

Original Article

Similar Efficacy with Omalizumab in Chronic Idiopathic/Spontaneous Urticaria Despite Different Background Therapy

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What is already known about this topic? Omalizumab is safe and efficacious in the treatment of chronic idiopathic urticaria/chronic spontaneous urticaria (CIU/CSU). Different background therapies were used in the 3 phase III clinical trials in patients with refractory CIU/CSU.

What does this article add to our knowledge? Findings from this *post hoc* analysis indicate similar efficacy with omalizumab 300 mg in patients with CIU/CSU regardless of the background therapy for urticaria. The safety profile was similar to that in allergic asthma.

How does this study impact current management guidelines? The study results support the use of omalizumab in refractory patients with CIU/CSU without concerns for previous background therapies. No dose-related adverse effects and no new safety concerns have been identified with the pooled data set.

BACKGROUND: Data from the 3 omalizumab pivotal trials in patients with chronic idiopathic urticaria/chronic spontaneous urticaria (CIU/CSU) represent the largest database of patients reported to date with refractory disease (omalizumab, $n = 733$; placebo, $n = 242$).

OBJECTIVE: The objective of this study was to compare results from ASTERIA I and II, which included only approved doses of H₁-antihistamine as background therapy based on regulatory authority requirements, to those from GLACIAL, which

permitted higher doses of H₁-antihistamines as well as other types of background therapy, in a *post hoc* analysis.

METHODS: Efficacy data from the placebo, omalizumab 150-mg, and omalizumab 300-mg treatment arms of ASTERIA I and II were pooled and analyzed ($n = 162$ and $n = 160$, respectively). The 300-mg treatment arm analyses were compared with the analysis of data from GLACIAL ($n = 252$) using analysis of covariance models. The key efficacy endpoint was change from baseline to week 12 in mean weekly itch severity score (ISS);

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Abbreviations used

AE- Adverse event
CI- Confidence interval
CIU- Chronic idiopathic urticaria
CSU- Chronic spontaneous urticaria
CU- Chronic urticaria
DLQI- Dermatology Life Quality Index
HR- Hazard ratio
HRQoL- Health-related quality of life
IgE- Immunoglobulin E
ISS- Itch severity score
LTRA- Leukotriene receptor antagonist
MID- Minimally important difference
mITT- Modified intention-to-treat
NE- Not evaluated
SAE- Serious adverse event
SC- Subcutaneous
UAS- Urticaria activity score
UAS7- Urticaria activity score over 7 days

other endpoints were also evaluated. Safety data were pooled from all 3 studies.

RESULTS: Mean ISS was significantly reduced from baseline at week 12 in the pooled ASTERIA I and II omalizumab 150- and 300-mg treatment arms and in the GLACIAL omalizumab 300-mg arm. The weekly ISS reduction magnitude at week 12 was similar between the omalizumab 300-mg groups in the ASTERIA I and II pooled and GLACIAL studies. Similar treatment effect sizes were observed across multiple endpoints.

Omalizumab was well tolerated and the adverse-event profile was similar regardless of background therapy for CIU/CSU. The overall safety profile was generally consistent with omalizumab therapy in allergic asthma.

CONCLUSION: Omalizumab 300 mg was safe and effective in reducing CIU/CSU symptoms regardless of background therapy. © 2015 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2015;■:■-■)

Key words: Omalizumab; Urticaria; Chronic spontaneous; Chronic idiopathic; Itch; Hive; Pruritus; Wheal; Antihistamine

Chronic idiopathic urticaria (CIU), also known as chronic spontaneous urticaria (CSU), is defined as wheals or angioedema that occurs together or separately on an intermittent or constant basis for at least 6 weeks with no apparent specific trigger.¹ Second-generation H₁-antihistamines are an effective first-line treatment in some patients with CIU/CSU.¹ An increase in H₁-antihistamine dose up to 4-fold is considered second-line therapy. However, some patients with severe CIU/CSU continue to experience symptoms despite treatment with increased doses of H₁-antihistamines.²⁻⁴ Third-line treatment options for patients who do not achieve complete control of their symptoms with increased dosages of H₁-antihistamines have included short-term corticosteroids, add-on therapy with cyclosporine, a leukotriene receptor antagonist (LTRA), or omalizumab.^{1,5,6}

