8.8)	8.8 (11.2)
In-Clinic UAS		
Mean (SD)	5.2 (0.8)	5.2 (0.8)
UAS7		
Mean (SD)	31.2 (6.6)	30.2 (6.7)
WISS		
Mean (SD)	14.0 (3.6)	13.8 (3.6)
WNHS		
Mean (SD)	17.1 (4.2)	16.4 (4.6)

BMI = body mass index; CIU = chronic idiopathic urticaria; OMA = omalizumab; PBO = placebo; SD = standard deviation; UAS = Urticaria Activity Score; UAS7 = Urticaria Activity Score over seven days; WISS = Weekly Itch Severity Score; WNHS = Weekly Number of Hives Score.
Source: Clinical Study Report for GLACIAL.[22]

The mandatory concomitant baseline medication in ASTERIA I and ASTERIA II was a second-generation H_1 antihistamine at its approved dose. Other medications for CIU (see list in Table 3), including OMA, were allowed only for the treatment of a condition other than CIU. In GLACIAL, patients had to be treated with H_1 antihistamine (up to four times the approved dose) and either H_2 antagonists or LTRAs, or both. The utilization of these medications in GLACIAL at day 1 is reported in Table 8. More than half of patients used a combination of H_1 antihistamines and H_2 antagonists, and more than 60% used H_1 antihistamine doses greater than the approved dose.

TABLE 8: CONCOMITANT BASELINE MEDICATIONS IN THE GLACIAL TRIAL

	GLACIAL	
	OMA 300 mg (N = 252)	PBO (N = 83)
Use of CIU Therapies on Study Day 1, N (%)		
H_1 antihistamines + H_2 antagonists only	141 (56.0%)	45 (54.2%)
H_1 antihistamines + H_2 antagonists + LTRAs only	64 (25.4%)	25 (30.1%)
H_1 antihistamines + LTRAs only	36 (14.3%)	11 (13.3%)
Other CIU medication combinations	11 (4.4%)	2 (2.4%)

	GLACIAL	
	OMA 300 mg (N = 252)	PBO (N = 83)
Use of H_1 Antihistamine Therapies on Study Day 1, N (%)		
1 × standard dose	98 (39.7%)	25 (30.5%)
2 × standard dose	80 (32.4%)	36 (43.9%)
3 × standard dose	30 (12.1%)	7 (8.5%)
4 × standard dose	39 (15.8%)	14 (17.1%)

CIU = chronic idiopathic urticaria; OMA = omalizumab; PBO = placebo; LTRA = leukotriene receptor antagonist.
Source: Clinical Study Report for GLACIAL.[22]

3.2.3 Interventions

The interventions were administered in the same manner across the three trials. On day 1, all patients received OMA (75 mg, 150 mg, or 300 mg) or placebo administered subcutaneously every four weeks. All vials were shipped blind to each study site. An individual not involved in the evaluation of patients was identified to administer the study drug. The 300 mg dose had to be administered as two injections of the 150 mg strength. To maintain masking, all patients received two injections (i.e., the 75 mg and 150 mg arms received one placebo injection in addition to the OMA injection) at each treatment visit.

Concomitant medications were allowed as follows: In ASTERIA I and ASTERIA II, long-acting H_1 antihistamines at approved doses were allowed during the study. Patients remained on a stable H_1 antihistamine treatment regimen throughout the study period. Diphenhydramine 25 mg was provided as rescue medication on an as-needed basis. In ASTERIA I, during the latter 12 weeks of the treatment period (i.e., after the assessment of the primary outcome), patients could add one additional second-generation H_1 antihistamine treatment, but the dose of antihistamine could not be increased above the approved dose. In GLACIAL, patients remained on stable H_1 antihistamine, and one or both of H_2 blocker and LTRA, throughout the study period. Diphenhydramine 25 mg was provided as rescue medication on an as-needed basis.

3.2.4 Outcomes

The efficacy outcomes in the included trials were based on UAS7 and its subcomponents, WISS and WNHS. The efficacy end points were collected twice daily with the Urticaria Patient Daily Diary using the eDiary. The content validity of the Urticaria Patient Daily Diary has been confirmed in both adult[24] and adolescent[25] patients. Quality of life was measured with the Dermatology Life Quality Index (DLQI), the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL), and the EuroQol 5-Dimensions Questionnaire (EQ-5D). The validity of outcomes is discussed in more detail in Appendix 5: Validity of Outcome Measures.

a) Urticaria Activity Score

The UAS end points were collected via the eDiary. The daily UAS is the sum of the daily Itch Severity Score (0 = none, 1 = mild, 2 = moderate, 3 = severe) and the daily Number of Hives Score (0 = none, 1 = between 1 and 6 hives, 2 = between 7 and 12 hives, 3 = greater than 12 hives), giving a range of 0 to 6 points per day.[26] The UAS7 is the sum of the daily UAS scores over a week and ranges from 0 to 42, with higher scores indicating more severe symptoms. The minimal clinically important difference (MCID) for UAS7 was reported to be 9.5 to 10.5 points. The MCID for WISS was reported to be 4.5 to 5.0 points, and the MCID for WNHS was reported to be 5.0 to 5.5 points.[26] According to the clinical expert consulted on this review, a UAS7 of 6 or less is commonly used as a threshold to define disease control.

b) Dermatology Life Quality Index

The DLQI is a validated[27,28] dermatology-specific quality of life measure. It is a 10-item questionnaire that assesses six different aspects that may affect quality of life: symptoms and feelings, daily activities, leisure activities, work or school, personal relationships, and treatment.[29] Each of the 10 questions is scored from 0 (not at all) to 3 (very much), and the overall DLQI is calculated by summing the score of each question, resulting in a numeric score between 0 and 30 (or a percentage of 30). Higher scores indicate a greater impairment in quality of life. The six individual domain scores of DLQI were also reported in the included trials. The MCID for the DLQI in CIU patients was reported to be in the range of 2.24 to 3.10 points.[28]

c) Chronic Urticaria Quality of Life Questionnaire

The Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) is a validated[30] CIU-specific quality of life measure. The CU-Q2oL is a 23-item, self-administered questionnaire that includes six quality of life dimensions: pruritus, swelling, impact on life activities, sleep problems, limits, and looks. Each item is scored on a 5-point Likert scale (1 = not at all, 5 = extremely) where patients indicate how troubled they are by each problem. Overall CU-Q2oL scores are converted to a 0 to 100 scale, with higher scores indicating greater quality of life impairment. The overall score and the domain scores (on a 0 to 100 scale) were reported in the included trials. No studies reporting an MCID for the CU-Q2oL were identified.

d) EuroQol 5-Dimensions Questionnaire

The EuroQol 5-Dimensions Questionnaire (EQ-5D) is a generic quality of life instrument.[31] The questionnaire consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a visual analogue scale. An EQ-5D index score (range from –0.59 to 1.00) was reported in the included trials using the five questions and the UK population-based scoring algorithm. The data from the visual analogue scale (range from 0 to 100) were reported in the "health state" variable. Higher EQ-5D index scores indicate a better health state. No studies specifically validating EQ-5D in patients with CIU were identified. The general MCID for EQ-5D is between 0.033 and 0.074.

e) Safety

Safety was monitored through the collection of adverse events (AEs), withdrawals due to adverse events (WDAEs), mortality, serious adverse events (SAEs), concomitant medications, laboratory test results, vital signs, and antibodies to omalizumab. AEs identified by the trialists as being of special interest, including anaphylaxis, malignancies, and arterial thrombotic events were also monitored.

f) Other outcomes

Other outcomes were assessed in the included trials. Since they were not specified in the review protocol, these outcomes are not presented in this report. For example, the Urticaria Patient Daily Diary included items such as largest hive size, sleep interference score, activity interference score, angioedema episodes and management, and health care provider contact. Also, the Medical Outcomes Study Sleep Scale questionnaire was used to capture more specific data on sleep.

3.2.5 Statistical analysis

In ASTERIA I and ASTERIA II, the primary analysis was the comparison of the OMA treatment groups with the placebo groups in terms of the change from baseline in WISS at week 12. The power calculation for this comparison assumed a mean change from baseline in WISS at week 12 of 9 points and 3.5 points for the OMA and placebo groups, respectively, with a common standard deviation of 6 points (based on data from two previous studies). Assuming a discontinuation rate of 15% (based on data from the same

two studies) by week 12, a total of 300 patients (1:1:1:1 randomization ratio with 75 patients in each treatment group) were required to yield approximately 98% power to detect a difference in the primary end point at the 0.05 level for any OMA group. A type I error control plan was used to adjust for the comparisons of multiple OMA groups to the placebo group in order to maintain an overall type I error rate of 0.05 (two-sided). The comparisons were performed using analysis of covariance, controlling for baseline WISS (< 13 versus ≥ 13) and baseline weight (< 80 kg versus ≥ 80 kg). A separate analysis of covariance model was run for each OMA dose group versus the placebo group. The least squares means, corresponding 95% confidence intervals (CIs), and *P* values were presented. The same statistical analyses were used for the change from baseline in UAS7 and the change from baseline in WNHS, with adjustment for baseline values of each variable (stratified as less than median versus greater than or equal to median). Missing end points were imputed by carrying forward the baseline values (i.e., a BOCF [baseline observation carried forward] approach). To control for multiplicity of analyses, a hierarchical analysis plan was applied to the secondary end points for each dose achieving statistical significance on the primary end point. Efficacy outcomes for GLACIAL were analyzed similarly.

Sensitivity analyses of the primary end point of ASTERIA I and ASTERIA II and the key efficacy end point of GLACIAL were conducted using a last observation carried forward (LOCF) method instead of BOCF; a mixed effects model, instead of analysis of covariance, with baseline WISS, baseline weight, treatment group, and time as covariates; and a BOCF approach to impute the week 12 value for patients who received any systemic steroids during the two weeks prior to the week 12 visit. A number of subgroup analyses based on demographic variables, study centre, disease characteristics, and medication use were presented for the primary efficacy outcome.

For GLACIAL, the primary outcome was safety. Approximately 320 patients were planned for randomization to either the OMA 300 mg group or the placebo group in a 3:1 ratio. The probability of observing one or more instances of an AE over the period of this study, assuming a background rate of 2% or 3%, was above 99% for both rates in the OMA group, and 80% and 91% in the placebo group, respectively. Combining the patients in the OMA group in GLACIAL with those in its CIU sister studies (ASTERIA I and ASTERIA II) was expected to provide a safety database with at least 300 patients treated with OMA 300 mg for 24 weeks. The analysis of safety consisted primarily of descriptive summaries. No formal statistical testing was performed on the safety end points.

MCIDs of 11 points for UAS7 and 5 points for WISS were used by the investigators to calculate outcomes based on MCID thresholds.

a) Analysis populations

Across the three trials, three analysis populations relevant to this report were defined:

- The *randomized population* included all randomized patients regardless of whether they received any study drug.
- The *modified intention-to-treat population* included all patients randomized in the study who received at least one dose of study drug. This analysis population was used for efficacy analysis.
- The *safety population* included patients who received at least one dose of study drug (the highest dose received defining the group for analysis) or placebo. This analysis population was used for safety analysis.

3.3 Patient Disposition

Patient disposition in ASTERIA I, ASTERIA II, and GLACIAL is summarized in Table 9, Table 10, and Table 11, respectively. Across studies, discontinuation rates ranged from 10% in ASTERIA II (the

shortest of the three trials) to 18% in ASTERIA I. Across all trials, the two most common reasons for discontinuation were disease progression (43% of all discontinuations) and the patient's (or legal guardian's) decision to withdraw consent (37% of all discontinuations). Although 10% more patients in the 300 mg OMA treatment group completed GLACIAL compared with the placebo group, there was no clear imbalance in discontinuation rates between treatment groups in ASTERIA I, and discontinuation was least frequent in the placebo group of ASTERIA II. There was also no clear trend with respect to reasons for discontinuation in the OMA groups versus placebo.

TABLE 9: PATIENT DISPOSITION — ASTERIA I

	ASTERIA I		
	OMA 150 mg	OMA 300 mg	PBO
Screened, N	483[a]		
Randomized, N	80	81	80
Discontinued, N (%)	16 (20.0)	12 (14.8)	15 (18.8)
• Adverse event	1 (1.3)	1 (1.2)	2 (2.5)
• Physician decision	1 (1.3)	1 (1.2)	NR
• Patient or legal guardian decision	8 (10.0)	5 (6.2)	2 (2.5)
• Disease progression	6 (7.5)	5 (6.2)	10 (12.5)
• Lost to follow-up	NR	NR	1 (1.3)
mITT, N (%)	80 (100.0)	81 (100.0)	80 (100.0)
Safety, N (%)	87[b] (108.8)	81 (100.0)	80 (100.0)

mITT = modified intention to treat; NR = not reported; OMA = omalizumab; PBO = placebo.
[a] Of the patients screened, 78 were randomized to the 75 mg OMA treatment group.
[b] Seven patients randomized to the 75 mg group received one dose of 150 mg OMA.
Source: Clinical Study Report for ASTERIA I.[20]

TABLE 10: PATIENT DISPOSITION — ASTERIA II

	ASTERIA II		
	OMA 150 mg	OMA 300 mg	PBO
Screened, N	466[a]		
Randomized, N	83	79	79
Discontinued, N (%)	9 (10.8)	12 (15.2)	5 (6.3)
• Adverse event	1 (1.2)	1 (1.3)	1 (1.3)
• Patient or legal guardian decision	3 (3.6)	3 (3.8)	3 (3.8)
• Disease progression	3 (3.6)	6 (7.6)	NR
• Lost to follow-up	2 (2.4)	2 (2.5)	1 (1.3)
mITT, N (%)	82[b] (98.8)	79 (100.0)	79 (100.0)
Safety, N (%)	88[c] (106.0)	79 (100.0)	79 (100.0)

mITT = modified intention to treat; NR = not reported; OMA = omalizumab; PBO = placebo.
[a] Of the patients screened, 82 were randomized to the 75 mg OMA treatment group.
[b] One patient randomized to the 150 mg group did not receive the study drug because of the patient's decision to withdraw and was therefore not included in the mITT population.
[c] Six patients randomized to the 75 mg OMA group received at least one dose of 150 mg OMA.
Source: Clinical Study Report for ASTERIA II.[21]

TABLE 11: PATIENT DISPOSITION — GLACIAL

	GLACIAL	
	OMA 300 mg	PBO
Screened, N	480	
Randomized, N	252	84
Discontinued, N (%)	28 (11.1)	18 (21.4)
• Adverse event	3 (1.2)	1 (1.2)
• Physician decision	1 (0.4)	1 (1.2)
• Patient or legal guardian decision	10 (4.0)	8 (9.5)
• Disease progression	11 (4.4)	8 (9.5)
• Lost to follow-up	3 (1.2)	0
mITT, N (%)	252 (100.0)	83[a] (98.8)
Safety, N (%)	252 (100.0)	83 (98.8)

mITT = modified intention to treat; OMA = omalizumab; PBO = placebo.
[a] One patient randomized to the PBO group did not receive the study drug as a result of not meeting all study eligibility criteria and was therefore not included in the mITT population.
Source: Clinical Study Report for GLACIAL.[22]

3.4 Exposure to Study Treatments

Medication exposure is presented in Table 12. In the three trials, most of the patients received their assigned treatment for the entire duration of the treatment period.