Omalizumab is a humanized monoclonal antibody to immunoglobulin E (IgE) that has been licensed for the treatment of moderate to severe allergic asthma in the United States since

2003 and for severe allergic asthma in Europe since 2005.^{7,8} It was recently approved for the treatment of CIU/CSU in Europe and the United States.^{7,8} Omalizumab was studied in 3 phase III, randomized, double-blind, placebo-controlled, clinical trials in patients with CIU/CSU. ASTERIA I⁹ and ASTERIA II¹⁰ evaluated the efficacy and safety of subcutaneous (SC) omalizumab 75 mg, 150 mg, and 300 mg every 4 weeks versus placebo in patients with CIU/CSU who remained symptomatic despite treatment with approved dosages of second-generation H₁-antihistamines. GLACIAL¹¹ evaluated the safety and efficacy of omalizumab 300 mg SC every 4 weeks versus placebo in patients who remained symptomatic despite treatment with up to 4 times the approved dose of second-generation H₁-antihistamines and add-on H₂-antagonists and/or LTRAs.

The data from the phase III clinical program represent the largest database of patients reported to date with refractory CIU/CSU with nearly 1000 patients included (omalizumab, n = 733; placebo, n = 242). Guideline recommendations for the use of omalizumab cite a strong, high level of evidence to support its use in CIU/CSU.¹ In this *post hoc* analysis, we compared the efficacy of omalizumab from the ASTERIA studies, which included only approved doses of H₁-antihistamines as background therapy, with the efficacy of omalizumab from the GLACIAL study, which permitted higher doses of antihistamines as well as other types of background therapy. An evaluation of the pooled safety data and time to loss of response are also included.

METHODS

Study design

ASTERIA I and ASTERIA II were multicenter, randomized, double-blind, placebo-controlled studies of omalizumab 75 mg (ASTERIA I, n = 77; ASTERIA II, n = 82), 150 mg (ASTERIA I, n = 80; ASTERIA II, n = 82), or 300 mg (ASTERIA I, n = 81; ASTERIA II, n = 79) versus placebo (ASTERIA I, n = 80; ASTERIA II, n = 79) administered SC every 4 weeks in patients who remained symptomatic despite treatment with approved doses of H₁-antihistamines. These studies were similar in design except for the duration of treatment, which was 24 weeks and 12 weeks, respectively (Figure 1). Observational follow-up continued in both studies for 16 weeks after the last dose of omalizumab. The primary efficacy endpoint in both studies was change from baseline to week 12 in weekly itch severity score (ISS), a component of the urticaria activity score over 7 days¹² (UAS7, daily ISS intensity ratings range from 0 [none] to 3 [intense and/or severe]; range 0-21). Both studies included the following secondary endpoints evaluated at week 12: change from baseline in UAS7, change from baseline in weekly number of hives score, time to minimally important difference (MID) response (≥ 5 -point reduction) in weekly ISS, proportion of patients with UAS7 ≤ 6 (well-controlled symptoms), proportion of patients who were weekly ISS MID responders, change from baseline in weekly size of largest hive score, change from baseline in overall Dermatology Life Quality Index (DLQI), proportion of angioedema-free days from week 4 to week 12 of therapy, and proportion of patients with UAS7 = 0 (complete response). The proportion of patients with complete response was an *ad hoc* analysis for ASTERIA II. Time to loss of response (defined as a loss of UAS7 ≤ 6) was included as a prespecified exploratory endpoint in both studies. GLACIAL was a 40-week (24 weeks of treatment and 16 weeks of observational follow-up), multicenter, randomized, double-blind, placebo-controlled study of omalizumab 300 mg (n = 252)