TABLE 12: EXTENT OF EXPOSURE TO STUDY DRUG

	ASTERIA I			ASTERIA II			GLACIAL	
	OMA 150 mg (N = 87)	OMA 300 mg (N = 81)	PBO (N = 80)	OMA 150 mg (N = 88)	OMA 300 mg (N = 79)	PBO (N = 79)	OMA 300 mg (N = 252)	PBO (N = 83)
Duration of Exposure (Weeks)								
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22.4 (4.7)	20.6 (6.4)
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	24.0	24.0
Number of Doses								
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5.6 (1.2)	5.1 (1.6)
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6.0	6.0

SD = standard deviation; OMA = omalizumab; PBO = placebo.
Source: Clinical Study Reports for ASTERIA I,[20] ASTERIA II,[21] and GLACIAL.[22]

Initiation of a new concomitant CIU medication during the treatment period of ASTERIA I, ASTERIA II, and GLACIAL is summarized in Table 16, Table 17, and Table 18, respectively (see Appendix 4). Fewer patients began a new CIU medication in ASTERIA II (from [redacted] to [redacted]% across groups), which may be related to the shorter duration of treatment in this trial. The proportions of patients using a new concomitant medication for CIU did not differ markedly between ASTERIA I and GLACIAL (from [redacted] to [redacted]% of patients across groups). However, across trials, the OMA 300 mg groups had a numerically lower number of patients who began a new concomitant CIU medication compared with the other treatment groups.

The change from baseline in rescue medication (diphenhydramine 25 mg) use at week 12 is presented in Table 19. Both doses of OMA in ASTERIA I and the 300 mg dose in ASTERIA II provided a [redacted] of diphenhydramine use versus placebo. The difference between OMA and placebo was [redacted] in GLACIAL.

3.5 Critical Appraisal

3.5.1 Internal validity

The three pivotal studies were double-blind, multi-centre, randomized, placebo-controlled trials. The randomization process was done using an interactive voice and web response system and appeared adequate. Treatment allocation appeared to be adequately concealed during the trials through the use of placebo injections as well as dummy injections to mask the OMA 300 mg group in which patients required two 150 mg injections. The reconstituted solution of active drug is described as viscous[8] and could be different in appearance from the placebo, but the drug was administered by an individual who was not involved in the assessment of the patients. The use of an eDiary for monitoring efficacy outcomes lowered the likelihood of recall issues.

Most of the baseline characteristics of patients were similar between groups and across trials. Some differences were observed for gender or duration of CIU, but none of the observed differences was considered to be clinically relevant by the consulting clinical expert. Some differences in completion rates were observed, notably in ASTERIA II (i.e., more discontinuations in OMA groups versus placebo group) and GLACIAL (more discontinuations in placebo group versus OMA groups), but no clear relation with the active treatment group could be inferred. The proportions of patients initiating a new concomitant medication for CIU during the trial were numerically lower in the OMA 300 mg treatment groups, which may reflect higher treatment efficacy of this dosage; the direction of bias, if any, from this trend would tend to favour placebo.

A sample size calculation was performed with credible assumptions for the primary outcomes of ASTERIA I and ASTERIA II. Analyses for efficacy outcomes were made on the modified intention-to-treat set with a BOCF approach, with only one patient lost from the modified intention-to-treat set in GLACIAL and one in ASTERIA II, and none in ASTERIA I. Sensitivity analyses of the primary outcome analysis were performed using different approaches to handle missing data (i.e., observed data, LOCF) and by being more restrictive on inputting values from patients who used steroids during the weeks preceding the week 12 visit. The results of the sensitivity analyses were similar to the main analyses. The statistical tests used, and the analysis of covariance model stratified for baseline disease severity, were appropriate since this baseline parameter could affect the observed effect size.

Despite the strengths of the pivotal trials, there were also some limitations in their conduct. Several major protocol violations were reported in the Clinical Study Reports. The rates of occurrence for these violations were [redacted]% in ASTERIA I, [redacted]% in ASTERIA II, and [redacted]% in GLACIAL. Protocol issues included open-label treatment with OMA during the follow-up periods of ASTERIA I and GLACIAL (these patients were excluded from further efficacy assessment) and patients who received a different dose than their assignment. It was also mentioned that some patients enrolled in ASTERIA I ([redacted]% of patients) and in GLACIAL ([redacted]% of patients) had not received a diagnosis of CIU. The proportion of patients not meeting inclusion or exclusion criteria was numerically higher in the OMA treatment groups (up to [redacted]% more) than in the placebo group for all studies. The overall repercussion of these limitations on the results of the trials is unclear.

3.5.2 External validity

With a majority (from 70% to 80%) of patients being from the United States, the trial populations were likely similar to the Canadian population. Included patients were in their early 40s on average, overweight, and predominantly Caucasian females. In terms of baseline disease characteristics, the study population from the three pivotal trials appeared to be representative of patients seen in Canadian clinics, according to the clinical expert consulted for the review. It is also noteworthy that a relatively large proportion (two-thirds) of screened patients was randomized.

Only the inclusion and exclusion criteria of GLACIAL were generally in line with common medical practice with respect to the use of prior treatments; still, 37% of patients in this trial were on standard doses of H_1 antihistamines at baseline, more than would be observed in clinical practice in the opinion of the consulting clinical expert. The populations enrolled in ASTERIA I and ASTERIA II did not reflect clinical management of CIU in Canada, as patients could have tried only standard doses of H_1 antihistamines. Following international guidelines,[5,6] clinicians in Canada normally use up to four times the indicated dose of second-generation H_1 antihistamine as second-line therapy to standard-dose antihistamine before adding additional medications for patients whose symptoms remain inadequately controlled. As third-line therapies, cyclosporin A and LTRAs are often added to H_1 antihistamines even though they do not have an indication for CIU. Guidelines also recommend OMA as an add-on third-line therapy and, according to the consulting clinical expert for this review, OMA would likely be used either as third- or fourth-line treatment in Canada. Although not approved and not recommended in the latest guidelines,[5,6] H_2 blockers are still used as a third-line therapy for CIU in Canada according to the consulting clinical expert. Hence, GLACIAL best reflects this scenario, although the ASTERIA trials can be considered valid from a regulatory perspective, as they based their inclusion criteria on the only medications approved in Canada for the treatment of CIU. The requested listing criteria for OMA also align with the ASTERIA trials with respect to treatment history.

A very small proportion of the included patients were adolescent (3.1% to 5.7%) or elderly (4.7% to 6.3%). Hence, caution is required in generalizing the conclusions of the three pivotal trials to these subpopulations.

Apart from the 75 mg dose that is not approved for treatment of CIU in Canada, the dosing, administration, and frequency of treatment were aligned with the product monograph. The length of treatment period was limited to 24 weeks. The efficacy of OMA beyond that point is uncertain. Given that CIU is a chronic illness that may persist over years or decades, the lack of efficacy and safety data beyond 24 weeks of treatment represents an important limitation of the evidence.

Outcome measures were mainly based on UAS7 and its subcomponents (WISS and WNHS), which were identified by the clinical expert consulted by CDR as being of primary importance in evaluating the efficacy of treatments for CIU. The consulting clinical expert confirmed that the inclusion criteria for the three trials related to UAS and its subcomponents reflected an appropriate level of severity that would be considered for treatment with OMA in clinical practice. The expert also considered UAS7 ≤ 6 points to be a valid definition for controlled disease; a score of 6 implies that daily itch would typically be rated "mild" at most and that there would be six hives at most per day. Among secondary and exploratory outcomes, quality of life measures like DLQI and CU-Q2oL were assessed. These are validated instruments for CIU. However, the construct validity of the EQ-5D instrument for CIU patients was uncertain. As with any generic health-related quality of life instrument, there is the possibility that items important to patients with a specific disease may be missed by the EQ-5D or that the instrument may lack sufficient sensitivity to detect clinically important changes.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol (see Section 2.2, Table 3) are reported below in Table 13 and Table 14. See Appendix 4: Detailed Outcome Dat for detailed efficacy data.

3.6.1 Urticaria Activity Score over seven days at week 12

The mean change from baseline in UAS7 by study week is reported in Figure 2, Figure 3, and Figure 4 for ASTERIA I, ASTERIA II, and GLACIAL, respectively. Across trials, the 150 mg treatment group and the 300 mg OMA treatment group demonstrated a statistically significant decrease (improvement) in UAS7 from baseline compared with placebo at week 12. Decreases were –6.54 (95% CI, –10.33 to –2.75) and −7.69 (95% CI, –11.49 to –3.88) with OMA 150 mg in ASTERIA I and ASTERIA II, respectively ($P < 0.001$). Only patients in the 300 mg treatment groups reached the MCID of 9.5 to 10.5 points, with a decrease ranging from −10.02 (95% CI, –13.17 to –6.86) (GLACIAL) to –12.80 (95% CI, –16.44 to –9.16) (ASTERIA I) compared with placebo ($P < 0.0001$).

The proportions of patients with controlled disease (i.e., UAS7 ≤ 6) at week 12 were statistically significantly higher in the OMA 150 mg treatment groups (40.0% and 42.7% in ASTERIA I and ASTERIA II, respectively, $P < 0.001$) and in the OMA 300 mg treatment groups (51.9% and 65.8% in ASTERIA I and ASTERIA II, respectively, $P < 0.0001$) compared with the placebo groups (11.3% and 19.0% in ASTERIA I and ASTERIA II, respectively). Similar results were observed in GLACIAL for this outcome.

The proportions of patients with a complete response (UAS7 = 0) at week 12 were statistically significantly higher in the OMA 300 mg treatment groups (range 33.7% [GLACIAL] to 44.3% [ASTERIA II], $P < 0.0001$) compared with the placebo groups (4.8% [GLACIAL] and 8.8% [ASTERIA I]). For the OMA 150 mg treatment groups, only ASTERIA II (22.0%, $P = 0.0019$) showed a statistically significant difference versus placebo (5.1%).

The time to reach MCID response (UAS7 reduction of 11 points) by week 12 was an exploratory outcome. Patients in both the OMA 150 mg and 300 mg groups demonstrated statistically significantly shorter times to reach the MCID than patients in the placebo group; median times were 3.0 weeks and 2.0 weeks in the 150 mg groups of ASTERIA I and ASTERIA II, respectively (hazard ratio 1.67 [95% CI, 1.15 to 2.44] and 1.86 [95% CI, 1.30 to 2.66] respectively versus placebo, $P < 0.01$ in both trials). Median times in the 300 mg groups ranged from 1.5 weeks to 2.0 weeks in GLACIAL and ASTERIA I, respectively (hazard ratio 2.33 [95% CI, 1.70 to 3.20] and 2.69 [95% CI, 1.86 to 3.90] respectively versus placebo, $P < 0.0001$ in both trials).

FIGURE 2: MEAN CHANGE FROM BASELINE IN URTICARIA ACTIVITY SCORE OVER SEVEN DAYS BY STUDY WEEK — ASTERIA I (BASELINE OBSERVATION CARRIED FORWARD METHOD): MODIFIED INTENTION-TO-TREAT POPULATION

Confidential figure was removed at the manufacturer's request.

BOCF = baseline observation carried forward; mITT = modified intention to treat; UAS7 = Urticaria Activity Score over seven days.
Source: Clinical Study Report for ASTERIA I.[20]

FIGURE 3: MEAN CHANGE FROM BASELINE IN URTICARIA ACTIVITY SCORE OVER SEVEN DAYS BY STUDY WEEK — ASTERIA II (BASELINE OBSERVATION CARRIED FORWARD METHOD): MODIFIED INTENTION-TO-TREAT POPULATION

Confidential figure was removed at the manufacturer's request.

BOCF = baseline observation carried forward; mITT = modified intention to treat; UAS7 = Urticaria Activity Score over seven days.
Source: Clinical Study Report for ASTERIA II.[21]

FIGURE 4: MEAN CHANGE FROM BASELINE IN URTICARIA ACTIVITY SCORE OVER SEVEN DAYS BY STUDY WEEK — GLACIAL (BASELINE OBSERVATION CARRIED FORWARD METHOD): MODIFIED INTENTION-TO-TREAT POPULATION

Confidential figure was removed at the manufacturer's request.

BOCF = baseline observation carried forward; mITT = modified intention to treat; UAS7 = Urticaria Activity Score over seven days.
Source: Clinical Study Report for GLACIAL.[22]

3.6.2 Weekly Itch Severity Score at week 12

The mean changes from baseline in WISS by study week are reported in Figure 8, Figure 9, and Figure 10 (Appendix 4) for ASTERIA I, ASTERIA II, and GLACIAL, respectively. Across trials, the OMA 150 mg ($P < 0.01$) and OMA 300 mg ($P < 0.0001$) groups had statistically significant decreases (improvement) in WISS from baseline compared with placebo at week 12. Decreases were –2.95 (95% CI, –4.72 to –1.18) and –3.04 (95% CI, –4.85 to –1.24) with the OMA 150 mg dose in ASTERIA I and ASTERIA II, respectively. Only patients in the OMA 300 mg treatment groups reached the MCID of 4.5 to 5.0 points with decreases ranging from –4.52 (95% CI, –5.97 to –3.08) in GLACIAL to –5.80 (95% CI, –7.49 to –4.10) in ASTERIA I.

The time to reach the MCID response for WISS (5 points) by week 12 was also reported. Both dose groups demonstrated statistically significantly shorter times to achieve this outcome than placebo; median times were 2.0 weeks in the 150 mg groups of ASTERIA I and ASTERIA II versus 6.0 weeks in the placebo groups of both trials (hazard ratio of 1.49 [95% CI, 1.04 to 2.14] and 1.59 [95% CI, 1.12 to 2.26] respectively versus placebo, $P < 0.05$ for both trials). In the OMA 300 mg groups, median times were 1.0 week and 2.0 weeks in the ASTERIA trials and GLACIAL, respectively; the hazard ratio ranged from 1.99 (95% CI, 1.47 to 2.68) in GLACIAL to 2.34 (95% CI, 1.63 to 3.36) in ASTERIA I versus placebo ($P < 0.0001$) in both trials. The proportions of patients with a WISS MCID response at week 12 were also statistically significantly higher in the OMA 150 mg groups (56.3% and 69.5%, $P < 0.05$ in ASTERIA I and ASTERIA II, respectively) and in the OMA 300 mg groups (range 69.8% [GLACIAL] to 78.5% [ASTERIA II], $P < 0.0001$) compared with the placebo groups (range 36.3% to 48.1% in ASTERIA I and ASTERIA II, respectively).

Dose-specific subgroup analyses for change from baseline in WISS at week 12 versus placebo are presented in Appendix 4 (Figure 14 and Figure 15 for ASTERIA I, Figure 16 and Figure 17 for ASTERIA II, and Figure 18 for GLACIAL). Most of the subgroup analyses were consistent with the main analysis. Nevertheless, in each trial, patients who used less than or equal to two CIU medications (which could have been two drugs from the same class) appeared to have a lower response in WISS compared with placebo. However, it should be noted that randomization was not stratified on this characteristic.

3.6.3 Weekly Number of Hives Score at week 12

The mean change from baseline in WNHS by study week is reported in Figure 11, Figure 12, and Figure 13 (Appendix 4) for ASTERIA I, ASTERIA II, and GLACIAL, respectively. Across trials, the OMA 150 mg ($P < 0.01$) and the OMA 300 mg ($P < 0.0001$) groups had a statistically significant decrease (improvement) in WNHS from baseline compared with placebo at week 12. Decreases were –3.44 (95% CI, –5.57 to –1.32) and –4.51 (95% CI, –6.65 to –2.36) with the OMA 150 mg dose in ASTERIA I and ASTERIA II, respectively. Only the OMA 300 mg groups reached the MCID of 5.0 to 5.5 points with a decrease ranging from –5.90 (95% CI, –7.72 to –4.07) (GLACIAL) to –7.09 (95% CI, –9.26 to –4.93) (ASTERIA II).

3.6.4 Change from baseline in Dermatology Life Quality Index Overall Score at week 12

Across trials, patients in the OMA 300 mg groups had a statistically significant decrease (improvement) in DLQI from baseline compared with patients on placebo at week 12 ($P < 0.001$). The effect estimates ranged from –3.79 (95% CI, –5.85 to –1.73) (ASTERIA II) to –4.67 (95% CI, –6.28 to –3.06) (GLACIAL) and reached the MCID. With respect to the OMA 150 mg groups, only in ASTERIA II was there a statistically significant decrease ($P < 0.05$) compared with placebo; the effect estimate of –2.51 (95% CI, –4.64 to −0.38) reached the MCID.

3.6.5 Change from baseline in Chronic Urticaria Quality of Life Questionnaire at week 12

The change from baseline in CU-Q2oL at week 12 was an exploratory outcome. Across trials, patients in the OMA 300 mg groups had a statistically significant decrease (improvement) in CU-Q2oL from baseline compared with patients on placebo at week 12 ($P < 0.01$). Effect estimates ranged from –10.6 (95% CI, −17.2 to –4.0) (ASTERIA I) to –14.0 (95% CI, –19.8 to –8.2) (ASTERIA II). For patients in the OMA 150 mg groups, only patients in ASTERIA II had a statistically significant decrease (of –8.2 [95% CI, –14.3 to –2.1, $P < 0.01$]).

3.6.6 Change from baseline in EuroQol 5-Dimensions Questionnaire Index Score at week 12

The change from baseline in EQ-5D index score at week 12 was an exploratory outcome. Across trials, only the OMA 150 mg group of ASTERIA I demonstrated a statistically significant increase in EQ-5D index score (of 0.13 [95% CI, 0.04 to 0.22, $P < 0.01$]) compared with placebo; this exceeded the reported MCID for this outcome in the general population. Other observed differences were smaller, ranging from 0.01 to 0.06, and not statistically significant.

3.6.7 Exploratory outcomes at week 24

Exploratory outcomes for UAS7, WISS, WNHS, DLQI, and CU-Q2oL at week 24 were reported for ASTERIA I and GLACIAL (see Table 20 in Appendix 4). Responses observed at week 24 were similar to those observed at week 12. However, it is noteworthy that none of the differences between the OMA 150 mg groups and the placebo group reached statistical significance at week 24. In contrast, the differences between OMA 300 mg and placebo were statistically significant for all outcomes at week 24, and most achieved the MCID.

3.6.8 Exploratory outcomes after the 16-week treatment-free follow-up period

Exploratory outcomes for UAS7, DLQI, CU-Q2oL, and EQ-5D after the 16-week treatment-free follow-up period are presented in Appendix 4. Table 21 presents data for ASTERIA II (at week 28) and Table 22 presents data for ASTERIA I and GLACIAL (at week 40). There were no statistically significant differences for the majority of efficacy outcomes at 16 weeks between the OMA and placebo groups. Of note, a numerically higher number of patients who achieved response (i.e., UAS7 ≤ 6) at the end of the treatment period in the OMA group maintained response 16 weeks after treatment discontinuation compared with patients in the placebo group who achieved response at the end of the treatment period.

TABLE 13: KEY EFFICACY OUTCOMES — URTICARIA ACTIVITY SCORE OVER SEVEN DAYS, WEEKLY ITCH SEVERITY SCORE, AND WEEKLY NUMBER OF HIVES SCORE AT WEEK 12

	ASTERIA I			ASTERIA II			GLACIAL	
	OMA 150 mg (N = 80)	OMA 300 mg (N = 81)	PBO (N = 80)	OMA 150 mg (N = 82)	OMA 300 mg (N = 79)	PBO (N = 79)	OMA 300 mg (N = 252)	PBO (N = 83)
UAS7								
Baseline (SD)	30.26 (7.26)	31.32 (5.79)	31.10 (6.67)	31.35 (6.99)	29.47 (6.90)	31.04 (6.58)	31.17 (6.57)	30.24 (6.66)
Mean at week 12 (SD)	15.83 (13.78)	10.57 (12.28)	23.09 (12.55)	13.47 (12.64)	7.74 (11.14)	20.69 (12.64)	12.16 (13.77)	21.74 (11.55)
Change from baseline, mean (SD)	–14.44 (12.95)	–20.75 (12.17)	–8.01 (11.47)	–17.89 (13.23)	–21.74 (12.78)	–10.36 (11.61)	–19.01 (13.15)	–8.50 (11.71)
Difference vs. PBO, LSM (95% CI)[a]	–6.54 (–10.33 to –2.75)	–12.80 (–16.44 to –9.16)	–	–7.69 (–11.49 to –3.88)	–12.40 (–16.13 to –8.66)	–	–10.02 (–13.17 to –6.86)	–
P value vs. PBO[b]	0.0008	< 0.0001	–	0.0001	< 0.0001	–	< 0.0001	–
Proportion of Patients With UAS7 ≤ 6								
N (%)	32 (40.0%)	42 (51.9%)	9 (11.3%)	35 (42.7%)	52 (65.8%)	15 (19.0%)	132 (52.4%)	10 (12.0%)
P value vs. PBO	< 0.0001	< 0.0001	–	0.0010	< 0.0001	–	< 0.0001	–
Proportion of Patients With Complete Response (UAS7 = 0)								
N (%)	12 (15.0%)	29 (35.8%)	7 (8.8%)	18 (22.0%)	35 (44.3%)	4 (5.1%)	85 (33.7%)	4 (4.8%)
P value vs. PBO	0.2087	< 0.0001	–	0.0019	< 0.0001	–	< 0.0001	–
Time to UAS7 MCID Response								
Median, weeks (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR vs. PBO (95% CI)	[redacted]	[redacted]	–	[redacted]	[redacted]	–	[redacted]	–
P value vs. PBO	[redacted]	[redacted]	–	[redacted]	[redacted]	–	[redacted]	–
WISS								
Baseline (SD)	14.09 (3.77)	14.20 (3.31)	14.37 (3.48)	14.23 (4.14)	13.66 (3.53)	14.02 (3.45)	14.05 (3.61)	13.82 (3.63)
Mean at week 12 (SD)	7.44 (6.59)	4.80 (5.55)	10.73 (5.99)	6.09 (5.94)	3.89 (5.30)	8.88 (5.83)	5.50 (6.32)	9.81 (5.41)
Change from baseline, mean (SD)	–6.66 (6.28)	–9.40 (5.73)	–3.63 (5.22)	–8.14 (6.44)	–9.77 (5.95)	–5.14 (5.58)	–8.55 (6.01)	–4.01 (5.87)
Difference vs. PBO, LSM (95% CI)[c]	–2.95 (–4.72 to –1.18)	–5.80 (–7.49 to –4.10)	–	–3.04 (–4.85 to –1.24)	–4.81 (–6.49 to –3.13)	–	–4.52 (–5.97 to –3.08)	–
P value vs. PBO	0.0012	< 0.0001	–	0.0011	< 0.0001	–	< 0.0001	–
Time to MCID Response in WISS								
Median, weeks (95% CI)	2.0 (2.0, 3.0)	1.0 (1.0, 2.0)	4.0 (2.0, 6.0)	2.0 (1.0, 2.0)	1.0 (1.0, 2.0)	4.0 (3.0, 5.0)	2.0 (1.0, 2.0)	5.0 (3.0, 7.0)
HR vs. PBO (95% CI)	1.49 (1.04 to 2.14)	2.34 (1.63 to 3.36)	–	1.59 (1.12 to 2.26)	2.12 (1.48 to 3.03)	–	1.99 (1.47 to 2.68)	–

	ASTERIA I			ASTERIA II			GLACIAL	
	OMA 150 mg (N = 80)	OMA 300 mg (N = 81)	PBO (N = 80)	OMA 150 mg (N = 82)	OMA 300 mg (N = 79)	PBO (N = 79)	OMA 300 mg (N = 252)	PBO (N = 83)
P value vs. PBO	0.0301	< 0.0001	–	0.0101	< 0.0001	–	< 0.0001	–
Proportion of WISS MCID Responders								
N (%)	45 (56.3%)	61 (75.3%)	29 (36.3%)	57 (69.5%)	62 (78.5%)	38 (48.1%)	176 (69.8%)	33 (39.8%)
P value vs. PBO	0.0226	< 0.0001	–	0.0045	< 0.0001	–	< 0.0001	–
WNHS								
Baseline (SD)	16.17 (4.61)	17.12 (3.82)	16.73 (4.42)	17.13 (4.14)	15.82 (4.62)	17.03 (4.20)	17.12 (4.20)	16.42 (4.59)
Mean at week 12 (SD)	8.39 (7.59)	5.77 (7.17)	12.36 (7.22)	7.38 (7.32)	3.85 (6.35)	11.80 (7.45)	6.66 (7.89)	11.93 (6.89)
Change from baseline, mean (SD)	–7.78 (7.08)	–11.35 (7.25)	–4.37 (6.60)	–9.75 (7.28)	–11.97 (7.58)	–5.22 (6.56)	–10.46 (7.74)	–4.49 (6.33)
Difference vs. PBO, LSM (95% CI)[d]	–3.44 (–5.57 to –1.32)	–6.93 (–9.10 to –4.76)	–	–4.51 (–6.65 to –2.36)	–7.09 (–9.26 to –4.93)	–	–5.90 (–7.72 to –4.07)	–
P value vs. PBO	0.0017	< 0.0001	–	< 0.0001	< 0.0001	–	< 0.0001	–

ANCOVA = analysis of covariance; CI = confidence interval; HR = hazard ratio; LSM = least squares mean; MCID = minimal clinically important difference; OMA = omalizumab; PBO = placebo; SD = standard deviation; UAS7 = Urticaria Activity Score over seven days; vs. = versus; WISS = Weekly Itch Severity Score; WNHS = Weekly Number of Hives Score.
[a] The LS mean was estimated using an ANCOVA model with baseline UAS7 (< median versus ≥ median) and baseline weight (< 80 kg versus ≥ 80 kg) as covariates.
[b] *P* value is derived from ANCOVA t-test.
[c] The LS means were estimated using an ANCOVA model with baseline WISS (< 13, ≥ 13) and baseline weight (< 80 kg versus ≥ 80 kg) as covariates.
[d] The LS mean was estimated using an ANCOVA model with baseline WNHS (< median versus ≥ median) and baseline weight (< 80 kg versus ≥ 80 kg) as covariates.
Source: Clinical Study Reports for ASTERIA I,[20] ASTERIA II,[21] and GLACIAL.[22]