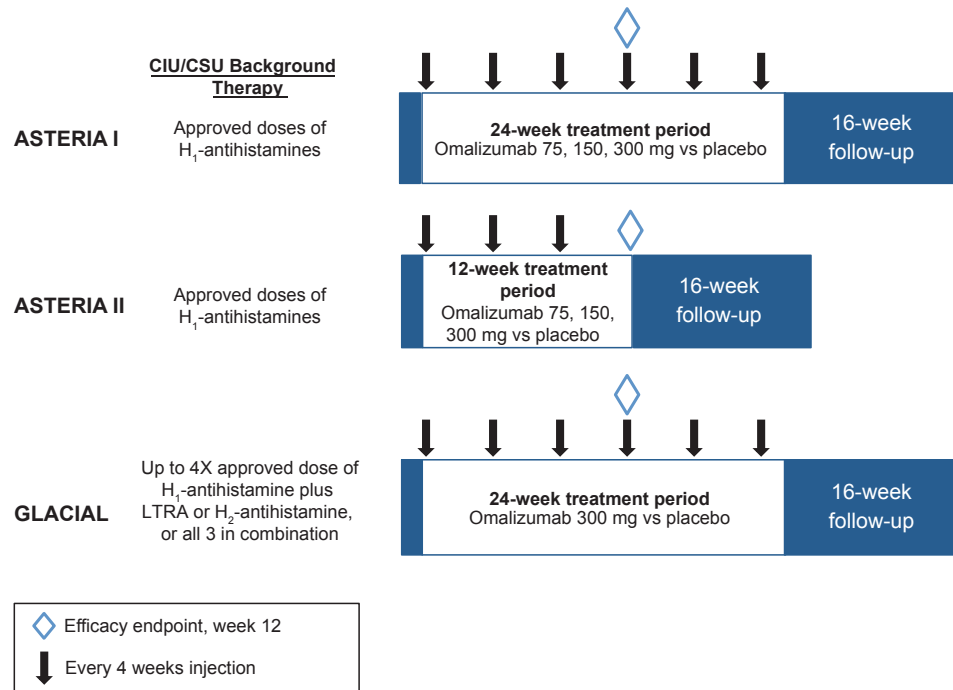


FIGURE 1. Study designs. *CIU*, chronic idiopathic urticaria; *CSU*, chronic spontaneous urticaria; *LTRA*, leukotriene receptor antagonist.

versus placebo ($n = 83$) SC every 4 weeks in patients who remained symptomatic despite treatment with up to 4 times the approved dosage of H₁-antihistamines and either H₂-antihistamines or LTRAs, or all 3 in combination (Figure 1). The primary objective of GLACIAL was to evaluate the safety of omalizumab versus placebo; efficacy was evaluated as a secondary objective. Secondary efficacy endpoints included the change from baseline in weekly ISS and the other 9 endpoints listed above from ASTERIA I and II and were evaluated at week 12. Time to loss of response was a prespecified exploratory endpoint in GLACIAL. Diphenhydramine 25 mg was allowed for itch relief in all 3 studies (up to a maximum of 3 doses or less in 24 hours based on local regulations). All 3 studies were conducted in accordance with US Food and Drug Administration regulations, the International Conference on Harmonisation E6 Guideline for Good Clinical Practice, and any other applicable country laws. Institutional review board approval and informed consent was obtained from all research subjects. These trials are registered with [ClinicalTrials.gov](https://clinicaltrials.gov), number NCT01287117 (ASTERIA I), number NCT01292473 (ASTERIA II), and number NCT01264939 (GLACIAL).

Patients

Patients were eligible for inclusion in these studies if they met the following criteria: age 12–75 years (18–75 years in Germany; per German regulatory requirements), diagnosis of CIU/CSU for ≥ 6 months, presence of itch and hives for ≥ 8 consecutive weeks before enrollment despite concurrent H₁-antihistamine treatment at approved doses (ASTERIA I and II) or presence of itch and hives for >6 consecutive weeks before enrollment despite treatment with H₁-antihistamines at up to 4 times the approved dose plus LTRAs or H₂-antihistamines, or all 3 in combination (GLACIAL; baseline medication use previously reported¹¹), UAS7 ≥ 16 (scale 0–42) and weekly ISS ≥ 8 (scale 0–21) for the 7 days before randomization,

in-clinic physician-assessed UAS ≥ 4 (scale 0–6) on 1 or more of the screening visit days, treatment with an approved dose of an H₁-antihistamine (ASTERIA I and II) or with an H₁-antihistamine up to 4 times the approved dose plus LTRAs or H₂-antihistamines, or all 3 for 3 or more consecutive days immediately before day –14 (GLACIAL), and no missing symptom diary (eDiary) entries in the 7 days before randomization. Exclusion criteria for all 3 studies included clearly defined inducible trigger for chronic urticaria (eg, cold, pressure); presence of a disease with symptoms of urticaria or angioedema; or routine doses (daily or every other day for ≥ 5 consecutive days) of systemic steroids, hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, or intravenous immunoglobulin within 30 days before day –14, or treatment with omalizumab in prior year. The individual study publications provide more detailed discussion of exclusion criteria.^{9,11}