TABLE 14: KEY EFFICACY OUTCOMES — DERMATOLOGY LIFE QUALITY INDEX, CHRONIC URTICARIA QUALITY OF LIFE QUESTIONNAIRE, AND EUROQOL 5-DIMENSIONS QUESTIONNAIRE AT WEEK 12

	ASTERIA I			ASTERIA II			GLACIAL	
	OMA 150 mg (N = 80)	OMA 300 mg (N = 81)	PBO (N = 80)	OMA 150 mg (N = 82)	OMA 300 mg (N = 79)	PBO (N = 79)	OMA 300 mg (N = 252)	PBO (N = 83)
DLQI (Overall Score)								
n	63	72	62	70	73	69	216	64
Baseline (SD)	13.6 (7.2)	13.1 (6.6)	13.2 (6.5)	12.7 (5.9)	12.9 (6.4)	12.6 (5.8)	13.1 (6.4)	12.8 (6.7)
Mean at week 12 (SD)	5.6 (6.7)	2.8 (4.1)	7.1 (6.7)	4.5 (5.4)	2.7 (4.7)	6.5 (6.4)	3.4 (5.2)	7.7 (6.5)
Change from baseline, mean (SD)	–8.00 (7.24)	–10.29 (7.23)	–6.13 (6.25)	–8.29 (6.31)	–10.15 (6.83)	–6.09 (7.47)	–9.69 (6.85)	–5.11 (7.53)
Difference vs. PBO, LSM (95% CI)[a]	–1.31 (–3.46 to 0.84)	–4.08 (–5.96 to –2.20)	–	–2.51 (–4.64 to –0.38)	–3.79 (–5.85 to –1.73)	–	–4.67 (–6.28 to –3.06)	–
P value vs. PBO[b]	0.2286	< 0.0001	–	0.0215	0.0004	–	< 0.0001	–

	ASTERIA I			ASTERIA II			GLACIAL	
	OMA 150 mg (N = 80)	OMA 300 mg (N = 81)	PBO (N = 80)	OMA 150 mg (N = 82)	OMA 300 mg (N = 79)	PBO (N = 79)	OMA 300 mg (N = 252)	PBO (N = 83)
CU-Q2oL								
n	48	57	49	61	65	62	210	61
Baseline (SD)	44.1 (21.5)	44.6 (18.4)	43.9 (17.4)	43.8 (16.1)	43.7 (16.9)	41.0 (14.7)	NR	NR
Mean at week 12 (SD)	21.0 (21.0)	14.1 (14.3)	24.3 (18.4)	16.8 (16.8)	12.2 (13.8)	23.3 (17.0)	NR	NR
Change from baseline, mean (SD)	–23.1 (18.6)	–30.5 (19.1)	–19.7 (19.7)	–27.0 (17.9)	–31.4 (20.2)	–17.7 (19.2)	–29.3 (18.8)	–16.3 (18.8)
Difference vs. PBO, LSM (95% CI)[c]	–3.9 (–11.2 to 3.4)	–10.6 (–17.2 to –4.0)	–	–8.2 (–14.3 to –2.1)	–14.0 (–19.8 to –8.2)	–	–13.4 (–18.2 to –8.6)	–
P value vs. PBO	0.2891	0.0019	–	0.0089	< 0.0001	–	< 0.0001	–
EQ-5D Index Score								
n	63	70	63	71	72	70	217	63
Baseline (SD)	0.72 (0.26)	0.68 (0.29)	0.66 (0.28)	0.67 (0.29)	0.73 (0.24)	0.73 (0.24)	NR	NR
Mean at week 12 (SD)	0.79 (0.26)	0.88 (0.17)	0.79 (0.22)	0.86 (0.23)	0.89 (0.20)	0.82 (0.23)	NR	NR
Change from baseline, mean (SD)	0.06 (0.22)	0.20 (0.31)	0.09 (0.27)	0.19 (0.32)	0.16 (0.30)	0.09 (0.28)	0.12 (0.26)	0.11 (0.23)
Difference vs. PBO, LSM (95% CI)[d]	–0.02 (–0.10 to 0.06)	0.13 (0.04 to 0.22)	–	0.06 (–0.04 to 0.15)	0.06 (–0.03 to 0.15)	–	0.01 (–0.06 to 0.07)	–
P value vs. PBO	0.6730	0.0062	–	0.2363	0.1689	–	0.8692	–

ANCOVA = analysis of covariance; CI = confidence interval; CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimensions Questionnaire; LSM = least squares mean; NE = not estimable; NR = not reported; OMA = omalizumab; PBO = placebo; SD = standard deviation; vs. = versus.

[a] The LSM was estimated using an ANCOVA model with baseline overall DLQI score (< median versus ≥ median) and baseline weight (< 80 kg versus ≥ 80 kg) as covariates.

[b] *P* value was derived from ANCOVA t-test.

[c] The LSM was estimated using an ANCOVA model with baseline overall CU-Q2oL score (< median versus ≥ median) and baseline weight (< 80 kg versus ≥ 80 kg) as covariates.

[d] The LSM was estimated using an ANCOVA model with baseline EQ-5D index score (< median versus ≥ median) and baseline weight (< 80 kg versus ≥ 80 kg) as covariates.

Source: Clinical Study Reports for ASTERIA I,[20] ASTERIA II,[21] and GLACIAL.[22]

3.7 Harms

Only those harms identified in the review protocol (see Section 2.2, Table 3) are reported (Table 15). AEs reported in the included studies were treatment-emergent AEs that occurred during the treatment period. In addition to AEs, SAEs, mortality, WDAEs, and notable AEs identified in consultation with the clinical expert are reported.

3.7.1 Adverse events

Patients in ASTERIA II had a lower incidence of AEs (from 40.5% to 47.7%) compared with patients in ASTERIA I (from 51.3% to 69.0%) or GLACIAL (63.9% and 65.1%), possibly due to its shorter duration. Compared with patients in the placebo groups, patients who received OMA were more likely to experience AEs across all trials.

The most common AEs were nasopharyngitis (total occurrence of 7.7%) and headache (total occurrence of 6.6%). Only the proportion of patients with headache was numerically higher in the OMA groups, occurring in 6.2% to 15.9% of patients who received OMA and in 2.5% to 6.3% of patients who received placebo. Other common AEs included sinusitis, bronchitis, arthralgia, urticaria, oropharyngeal pain, urinary tract infection, nausea, and diarrhea. None of these appeared to occur more often in the OMA groups than in the placebo groups.

3.7.2 Serious adverse events

SAEs occurred in 2.1% of all patients. SAEs did not occur more often in the OMA groups than in the placebo groups. No trend in the nature of SAEs was observed.

3.7.3 Withdrawals due to adverse events

WDAEs occurred in 1.1% of all patients. WDAEs did not occur more often in the OMA treatment groups than in the placebo groups. The most frequent cause of WDAEs was urticaria of all kinds, representing 54.5% of all WDAEs.

AEs leading to withdrawal from treatment, which presumably differed from WDAEs in that patients remained in the study for follow-up in the former category, occurred in a total of 3.4% of patients across trials and did not appear to be more frequent in patients who received OMA than in patients who received placebo.

3.7.4 Mortality

No deaths occurred during the trials.

3.7.5 Notable harms

Notable harms identified in consultation with the clinical expert were arterial thrombotic events, anaphylaxis, and malignancies. None of these occurred more than once in each study.

TABLE 15: HARMS

	ASTERIA I			ASTERIA II			GLACIAL	
	OMA 150 mg (N = 87)	OMA 300 mg (N = 81)	PBO (N = 80)	OMA 150 mg (N = 88)	OMA 300 mg (N = 79)	PBO (N = 79)	OMA 300 mg (N = 252)	PBO (N = 83)
AEs								
Subjects with > 0 AEs, N (%)	60 (69.0%)	46 (56.8%)	41 (51.3%)	42 (47.7%)	35 (44.3%)	32 (40.5%)	164 (65.1%)	53 (63.9%)
AEs leading to withdrawal from treatment[a]	4 (4.6%)	2 (2.5%)	7 (8.8%)	2 (2.3%)	0	0	12 (4.8%)	6 (7.2%)
Most Common AEs[b]								
Nasopharyngitis	11 (12.6%)	9 (11.1%)	10 (12.5%)	5 (5.7%)	7 (8.9%)	4 (5.1%)	22 (8.7%)	7 (8.4%)
Headache	8 (9.2%)	5 (6.2%)	2 (2.5%)	14 (15.9%)	6 (7.6%)	5 (6.3%)	22 (8.7%)	3 (3.6%)
Sinusitis	4 (4.6%)	3 (3.7%)	4 (5.0%)	0	3 (3.8%)	1 (1.3%)	19 (7.5%)	5 (6.0%)
Bronchitis	2 (2.3%)	1 (1.2%)	5 (6.3%)	0	3 (3.8%)	2 (2.5%)	6 (2.4%)	0
Arthralgia	5 (5.7%)	3 (3.7%)	0	1 (1.1%)	3 (3.8%)	1 (1.3%)	7 (2.8%)	2 (2.4%)
Urticaria	4 (4.6%)	2 (2.5%)	6 (7.5%)	0	0	0	5 (2.0%)	1 (1.2%)
Oropharyngeal pain	5 (5.7%)	0	4 (5.0%)	1 (1.1%)	0	0	6 (2.4%)	3 (3.6%)
Urinary tract infection	4 (4.6%)	1 (1.2%)	2 (2.5%)	0	0	0	7 (2.8%)	1 (1.2%)
Nausea	0	0	1 (1.3%)	2 (2.3%)	2 (2.5%)	0	10 (4.0%)	5 (6.0%)
Diarrhea	0	1 (1.2%)	0	2 (2.3%)	2 (2.5%)	3 (3.8%)	9 (3.6%)	5 (6.0%)
SAEs								
Subjects with > 0 SAEs, N (%)	3 (3.4%)	0 (0.0%)	4 (5.0%)	0	2 (2.5%)	2 (2.5%)	7 (2.8%)	3 (3.6%)
WDAEs								
WDAEs, N (%)	2 (2.3%)	1 (1.2%)	2 (2.5%)	1 (1.1%)	0	1 (1.3%)	3 (1.2%)	1 (1.2%)
Most common reasons								
Urticaria	0	1 (1.2%)	1 (1.3)	1 (1.1%)	0	0	2 (0.8%)	1 (1.2%)
Deaths								
Number of deaths, N (%)	0	0	0	0	0	0	0	0
Notable Harms								
Arterial thrombotic events	1 (1.1%)	0	0	0	0	0	0	1 (1.2%)
Anaphylaxis	0	1 (1.2%)	0	0	0	0	0	0
Malignancies	0	0	1 (1.3)	0	1 (1.3%)	0	0	0

AE = adverse event; OMA = omalizumab; PBO = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
[a] Distinct from WDAEs in that patients remained in the study for follow-up.
[b] Frequency > 3.5%.
Source: Clinical Study Reports for ASTERIA I,[20] ASTERIA II,[21] and GLACIAL.[22]

4. DISCUSSION

4.1 Summary of Available Evidence

The evidence included in this review was derived from three phase 3, double-blind, multi-centre trials that compared three different doses of OMA (75 mg, 150 mg, and 300 mg, administered every four weeks) with placebo in a total of 978 adult and adolescent patients with H_1 antihistamine–refractive CIU. Since 75 mg is not an approved dose in Canada, data for the 75 mg dose groups were excluded from this report. ASTERIA I and GLACIAL had a treatment period of 24 weeks' duration, whereas ASTERIA II was 12 weeks in duration. All trials had a 16-week treatment-free follow-up period thereafter. The primary objective of ASTERIA I and ASTERIA II was to evaluate whether OMA was superior to placebo for improving WISS after 12 weeks in patients with refractory CIU receiving concomitant standard-dose H_1 antihistamine therapy. The primary objective of GLACIAL was to evaluate the safety of OMA compared with placebo in patients with refractory CIU receiving H_1 antihistamines (up to four times the approved dose) and either H_2 blockers or LTRAs, or both as concomitant therapies. Other efficacy outcomes included UAS7 and WNHS. Quality of life was assessed with DLQI, CU-Q2oL, and EQ-5D. End points were measured at 12 weeks, at 24 weeks, and at the end of the treatment-free follow-up period.

The studies were generally of adequate design and assessed clinically relevant outcomes, but relatively high rates of major protocol violations and protocol issues were reported, including enrolment of patients not meeting inclusion and exclusion criteria. The impact of these limitations on the results of the trials is unclear. Baseline characteristics were mostly balanced between groups and were generally reflective of patients with CIU in Canada according to the consulting clinical expert. However, the inclusion and exclusion criteria of GLACIAL were most aligned with common medical practice in Canada in terms of therapies tried before progressing to OMA. A very low proportion of the included patients were adolescent or elderly, thereby limiting conclusions for these subpopulations.

4.2 Interpretation of Results

4.2.1 Efficacy

The GLACIAL trial was identified as the most relevant trial to Canadian clinical practice in terms of study population, as patients were required to be symptomatic despite the use of H_1 antihistamines at up to four times the approved dose along with H_2 antagonists or LTRAs, or both. Results from GLACIAL suggest that OMA 300 mg is superior to placebo for improving UAS7 and its subcomponents (WISS and WNHS) in this population. When compared with placebo at week 12, OMA 300 mg was associated with statistically significant and clinically relevant improvement in UAS7 of approximately 10 points, in WISS of approximately 4.5 points, and in WNHS of approximately 6 points. These responses were maintained at 24 weeks. In comparison with ASTERIA I and ASTERIA II, the magnitude of treatment effects for efficacy outcomes (UAS7, WISS, and WNHS) were generally smaller in GLACIAL, while effect sizes for quality of life measures (DLQI, CU-Q2oL, and EQ-5D) tended to be higher. These observations may reflect a population in GLACIAL that was more resistant to treatment, but one in which improvements in symptoms were associated with a greater potential for improvements in health-related quality of life compared with the less treatment-resistant populations in ASTERIA I and ASTERIA II. Patient group input received by CDR on this submission reflected anxiety, depression, shame (regarding the appearance of affected skin), insomnia, and absenteeism from work as key concerns associated with CIU. Although not all of these outcomes were measured in the included trials, the observed benefits of OMA on CIU symptoms and quality of life can be expected to address these concerns of relevance to patients.

Most of the subgroup analyses of efficacy outcomes were consistent with the main analysis. Nevertheless, patients who had used less than or equal to two prior CIU medications had a statistically non-significant response in WISS compared with placebo, in all trials. This characteristic may reflect less severe or recalcitrant disease; such patients may have had a higher placebo response compared with patients who used more than two prior CIU medications. However, since patients in the studies were not randomized based on number of medications used, this observation is hypothesis-generating at best.

The product monograph for OMA recommends the use of either the 150 mg or the 300 mg dose for CIU. However, in ASTERIA I and ASTERIA II, the 150 mg dose failed to provide a clinically significant response on UAS7, WISS, and WNHS compared with placebo at week 12, even though the differences were statistically significant. After 24 weeks, the differences observed at week 12 were reduced compared with the week 12 results and were not statistically significant. The potential utility of the 150 mg dose was also evaluated by the proportion of patients achieving the WISS MCID or achieving a UAS7 ≤ 6. A statistically significantly higher proportion of patients in the OMA 150 mg group reached the WISS MCID and reached a UAS7 ≤ 6 compared with patients in the placebo groups at 12 weeks. After 24 weeks, only the proportions of patients who reached a UAS7 ≤ 6 were reported, and the difference between the 150 mg group and the placebo group was not statistically significant. Although there were no formal comparisons of the 150 mg and 300 mg doses in the included trials, the available results suggest that the former dose may have lower efficacy and that an appreciable proportion of patients initiated on 150 mg may eventually need to have the dose increased to 300 mg. Moreover, the 150 mg dose was studied in ASTERIA I and ASTERIA II only, therefore the generalizability of the results to real-world practice in which patients are likely to have failed on high doses of H_1 antihistamines and one or more unapproved therapies is uncertain.

Other efficacy outcomes in the included trials were quality of life measures such as DLQI, CU-Q2oL, and EQ-5D. OMA 300 mg appeared to be effective for improving quality of life as measured with DLQI and CU-Q2oL compared with placebo at week 12 and week 24. Change from baseline in DLQI exceeded the MCID at both time points, whereas no MCID is known for CU-Q2oL. Results for EQ-5D did not show any statistically significant improvements with OMA at week 12 or week 24. Indeed, the construct validity and the sensitivity to change of this generic instrument for CIU was considered uncertain, as no studies specifically validating EQ-5D in patients with CIU were identified (see Appendix 5: Validity of Outcome Measures); this view was confirmed by the clinical expert consulted for the review.

Outcomes reported after the 16-week treatment-free follow-up period showed that the majority of efficacy outcomes did not maintain statistically significant improvements compared with placebo. This indicates that the response observed following OMA treatment after 24 weeks attenuates after cessation of treatment for most patients. There were no data on the efficacy of OMA upon re-treatment. The duration of treatment required to have a sustained OMA-elicited response has also not been investigated, nor were how or when treatment should be stopped or reinitiated after discontinuation. According to the consulting clinical expert, if patients are hive-free for six months, treatment may be weaned off, but some patients may have CIU for the rest of their lives. Given the chronic nature of the condition, it is possible that OMA will be used as a long-term treatment for CIU, administered either continuously or intermittently.

The listing criteria requested by the manufacturer specify thresholds for UAS7 and DLQI (i.e., UAS7 ≥ 16 or DLQI ≥ 10); these imply that coverage should be restricted to patients with moderate to severe CIU. The threshold for UAS7 was the same as that used for inclusion in the pivotal trials, but no inclusion criteria for DLQI were mentioned in these studies. Furthermore, the consulting clinical expert indicated

that these instruments are not generally used in clinical practice, hence the requested listing criteria may be considered burdensome to implement by clinicians and patients.

4.2.2 Harms

According to the patient group input received by CDR on this submission (see Appendix 1: Patient Input S), patients who had used OMA experienced relatively mild adverse effects that would not prevent them from using the drug. The safety results of the included trials appeared aligned with this experience. Patients randomized to both OMA doses experienced more AEs than patients in the placebo groups. The most common AEs were nasopharyngitis (7.7%) and headache (6.6%). Nevertheless, the only AE that appeared to be associated with OMA was headache. According to the clinical expert consulted on the review and patient input received by CDR, this AE is unlikely to significantly affect the tolerability of the treatment or result in treatment discontinuation.

AEs leading to withdrawal from treatment (3.4%), WDAEs (1.1%), and SAEs (2.1%) did not occur more frequently in patients who received OMA than in patients who received placebo. The most frequent cause of WDAEs was urticaria (54.5% of all WDAEs). No deaths occurred during the trials. Based on previous studies on OMA for asthma, expert opinion, and drug safety communications from regulatory agencies, three notable harms — arterial thrombotic events, anaphylaxis and malignancies — were identified in the protocol for this review. In the included trials, these notable harms occurred rarely and none of them appeared to be related to study drug. The US FDA[7] noted that arterial thrombotic events were shown to be slightly elevated in patients who used OMA (incidence of 0.135% over five years) compared with placebo (incidence of 0.081% over five years). As with other biologic drugs, anaphylaxis may occur with OMA; approximately 0.2% of patients who use OMA experience this AE.[8] Malignancies were found to be numerically higher in patients who had OMA (0.5%) versus placebo (0.2%) in the early studies with this drug;[8] however, the consulting clinical expert indicated that the concern regarding malignancy risk has waned since these studies were published. A long-term, prospective, observational cohort study in 5,007 patients using OMA and 2,829 not using OMA found that patients who were treated with OMA were not at higher risk of malignancies than those who were not treated with OMA. However, this study reported a higher incidence of AEs (5% more) in patients who used OMA, especially for the following system organ classes: respiratory, thoracic and mediastinal disorders; infections and infestations; and cardiac disorders.[9]

5. CONCLUSIONS

The results of three double-blind, multi-centre, randomized placebo-controlled trials suggest that 12 weeks of OMA 150 mg or 300 mg administered every four weeks statistically significantly improves UAS7 and its subcomponents (WISS and WNHS) compared with placebo in patients with CIU refractory to H_1 antihistamines. However, only OMA 300 mg every four weeks was associated with a statistically and clinically significant improvement in UAS7 of 10 points compared with placebo at 12 weeks, an improvement that was maintained at 24 weeks. Patients who received OMA 300 mg also demonstrated statistically and clinically significant improvements in quality of life measures such as DLQI and CU-Q2oL at 12 and 24 weeks compared with placebo. Upon discontinuation of OMA, treatment response was not sustained over time, such that differences between OMA and placebo were no longer statistically significant at 16 weeks after discontinuation. Due to the chronic nature of the condition, it is likely that many patients with CIU will require long-term therapy with OMA; however there were no data regarding its efficacy upon re-treatment nor was there evidence to inform the optimal interval between courses of treatment. Patients receiving OMA 300 mg appeared more likely to experience adverse effects overall, and headaches in particular, than patients in the PBO groups, but the risks of other harm outcomes did not appear to differ across treatment groups.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

The Canadian Skin Patient Alliance is a non-profit, patient-centred organization that serves patients with dermatological conditions in Canada by providing education, support, and advocacy. It also acts as an umbrella organization for more than 20 affiliated skin disease–specific organizations across Canada. The Canadian Skin Patient Alliance has received unrestricted grants from Novartis, AbbVie, Amgen, Celgene, GlaxoSmithKline, Leo Pharma Inc., Janssen, Merck, Roche, and Valeant. It declares no conflict of interest in the preparation of its submission.

2. Condition and Current Therapy-Related Information

Information was gathered via paper questionnaires distributed by two dermatologists to their patients with chronic idiopathic urticaria (CIU) and online questionnaires distributed via Facebook to CIU patients who had experience with omalizumab. Twenty-five questionnaire responses were received, and two patients who gave permission were contacted by phone for an interview.

CIU or chronic spontaneous urticaria is characterized by the spontaneous occurrence of itchy hives, often accompanied by angioedema, and can last up to six weeks per attack.

Patients reported that attacks are unpredictable, causing a significant amount of anxiety (88%), affecting sleep (96%), and impacting what foods they can eat (72%) and what jobs they can obtain (50%). In addition, the majority of patients reported a decrease in self-confidence (92%) and constantly feeling the need to hide the affected skin (96%). A patient described the impact of CIU in this way: "I've had severe swelling of the lips, leading to feeling uncomfortable in public situations and affecting my self-esteem. Because instances of CIU have been unpredictable, I have also been anxious in not knowing if I will have a flare during an important life event."

Patients also reported that their disease had a negative impact on family members and caregivers: "They have to put up with my anxiety and depression. Plus now that I have damage to my back due to prednisone use, I need help doing household chores and cannot participate in some sports." Due to the debilitating effects of attacks on patients and the side effects of current therapies, caregivers often need to help the patient with self-care, grooming, washing, and other basic functions.

Survey respondents reported using over-the-counter antihistamines, doxepin, hydroxychloroquine, and prednisone. Concerns with current treatment include treatment effectiveness and intolerable side effects. Patients expressed a need for a treatment that effectively deals with the urticaria, itch, and angioedema while having tolerable side effects. At this moment, an effective therapy with tolerable side effects is lacking.

3. Related Information About the Drug Being Reviewed

All respondents except one had experience with omalizumab as part of a clinical trial. All patients expressed that omalizumab managed their symptoms better than previous treatments with a great reduction or complete eradication. Omalizumab was the only medication that could treat the skin eruptions and swelling. Although the subcutaneous administration of omalizumab by a specialist may be more complicated than self-administered pills, patients were willing to undergo the time and effort of

monthly specialist visits for the benefits experienced with omalizumab. Side effects of omalizumab included headaches and fatigue after receiving the injection, but patients noted that these would disappear: “Minor headache, joint pain, and tired for a few days after monthly injection. *So worth it*.” Five patients were able to reduce their intake of prednisone or antihistamines after receiving omalizumab. Patients feel that omalizumab could be a “life-changer.”

4. Additional Information

Given that CIU affects the patient’s ability to work, patients with this condition may be less likely to have access to private insurance.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	December 1, 2014
Alerts:	Weekly search updates until April 8, 2015.
Study Types:	No search filters were applied
Limits:	No language or date limits Human only Conference abstracts were excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY		
#	**Searches**	**Results**
1	(Xolair* or omalizumab* or rhuMab-E25 or rhuMabE25 or HSDB 5742 or HSDB5742 or 2P471X1Z11 or UNII2P471X1Z11 or hu 901 or hu901).ti,ab,ot,sh,hw,rn,nm.	5231
2	("242138 07 4" or "242138074" or 24213807 4 or "242318 074" or 2421380 74).rn,nm.	3224
3	1 or 2	5231
4	3 use pmez	1220
5	exp Urticaria Pigmentosa/ or exp Urticaria/	47493
6	(Urticar* or CIU or hive or hives or wheal or wheals or welt or welts or skin or bump or rash or rashes).ti,ab,ot,sh,hw,rn,nm.	1533287
7	5 or 6	1536939
8	7 use pmez	649566
9	4 and 8	249
10	*omalizumab/	1388
11	(Xolair* or omalizumab* or rhuMab-E25 or rhuMabE25 or HSDB 5742 or HSDB5742 or 2P471X1Z11 or UNII2P471X1Z11 or hu 901 or hu901).ti,ab.	3014
12	10 or 11	3130
13	12 use oemezd	2056
14	exp urticaria/	46435
15	(Urticar* or CIU or hive or hives or wheal or wheals or welt or welts or skin or bump or rash or rashes).ti,ab.	971097
16	14 or 15	990826
17	16 use oemezd	556816
18	13 and 17	652
19	18 not conference abstract.pt.	368
20	9 or 19	617
21	remove duplicates from 20	408
22	exp animal experimentation/ or exp animal experiment/	1825352
23	exp models animal/	1248205
24	nonhuman/	4415210
25	exp vertebrate/ or exp vertebrates/	36915632
26	animal.po.	0
27	or/22-26	39145850
28	exp humans/	29475376
29	exp human experimentation/ or exp human experiment/	344627
30	human.po.	0
31	or/28-30	29477480
32	27 not 31	9669982
33	21 not 32	407

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	November 28, 2014
Keywords:	Drug name, Indication
Limits:	No language or date limits used

Relevant websites from the following sections of the CADTH grey literature checklist, *Grey matters: a practical tool for evidence-based searching* (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

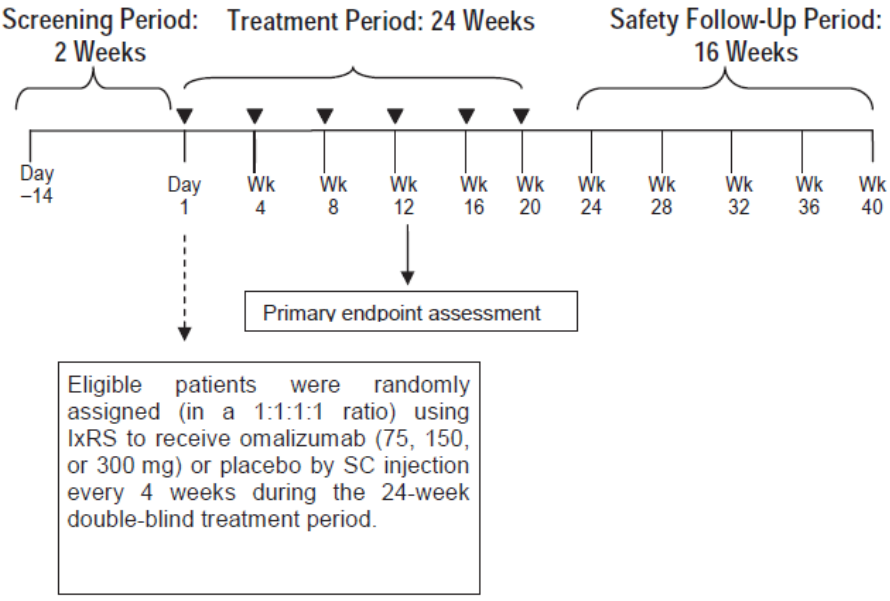
- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Saini et al. J Allergy Clin Immunol. 2011.[32]	Results were not reported separately for the different doses; some of these doses were off-label
Maurer et al. J Allergy Clin Immunol. 2011.[33]	Improper study design (phase 2 study, single dose).