Assessments

Detailed descriptions of the assessments used in the studies have been published.^{9–11} Briefly, patients completed a symptom diary each morning and evening that recorded scores (scale range: 1–3) for itch severity, the number of hives, and size of largest hive using a hand-held electronic device. The means of the morning and evening scores for itch severity and number of hives were summed to derive the UAS7 (total score range 0–42; higher score reflects greater disease activity). The weekly ISS is the sum of the daily ISS for 7 days (total score range 0–21; higher score reflects greater itch severity). Patients also recorded the presence of angioedema (yes/no) in the electronic diary. They completed the DLQI at baseline and weeks 4 and 12 (score range 0–30; higher score represents greater impairment).

Data analyses

For the analyses of efficacy endpoints, data from the placebo, omalizumab 150-mg, and omalizumab 300-mg treatment arms of ASTERIA I and II were pooled and analyzed. The 300-mg treatment

TABLE I. Patient characteristics at baseline*

	ASTERIA I/II			GLACIAL ¹¹	
	Placebo (n = 159)	Omalizumab 150 mg (n = 162)	Omalizumab 300 mg (n = 160)	Placebo (n = 83)	Omalizumab 300 mg (n = 252)
Age (y)	41.7 (14.2)	42.1 (13.6)	43.3 (13.4)	44.3 (14.7)	42.7 (13.9)
Female sex, n (%)	107 (67.3)	129 (79.6)	123 (76.9)	55 (66.3)	186 (73.8)
Race, n (%)					
White	134 (84.3)	133 (82.1)	142 (88.8)	75 (90.4)	223 (88.5)
Weight (kg)	83.7 (23.2)	82.8 (22.5)	80.9 (19.7)	87.2 (25.2)	82.8 (21.5)
<80 kg, n (%)	76 (47.8)	81 (50.0)	86 (53.8)	40 (48.2)	128 (50.8)
Body mass index (kg/m ²)	29.3 (7.0)	29.9 (7.5)	29.2 (6.6)	31.0 (9.6)	29.4 (7.1)
Time since diagnosis of CIU/CSU [†] (y)	7.1 (10.1)	7.4 (9.0)	6.2 (7.6)	8.8 (11.2)	7.0 (8.8)
Positive CU index test, [‡] n (%)	48 (30.2)	43 (26.7)	39 (24.5)	27 (32.5)	76 (30.4)
No. of previous CIU/CSU medications, mean (median)	4.7 (4)	4.5 (4.0)	4.4 (4)	6.4 (6)	5.9 (6)
Previous use of systemic steroids, n (%)	68 (42.8)	65 (40.1)	66 (41.3)	44 (53.0)	121 (48.0)
Total IgE level [§] (IU/mL), median (range)	80.5 (1-1010)	71.0 (1-5000)	89.0 (1-2330)	71.0 (1-1230)	79.0 (1-3050)
In-clinic UAS	5.3 (0.7)	5.3 (0.7)	5.3 (0.8)	5.2 (0.8)	5.2 (0.8)
UAS7 [¶]	31.1 (6.6)	30.8 (7.1)	30.4 (6.4)	30.2 (6.7)	31.2 (6.6)
Weekly ISS [¶]	14.2 (3.5)	14.2 (4.0)	13.9 (3.4)	13.8 (3.6)	14.0 (3.6)
≥13, n (%)	99 (62.3)	100 (61.7)	95 (59.4)	50 (60.2)	154 (61.1)
Weekly number of hives score [¶]	16.9 (4.3)	16.7 (4.4)	16.5 (4.3)	16.4 (4.6)	17.1 (4.2)
Weekly size of largest hives score [¶]	15.3 (3.9)	15.2 (4.3)	15.1 (4.0)	15.2 (3.6)	15.1 (4.3)
Overall DLQI score	13.3 (6.3)	13.3 (6.6)	12.9 (6.5)	13.0 (6.9)	13.8 (6.7)
Angioedema present, n (%) [¶]	74 (46.5)	76 (46.9)	66 (41.3)	41 (49.4)	137 (54.4)