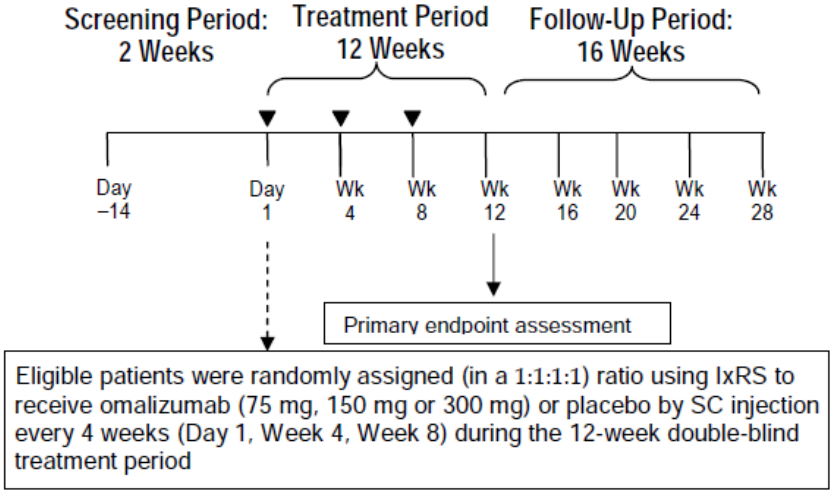
APPENDIX 4: DETAILED OUTCOME DATA

FIGURE 5: ASTERIA I STUDY DESIGN



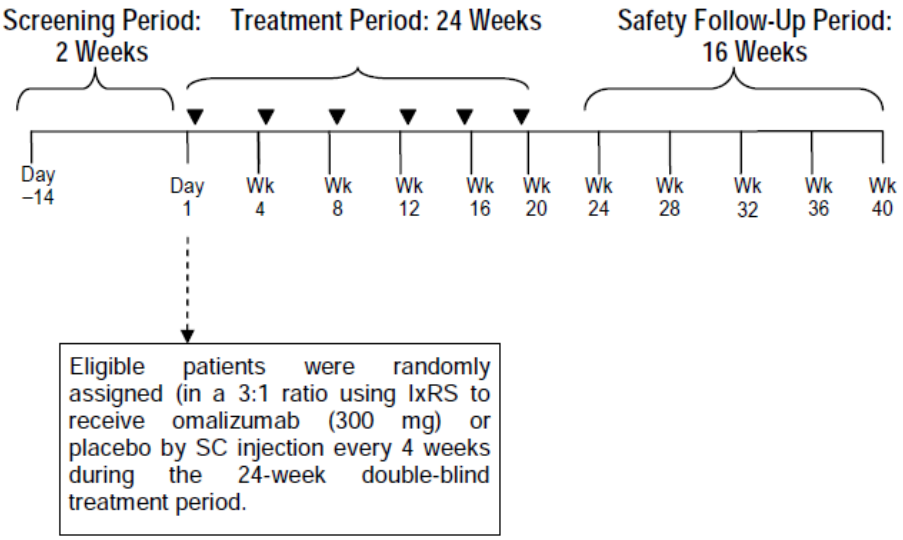
IxRS = interactive voice and web response system; SC = subcutaneous; Wk = week.
Source: Clinical Study Report for ASTERIA I.[20]

FIGURE 6: ASTERIA II STUDY DESIGN



IxRS = interactive voice and web response system; SC = subcutaneous; Wk = week.
Source: Clinical Study Report for ASTERIA II.[21]

FIGURE 7: GLACIAL STUDY DESIGN



IxRS = interactive voice and web response system; SC = subcutaneous; Wk = week.
Source: Clinical Study Report for GLACIAL.[22]

TABLE 16: CONCOMITANT MEDICATIONS — NEW ONSET DURING THE TREATMENT PERIOD: ASTERIA I (MODIFIED INTENTION-TO-TREAT)

Class of CIU Medication	ASTERIA I		
	OMA 150 mg (N = 80)	OMA 300 mg (N = 81)	PBO (N = 80)
Any medication use for CIU	16 (20.0%)	8 (9.9%)	19 (23.8%)
Antihistamines[a]	10 (12.5%)	5 (6.2%)	11 (13.8%)
Histamine H_2 receptor antagonists	1 (1.3%)	0	4 (5.0%)
Steroids	5 (6.3%)	2 (2.5%)	8 (10.0%)

CIU = chronic idiopathic urticaria; OMA = omalizumab; PBO = placebo.
[a] New onsets of antihistamine treatment were either a different medication or a change in dose from baseline, including a stop and restart of the baseline H_1 antihistamine.
Source: Clinical Study Report for ASTERIA I.[20]

TABLE 17: CONCOMITANT MEDICATIONS — NEW ONSET DURING THE TREATMENT PERIOD: ASTERIA II (MODIFIED INTENTION-TO-TREAT)

Class of CIU Medication	ASTERIA II		
	OMA 150 mg (N = 82)	OMA 300 mg (N = 79)	PBO (N = 79)
Any medication use for CIU	8 (9.8%)	3 (3.8%)	4 (5.1%)
Antihistamines[a]	5 (6.1%)	2 (2.5%)	1 (1.3%)
Histamine H_2 receptor antagonists	3 (3.7%)	1 (1.3%)	0
Steroids	6 (7.3%)	2 (2.5%)	3 (3.8%)

CIU = chronic idiopathic urticaria; OMA = omalizumab; PBO = placebo.
[a] New onsets of antihistamine treatment were either a different medication or a change in dose from baseline, including a stop and restart of the baseline H_1 antihistamine.
Source: Clinical Study Report for ASTERIA II.[21]

TABLE 18: CONCOMITANT MEDICATIONS — NEW ONSET DURING THE TREATMENT PERIOD: GLACIAL (MODIFIED INTENTION-TO-TREAT)

Class of CIU Medication	GLACIAL	
	OMA 300 mg (N = 252)	PBO (N = 83)
Any medication use for CIU	[redacted]	[redacted]
Antihistamines	[redacted]	[redacted]
Histamine H_2 receptor antagonists	[redacted]	[redacted]
Steroids	[redacted]	[redacted]
LTRAs	[redacted]	[redacted]

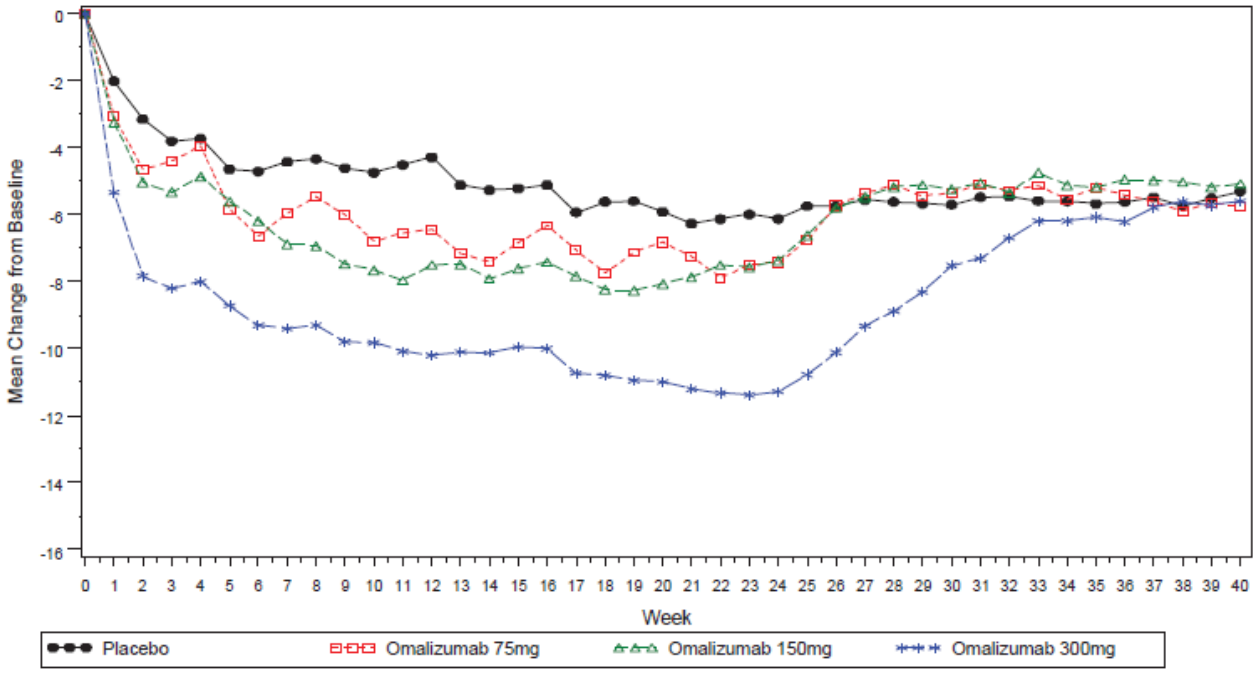
CIU = chronic idiopathic urticaria; LTRA = leukotriene receptor antagonist; OMA = omalizumab; PBO = placebo.
Source: Clinical Study Report for GLACIAL.[22]

TABLE 19: USE OF RESCUE MEDICATION AT WEEK 12: MODIFIED INTENTION-TO-TREAT POPULATION

	ASTERIA I			ASTERIA II			GLACIAL	
	OMA 150 mg (N = 80)	OMA 300 mg (N = 81)	PBO (N = 80)	OMA 150 mg (N = 82)	OMA 300 mg (N = 79)	PBO (N = 79)	OMA 300 mg (N = 252)	PBO (N = 83)
Tablets/Week of Diphenhydramine 25 mg								
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. PBO, LSM (95% CI)[a]	[redacted]	[redacted]	–	[redacted]	[redacted]	–	[redacted]	–
P value vs. PBO	[redacted]	[redacted]	–	[redacted]	[redacted]	–	[redacted]	–

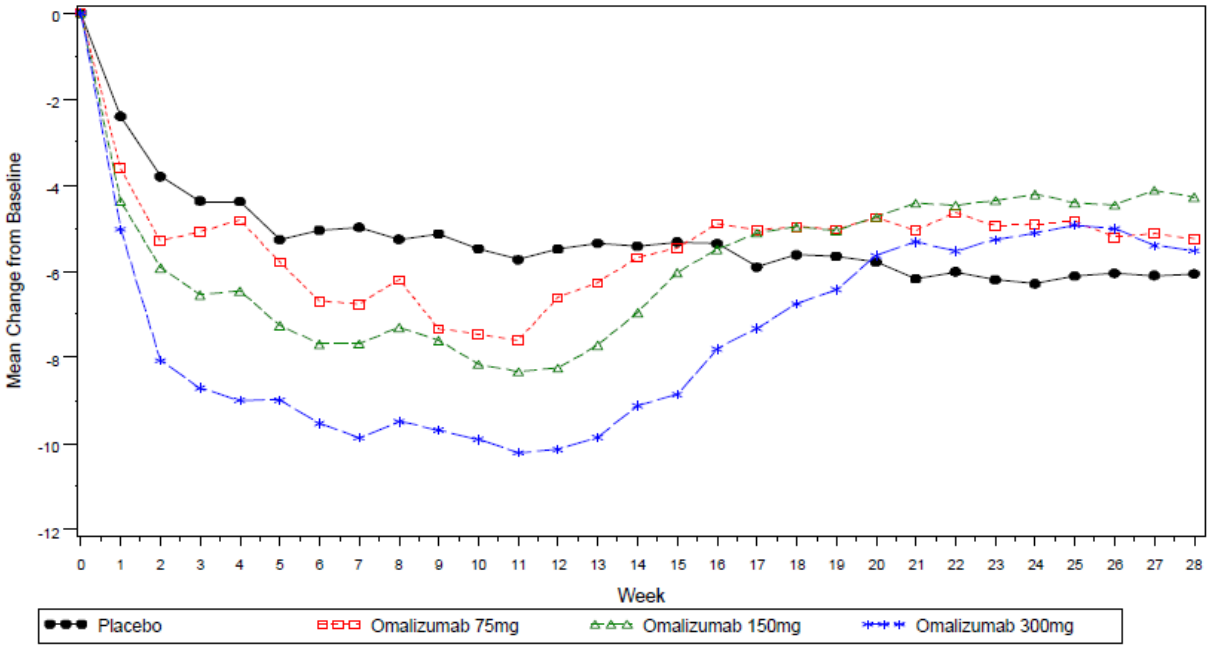
ANCOVA = analysis of covariance; CI = confidence interval; LSM = least squares mean; OMA = omalizumab; PBO = placebo; SD = standard deviation; vs. = versus.
[a] The LSM was estimated using an ANCOVA model. The strata are baseline number of tablets/week (less than median versus greater than or equal to median) and baseline weight (< 80 kg versus ≥ 80 kg).
Source: Clinical Study Reports for ASTERIA I,[20] ASTERIA II,[21] and GLACIAL.[22]

FIGURE 8: MEAN CHANGE FROM BASELINE IN WEEKLY ITCH SEVERITY SCORE BY STUDY WEEK — ASTERIA I (BASELINE OBSERVATION CARRIED FORWARD METHOD): MODIFIED INTENTION-TO-TREAT POPULATION



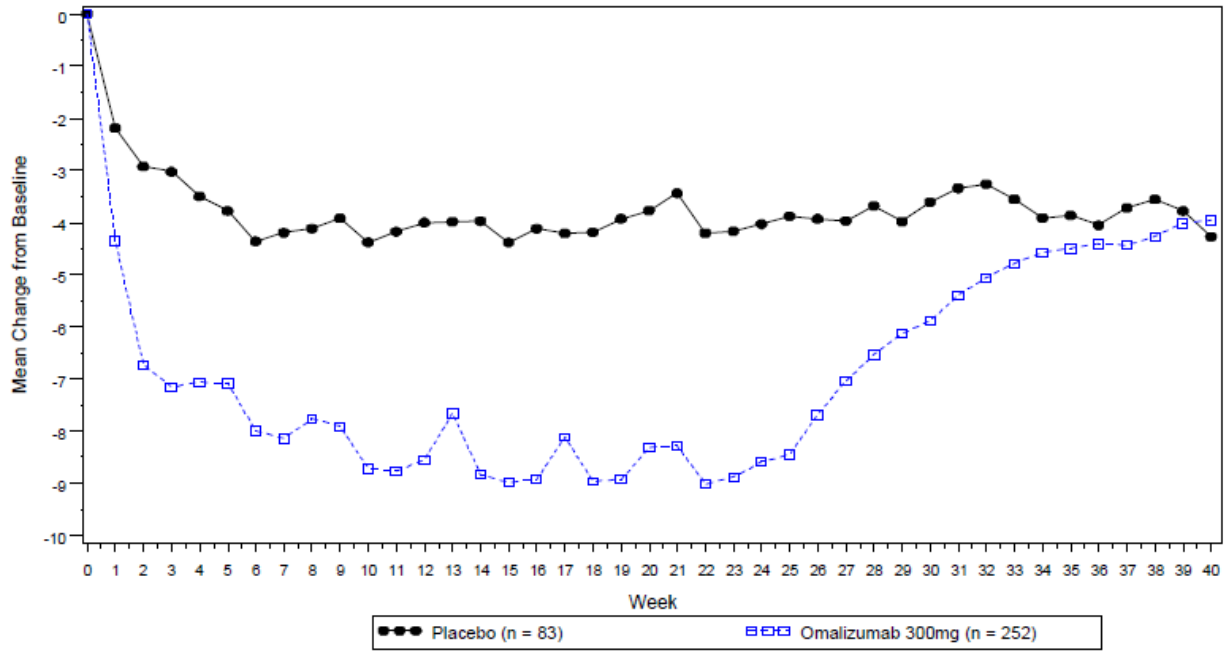
Source: Clinical Study Report for ASTERIA I.[20]

FIGURE 9: MEAN CHANGE FROM BASELINE IN WEEKLY ITCH SEVERITY SCORE BY STUDY WEEK — ASTERIA II (BASELINE OBSERVATION CARRIED FORWARD METHOD): MODIFIED INTENTION-TO-TREAT POPULATION



Source: Clinical Study Report for ASTERIA II.[21]

FIGURE 10: MEAN CHANGE FROM BASELINE IN WEEKLY ITCH SEVERITY SCORE BY STUDY WEEK — GLACIAL (BASELINE OBSERVATION CARRIED FORWARD METHOD): MODIFIED INTENTION-TO-TREAT POPULATION



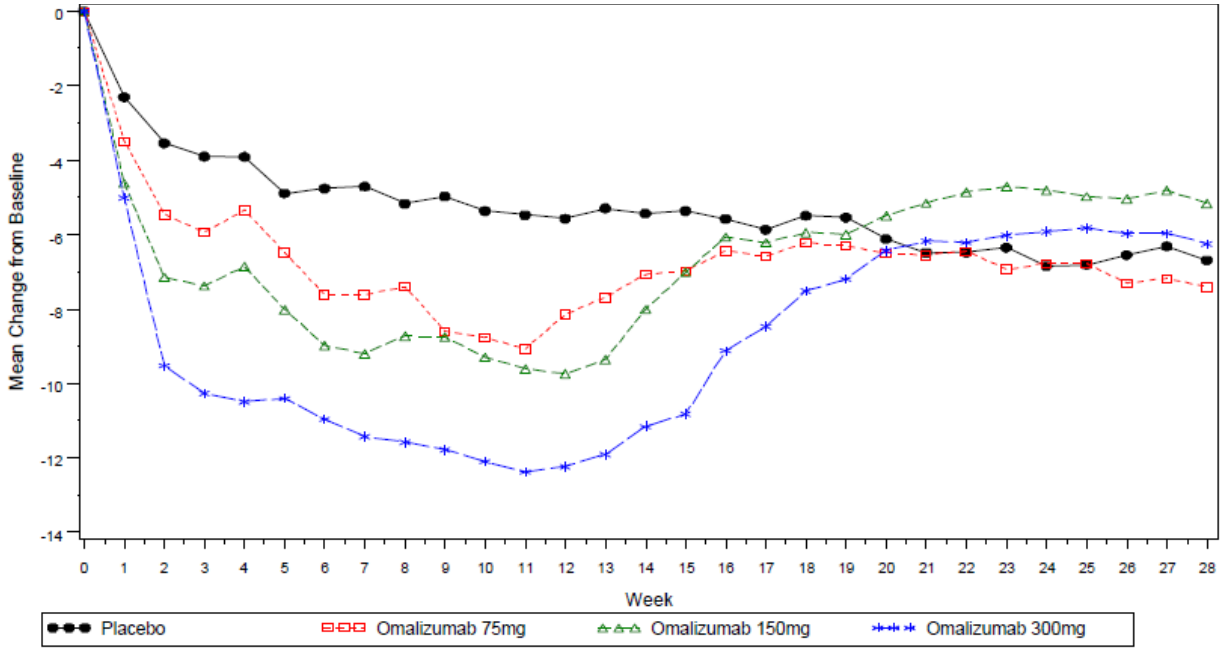
Source: Clinical Study Report for GLACIAL.[22]

FIGURE 11: MEAN CHANGE FROM BASELINE IN WEEKLY NUMBER OF HIVES SCORE BY STUDY WEEK — ASTERIA I (BASELINE OBSERVATION CARRIED FORWARD METHOD): MODIFIED INTENTION-TO-TREAT POPULATION

Confidential figure was removed at the manufacturer's request.

Source: Clinical Study Report for ASTERIA I.[20]

FIGURE 12: MEAN CHANGE FROM BASELINE IN WEEKLY NUMBER OF HIVES SCORE BY STUDY WEEK — ASTERIA II (BASELINE OBSERVATION CARRIED FORWARD METHOD): MODIFIED INTENTION-TO-TREAT POPULATION



Source: Clinical Study Report for ASTERIA II.[21]

FIGURE 13: MEAN CHANGE FROM BASELINE IN WEEKLY NUMBER OF HIVES SCORE BY STUDY WEEK — GLACIAL (BASELINE OBSERVATION CARRIED FORWARD METHOD): MODIFIED INTENTION-TO-TREAT POPULATION

Confidential figure was removed at the manufacturer's request.

Source: Clinical Study Report for GLACIAL.[22]

FIGURE 14: SUBGROUP ANALYSIS OF CHANGE FROM BASELINE IN WEEKLY ITCH SEVERITY SCORE AT WEEK 12 (BASELINE OBSERVATION CARRIED FORWARD) — ASTERIA I: 300 MG VERSUS PLACEBO

Confidential figure was removed at the manufacturer's request.

Source: Clinical Study Report for ASTERIA I.[20]

FIGURE 15: SUBGROUP ANALYSIS OF CHANGE FROM BASELINE IN WEEKLY ITCH SEVERITY SCORE AT WEEK 12 (BASELINE OBSERVATION CARRIED FORWARD) — ASTERIA I: 150 MG VERSUS PLACEBO

Confidential figure was removed at the manufacturer's request.

Source: Clinical Study Report for ASTERIA I.[20]

FIGURE 16: SUBGROUP ANALYSIS OF CHANGE FROM BASELINE IN WEEKLY ITCH SEVERITY SCORE AT WEEK 12 (BASELINE OBSERVATION CARRIED FORWARD) — ASTERIA II: 300 MG VERSUS PLACEBO

Confidential figure was removed at the manufacturer's request.

Source: Clinical Study Report for ASTERIA II.[21]

FIGURE 17: SUBGROUP ANALYSIS OF CHANGE FROM BASELINE IN WEEKLY ITCH SEVERITY SCORE AT WEEK 12 (BASELINE OBSERVATION CARRIED FORWARD) — ASTERIA II: 150 MG VERSUS PLACEBO

Confidential figure was removed at the manufacturer's request.

Source: Clinical Study Report for ASTERIA II.[21]

FIGURE 18: SUBGROUP ANALYSIS OF CHANGE FROM BASELINE IN WEEKLY ITCH SEVERITY SCORE AT WEEK 12 (BASELINE OBSERVATION CARRIED FORWARD) — GLACIAL: 300 MG VERSUS PLACEBO

Confidential figure was removed at the manufacturer's request.

Source: Clinical Study Report for GLACIAL.[22]

TABLE 20: EXPLORATORY EFFICACY END POINTS DURING TREATMENT PERIOD UP TO WEEK 24: MODIFIED INTENTION-TO-TREAT POPULATION

	ASTERIA I			GLACIAL	
	OMA 150 mg (N = 80)	OMA 300 mg (N = 81)	PBO (N = 80)	OMA 300 mg (N = 252)	PBO (N = 83)
Change From Baseline in UAS7 at Week 24					
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean value at week 24 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. PBO, LSM (95% CI)	[redacted]	[redacted]	–	[redacted]	–
P value vs. PBO	[redacted]	[redacted]	–	[redacted]	–
Proportion of Patients With UAS7 ≤ 6 at Week 24					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value vs. PBO	[redacted]	[redacted]	–	[redacted]	–
Proportion of Complete Responders (UAS7 = 0) at Week 24					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value vs. PBO	[redacted]	[redacted]	–	[redacted]	–

	ASTERIA I			GLACIAL	
	OMA 150 mg (N = 80)	OMA 300 mg (N = 81)	PBO (N = 80)	OMA 300 mg (N = 252)	PBO (N = 83)
Change From Baseline in WISS at Week 24					
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean value at week 24 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. PBO, LSM (95% CI)	[redacted]	[redacted]	–	[redacted]	–
P value vs. PBO	[redacted]	[redacted]	–	[redacted]	–
Change From Baseline in WNHS at Week 24					
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean value at week 24 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. PBO, LSM (95% CI)	[redacted]	[redacted]	–	[redacted]	–
P value vs. PBO	[redacted]	[redacted]	–	[redacted]	–
Change From Baseline in DLQI Overall Score at Week 24					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean value at week 24 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. PBO, LSM (95% CI)	[redacted]	[redacted]	–	[redacted]	–
P value vs. PBO	[redacted]	[redacted]	–	[redacted]	–
Change From Baseline in CU-Q2oL Overall Score at Week 24					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean value at week 24 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. PBO, LSM (95% CI)	[redacted]	[redacted]	–	[redacted]	–
P value vs. PBO	[redacted]	[redacted]	–	[redacted]	–

CI = confidence interval; CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index; LSM = least squares mean; NR = not reported; OMA = omalizumab; PBO = placebo; SD = standard deviation; UAS7 = Urticaria Activity Score over seven days; vs. = versus; WISS = Weekly Itch Severity Score; WNHS = Weekly Number of Hives Score.
Source: Clinical Study Reports for ASTERIA I[20] and GLACIAL.[22]

TABLE 21: EXPLORATORY EFFICACY END POINTS DURING FOLLOW-UP PERIOD UP TO WEEK 28 — ASTERIA II: MODIFIED INTENTION-TO-TREAT POPULATION

	ASTERIA II		
	OMA 150 mg (N = 82)	OMA 300 mg (N = 79)	PBO (N = 79)
Proportion of Patients With UAS7 ≤ 6 at Week 28			
N (%)	[redacted]	[redacted]	[redacted]
P value vs. PBO	[redacted]	[redacted]	–
Proportion of Week 12 Responders Who Maintain Their Response (UAS7 ≤ 6) to the Week 28 Visit			
Number of week 12 responders (%)	[redacted]	[redacted]	[redacted]
Number of patients who maintained UAS7 ≤ 6 at week 28 (%)	[redacted]	[redacted]	[redacted]
Time to Relapse After Week 12 (Loss of UAS7 ≤ 6 Response) in Week 12 Responders (UAS7 ≤ 6)			
Number of week 12 responders (%)	[redacted]	[redacted]	[redacted]
Number of patients relapsed (UAS7 > 6) (%)	[redacted]	[redacted]	[redacted]
Median time to relapse in weeks (95% CI)	[redacted]	[redacted]	[redacted]
Change From Baseline in DLQI at Week 28			
n	[redacted]	[redacted]	[redacted]
Baseline (SD)	[redacted]	[redacted]	[redacted]
Mean value at week 28 (SD)	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Difference vs. PBO, LSM (95% CI)	[redacted]	[redacted]	–
P value vs. PBO	[redacted]	[redacted]	–
Change From Baseline in CU-Q2oL at Week 28			
n	[redacted]	[redacted]	[redacted]
Baseline (SD)	[redacted]	[redacted]	[redacted]
Mean value at week 28 (SD)	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Difference vs. PBO, LSM (95% CI)	[redacted]	[redacted]	–
P value vs. PBO	[redacted]	[redacted]	–
Change From Baseline in EQ-5D Index Score at Week 28			
n	[redacted]	[redacted]	[redacted]
Baseline (SD)	[redacted]	[redacted]	[redacted]
Mean value at week 28 (SD)	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Difference vs. PBO, LSM (95% CI)	[redacted]	[redacted]	–
P value vs. PBO	[redacted]	[redacted]	–