CIU/CSU, chronic idiopathic urticaria/chronic spontaneous urticaria; CU, chronic urticaria; DLQI, Dermatology Life Quality Index; IgE, immunoglobulin E; ISS, itch severity score; mITT, modified intention-to-treat; UAS, urticaria activity score; UAS7, urticaria activity score over 7 d.

*Analyses are based on the mITT population. Data are presented as means (standard deviation) unless otherwise stated.

[†]ASTERIA I/II pooled: placebo, n = 155, omalizumab 150 mg, n = 159, omalizumab 300 mg, n = 157; GLACIAL: placebo, n = 83; omalizumab 300 mg, n = 246.

[‡]ASTERIA I/II pooled: omalizumab 150 mg, n = 161 and 300 mg, n = 159; GLACIAL: placebo, n = 83; omalizumab 300 mg = 250.

[§]ASTERIA I/II pooled: placebo, n = 154, omalizumab 150 mg, n = 154, 300 mg, n = 152; GLACIAL: placebo, n = 82; omalizumab 300 mg, n = 244.

^{||}Defined as the largest value from the day -14 screening visit, day -7 screening visit, and day 1 visit.

[¶]Based on data collected in a patient daily diary in the 7 d before the first treatment date.

arm analyses were compared with the analysis of data from the GLACIAL study. Data from the 75-mg arm of ASTERIA I and II were not evaluated in this pooled analysis because 75 mg was considered an ineffective dose in ASTERIA I (did not reach the primary endpoint) and this dose was not evaluated in the GLACIAL study. The results for the omalizumab 75-mg dose in patients with CIU/CSU have been reported separately.^{9,10} For the primary endpoint, analysis of covariance models stratified by baseline weekly ISS (<13, ≥13) and baseline weight (<80, ≥80 kg) were used to generate the differences between each of the omalizumab groups and the placebo group in the least-squares means of the change from baseline in weekly ISS at week 12. Similar models were used for the other endpoints that measured change from baseline. The modified intention-to-treat (mITT) population included all randomized patients who received at least 1 dose of study drug. Efficacy analyses were conducted using data from the mITT population, except for the analysis of proportion of angioedema-free days from week 4 to week 12. For the evaluation of this endpoint, patients who withdrew before the week 4 visit or who had missing responses for more than 40% of the daily diary entries between the week 4 study visit and the week 12 study visit were not included. In analyses of endpoints evaluating change from baseline to week 12, missing data at week 12 were imputed with the baseline observation carried forward, except for DLQI, for which no imputation was performed. Safety data in the form of adverse events (AEs) reported during week 1 to week 12 of treatment were pooled from all 3 studies. Safety data from the placebo

and omalizumab 150-mg and 300-mg arms of each study were summarized descriptively. Potential anaphylactic events were identified through an automated search of the AE database using a narrow search for terms representing core anaphylactic terms and a broad search that included signs and symptoms of anaphylaxis based on the Sampson criteria.¹³ Identified events with a temporal association with omalizumab administration were sent for external adjudication (see the Online Repository available at www.jaci-inpractice.org for members of the Anaphylaxis Review Committee).

RESULTS

Efficacy

The baseline demographic and disease characteristics for the ASTERIA I and II pooled populations and the GLACIAL population were generally similar, except for previous and current therapy for CIU/CSU, which were in accordance with the eligibility criteria in the studies. The median number of previous medications for CIU/CSU was higher in patients in GLACIAL than in the ASTERIA I and II pooled population (Table I). The mean weekly ISS was significantly reduced from baseline at week 12 in the pooled ASTERIA I and II omalizumab 150- and 300-mg treatment arms and in the GLACIAL omalizumab 300-mg arm (Table II). The magnitude of the reduction in weekly ISS at week 12 was similar between the omalizumab 300-mg groups in the ASTERIA I and II pooled and GLACIAL studies