CI = confidence interval; CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimensions Questionnaire; LSM = least squares mean; OMA = omalizumab; PBO = placebo; SD = standard deviation; UAS7 = Urticaria Activity Score over seven days; vs. = versus.
Source: Clinical Study Report for ASTERIA II.[21]

TABLE 22: EXPLORATORY EFFICACY END POINTS DURING FOLLOW-UP PERIOD UP TO WEEK 40: MODIFIED INTENTION-TO-TREAT POPULATION

	ASTERIA I			GLACIAL	
	OMA 150 mg (N = 80)	OMA 300 mg (N = 81)	PBO (N = 80)	OMA 300 mg (N = 252)	PBO (N = 83)
Proportion of Patients With UAS7 ≤ 6 at Week 40					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value vs. PBO	[redacted]	[redacted]	–	[redacted]	–
Proportion of Week 24 Responders Who Maintain Their Response (UAS7 ≤ 6) to the Week 40 Visit					
Number of week 24 responders (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients who maintained UAS7 ≤ 6 at week 40 (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Time to Relapse After Week 24 (loss of UAS7 ≤ 6 Response) in Week 24 Responders (UAS7 ≤ 6)					
Number of week 24 responders (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients relapsed (UAS7 > 6) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median time to relapse in weeks (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of Patients With a Complete Response (UAS = 0) at Week 40					
N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
P value vs. PBO	[redacted]	[redacted]	–	[redacted]	–
Change From Baseline in DLQI at Week 40					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean value at week 40 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. PBO, LSM (95% CI)	[redacted]	[redacted]	–	[redacted]	–
P value vs. PBO	[redacted]	[redacted]	–	[redacted]	–
Change From Baseline in CU-Q2oL at Week 40					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean value at week 40 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. PBO, LSM (95% CI)	[redacted]	[redacted]	–	[redacted]	–
P value vs. PBO	[redacted]	[redacted]	–	[redacted]	–
Change From Baseline in EQ-5D Index Score at Week 40					
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean value at week 40 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from baseline, mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference vs. PBO, LSM (95% CI)	[redacted]	[redacted]	–	[redacted]	–
P value vs. PBO	[redacted]	[redacted]	–	[redacted]	–

CI = confidence interval; CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol 5-Dimensions Questionnaire; LSM = least squares mean; OMA = omalizumab; NE = not estimable; NR = not reported; PBO = placebo; SD = standard deviation; UAS7 = Urticaria Activity Score over seven days; vs. = versus.
Source: Clinical Study Reports for ASTERIA I[20] and GLACIAL.[22]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the characteristics, validity, and minimal clinically important differences (MCIDs) of the outcome measures used in the trials of CIU included in the systematic CADTH Common Drug Review of omalizumab:

- Urticaria Activity Score (UAS)
- Urticaria Activity Score over seven days (UAS7)
- Dermatology Life Quality Index (DLQI)
- Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL)
- EuroQol 5-Dimenions Questionnaire (EQ-5D).

Findings

TABLE 23: SUMMARY OF OUTCOME MEASURES USED IN THE INCLUDED TRIALS

Instrument	Type	Evidence for Validation	MCID	References
UAS, UAS7, and Subcomponents WISS and WNHS	Disease-specific tool to assess disease activity and response to treatment. The daily UAS is a sum of the daily Itch Severity Score (3 points) and the daily Number of Hives Score (3 points), giving a range of 0 to 6 points per day and 0 to 42 over one week, with higher scores indicating more severe symptoms.	Yes	UAS7: 9.5 to 10.5 points WISS: 4.5 to 5.0 points WNHS: 5.0 to 5.5 points	26
DLQI	The DLQI is a dermatology-specific 10-item QoL instrument. The questionnaire assesses six 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.	Yes	2.2 to 3.1 points	29,28
CU-Q2oL	A 23-item disease-specific self-administered questionnaire that includes six QoL dimensions: pruritus, swelling, impact on life activities, sleep problems, limits, and looks. Each item is scored on a 5-point Likert scale. The individual items are summed to generate the overall CU-Q2oL score, which are then converted to a 0-to-100 scale; higher scores indicate greater QoL impairment.	Yes	Not known	30
EQ-5D	The EQ-5D is a generic QoL instrument consisting of five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a VAS for rating health today. Weighted scoring produces an EQ-5D index score.	No	0.033 to 0.074, but not specific for CIU	34,35

CIU = chronic idiopathic urticaria; CU-Q2oL = Chronic Urticaria Quality of Life Questionnaire; DLQI = Dermatology Quality Of Life Index; EQ-5D = EuroQol 5-Dimensions Questionnaire; QoL = quality of life; UAS = Urticaria Activity Score; UAS7 = Urticaria Activity Score over seven days; VAS = visual analogue scale; WISS = Weekly Itch Severity Score; WNHS = Weekly Number of Hives Score.

Urticaria Activity Score

The UAS was developed specifically for use in CIU patients and is recommended as a tool to assess disease activity and response to treatment by the World Allergy Organization guidelines.[26] The daily UAS is a sum of the daily Itch Severity Score (0 = none, 1 = mild, 2 = moderate, 3 = severe) and the daily Number of Hives Score (0 = none, 1 = between 1 and 6 hives, 2 = between 7 and 12 hives, 3 = greater than 12 hives), giving a range of 0 to 6 points per day.[26] UAS7 is the sum of daily UAS scores over one week (range 0 to 42), with higher scores indicating more severe symptoms.[26] The components of UAS are captured in an Urticaria Patient Daily Diary in addition to the largest hive size, sleep interference, activity interference, and angioedema episodes.[24,25] The content validity of the Urticaria Patient Daily Diary has been confirmed in both adult[24] and adolescent[25] patients through structured in-person interviews.

The internal consistency, test–retest reliability, construct validity, and MCID of UAS was determined in one phase 2, randomized, double-blind, placebo-controlled study of omalizumab (75 mg, 300 mg, or 600 mg monthly) as add-on therapy for the treatment of CIU.[26] A total of 73 patients from the United States (70% female, mean age 39.7 years) with moderate to severe CIU as defined by itching and hives for greater than three days in a seven-day period (UAS7 ≥ 16) for more than six consecutive weeks despite H_1 antihistamine treatment were included in the analyses. Thirteen patients from Germany were excluded from the analyses due to potential variations by country. Patients were required to record scores for itch severity, number of hives, and hive size twice daily, and the two daily scores were averaged to compute a weekly UAS7. The study consisted of a screening (day –14 to –7), run-in (day –7 to day 0), treatment (day 0 through week 4), and follow-up (week 4 through 16) phase.

The internal consistency, as measured by Cronbach's alpha coefficients, was calculated using UAS7 scores before baseline and were all reported to be at least 0.819 (itch severity). The test–retest reliability, as measured by the intraclass correlation coefficient, was calculated using UAS scores from day –14 (screening) and day –7 (start of run-in) and was reported to be 0.602 (itch severity), 0.764 (number of hives), and 0.659 (UAS7). The construct validity was measured using Spearman's correlation coefficients between UAS scores and the DLQI and reported as a range of 0.283 to 0.459.

The MCID of the UAS7 score and its individual components was estimated using an integrated analysis of distribution and anchor-based approaches using changes in patient and physician UAS ratings and the DLQI from baseline to week 4. The MCID for UAS7 was reported to be 9.5 to 10.5 points. The MCID for the Weekly Itch Severity Score (WISS) was reported to be 4.5 to 5.0 points, and the MCID for weekly number of hives was reported to be 5.0 to 5.5 points.

Dermatology Life Quality Index

The DLQI is a widely used dermatology-specific quality of life instrument. It is a 10-item questionnaire that assesses six different aspects that may affect quality of life: symptoms and feelings, daily activities, leisure activities, work or school, personal relationships, and treatment.[29] The maximum score per aspect is either 3 or 6 and the scores for each can be expressed as a percentage of either 3 or 6. Each of the 10 questions is scored from 0 (not at all) to 3 (very much) and the overall DLQI is calculated by summing the score of each question, resulting in a numeric score between 0 and 30 (or a percentage of 30). Higher scores indicate a greater impairment in quality of life. The impact of the DLQI scores on a patient's life is as follows: 0 to 1 = no effect, 2 to 5 = small effect, 6 to 10 = moderate effect, 11 to 20 = very large effect, 21 to 30 = extremely large effect.

The internal consistency, construct validity, reliability, and MCID of the DLQI in CIU patients has been determined using data from two phase 3, multi-centre, randomized, double-blind, placebo-controlled studies of fexofenadine hydrochloride (20 mg, 60 mg, 120 mg, or 240 mg twice daily) as treatment for CIU (N = 476 and N = 468, respectively).[27,28] Both studies were four weeks in duration and enrolled CIU patients who had moderate to severe itching. The DLQI was used to assess health-related quality of life at baseline, week 2, and week 4.

The internal consistency of the DLQI in CIU patients, as measured by Cronbach's alpha coefficients, was reported to be 0.89 and 0.87 for the two studies.[27] The construct validity, as measured using Spearman's correlation coefficients, between the DLQI and clinical outcomes was reported as a range of 0.21 to 0.45.[27] The MCID of the DLQI in CIU patients was estimated using an integrated analysis of distribution and anchor-based approaches using the change in DLQI total score and patient-assessed itch severity scores.[28] The MCID for the DLQI in CIU patients was reported to be in the range of 2.24 to 3.10 points.

A recent review of validation data and clinical results for the DLQI in publications from 1994 to 2007 identified some limitations.[36] Concerns have been identified regarding unidimensionality and the behaviour of items of the DLQI in different psoriatic patient populations with respect to their age, gender, culture, etc. In addition, emotional aspects may be underrepresented, and this may be one reason for unexpectedly low DLQI scores in patients with more emotionally disabling diseases such as vitiligo. To overcome this, it is suggested that the DLQI be combined with more emotionally oriented measures such as the mental component of the Short-Form 36-Item Health Survey (SF-36) or hospital anxiety and depression (HAD) scales.

Chronic Urticaria Quality of Life Questionnaire

The CU-Q2oL is a disease-specific instrument used to assess the quality of life in patients with CIU.[30] The CU-Q2oL is a 23-item, self-administered questionnaire that includes six quality of life dimensions: pruritus, swelling, impact on life activities, sleep problems, limits, and looks. Each item is scored on a 5-point Likert scale (1 = not at all, 5 = extremely) where patients indicate how troubled they are within each dimension. The individual items are summed to generate the overall CU-Q2oL score, which is then converted to a 0 to 100 scale; higher scores indicate greater quality of life impairment. The CU-Q2oL was originally developed by an Italian team and has been translated and adapted for use in several countries.[37-42]

The internal consistency, validity, and test–retest reliability of the CU-Q2oL were determined in a survey cohort of 130 adult patients with a consistent clinical history of intermittent or daily symptoms of urticaria for at least six weeks.[30] Patients completed both the CU-Q2oL and the SF-36 health surveys. All dimensions of the CU-Q2oL had good internal consistency, with Cronbach's alpha values falling between 0.74 and 0.83. The correlation between CU-Q2oL and SF-36 scores were in the expected direction depending on the domain. The test–retest reliability was good for the majority of items, with intraclass coefficients exceeding 0.75 for all except the following: Physical Activity, Social Relationship, "Do you have difficulties falling asleep?," and "Do you feel in a bad mood?"

No studies reporting an MCID for the CU-Q2oL were identified.

EuroQol 5-Dimensions Questionnaire

The EQ-5D is a generic quality of life instrument that may be applied to a wide range of health conditions and treatments.[31] The first of two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and

anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[31] The second part is a 20 cm visual analogue scale that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the visual analogue scale that best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

- a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- a population preference-weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the visual analogue scale.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than death, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. Reported clinically important differences for this scale, although not specific for CIU patients, have ranged from 0.033 to 0.074. The clinically important differences were derived from patients with a variety of chronic and acute conditions, including rheumatoid arthritis, osteoarthritis, irritable bowel syndrome, and acute myocardial infarction.[34,35]

No studies specifically validating EQ-5D in patients with CIU were identified. As with any generic health-related quality of life instrument, there is the possibility that items important to patients with a specific disease may be missed by the EQ-5D or that the instrument may lack sufficient sensitivity to detect clinically important changes.

Conclusion

Both disease-specific and generic scales were used in the ASTERIA I, ASTERIA II, and GLACIAL trials. The UAS is widely used to evaluate disease severity in CIU patients in clinical trials and incorporates both itch severity and number of hives into a single score. The UAS7, a weekly sum of daily UAS scores, showed good construct validity, reliability, and internal consistency. The MCID for UAS7 was reported to be 9.5 to 10.5, while the MCID for WISS was 4.5 to 5.0, and the MCID for the weekly hives score was 5.0 to 5.5. Three quality of life scales were used in the trials, including the generic EQ-5D, the dermatologic-specific DLQI, and the disease-specific CU-Q2oL. Both the DLQI and CU-Q2oL showed reasonable construct validity, reliability, and internal consistency in CIU patients. The MCID for the DLQI in CIU patients was reported to be between 2.24 and 3.10. No MCID for the CU-Q2oL was reported. The EQ-5D is a generic quality of life instrument that has not been specifically validated in patients with CIU.

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