TABLE II. Mean change from baseline in endpoints at week 12

Endpoint*	ASTERIA I/II			GLACIAL ¹¹	
	Placebo (n = 159)	Omalizumab 150 mg (n = 162)	Omalizumab 300 mg (n = 160)	Placebo (n = 83)	Omalizumab 300 mg (n = 252)
Primary/key efficacy endpoint					
Change from baseline to week 12 in weekly ISS	−4.38 (5.44)	−7.40 (6.39)	−9.58 (5.83)	−4.01 (5.87)	−8.55 (6.01)
<i>P</i> vs placebo	-	<.0001	<.0001	-	<.0001
Additional endpoints					
Change from baseline to week 12 in UAS7	−9.17 (11.56)	−16.18 (13.17)	−21.24 (12.45)	−8.50 (11.71)	−19.01 (13.15)
<i>P</i> vs placebo	-	<.0001	<.0001	-	<.0001
Change from baseline to week 12 in weekly no. of hives score	−4.79 (6.57)	−8.78 (7.23)	−11.66 (7.40)	−4.49 (6.33)	−10.46 (7.74)
<i>P</i> vs placebo	-	<.0001	<.0001	-	<.0001
Median (95% CI) time to weekly ISS MID response up to week 12 (wk) [†]	4.0 (3.0, 5.0)	2.0 (NE, NE)	1.0 (1.0, 2.0)	5.0 (3.0, 7.0)	2.0 (1.0, 2.0)
HR vs placebo (95% CI)	-	1.53 (1.19, 1.96)	2.16 (1.68, 2.77)	-	1.99 (1.47, 2.68)
<i>P</i> vs placebo	-	.0009	<.0001	-	<.0001
Patients with weekly ISS MID response, n (%) [‡]	62 (42.1)	102 (63.0)	123 (76.9)	33 (39.8)	176 (69.8)
<i>P</i> vs placebo	-	.0002	<.0001	-	<.0001
Change from baseline to week 12 in weekly size of largest hive score	−3.99 (5.48)	−7.41 (6.71)	−10.38 (6.93)	−3.09 (5.46)	−8.82 (7.23)
<i>P</i> vs placebo	-	<.0001	<.0001	-	<.0001
Change from baseline to week 12 in DLQI score [‡]	−6.11 (6.89)	−8.15 (6.74)	−10.22 (7.01)	−5.11 (7.53)	−9.69 (6.85)
<i>P</i> vs placebo	-	.0109	<.0001	-	<.0001
Proportion of angioedema-free days from week 4 to week 12 [§]	88.7 (19.1)	90.6 (19.0)	95.8 (12.9)	88.1 (18.9)	91.0 (21.0)
<i>P</i> vs placebo	-	.0301	<.0001	-	.0006

CI, confidence interval; DLQI, Dermatology Quality of Life Index; HR, hazard ratio; ISS, itch severity score; MID, minimally important difference; NE, not evaluated; UAS7, urticaria activity score over 7 d.

*Mean (standard deviation) based on modified intention-to-treat population unless otherwise noted.

[†]Minimally important difference response in weekly ISS was defined as ≥ 5 -point reduction.

[‡]ASTERIA I/II pooled: placebo, n = 131, omalizumab 150 mg, n = 133, 300 mg, n = 145; GLACIAL: placebo, n = 64; omalizumab 300 mg, n = 216.

[§]ASTERIA I/II pooled: placebo, n = 136, omalizumab 150 mg, n = 144, 300 mg, n = 148; GLACIAL: placebo, n = 68; omalizumab 300 mg, n = 224.

(Table II). The results in the pooled ASTERIA I and II 150-mg group were consistent with the known dose response of omalizumab (Table II). The proportions of patients with well-controlled symptoms (UAS7 ≤ 6) and with complete symptom control (UAS7 = 0) were significantly greater than placebo in each of the omalizumab groups and were comparable in the 300-mg treatment arms of the pooled ASTERIA I and II and GLACIAL populations (Figure 2). Compared with placebo, the duration of time to MID response was significantly shorter for patients in the omalizumab groups and a higher proportion of patients in the omalizumab groups were weekly ISS MID responders (≥ 5 -point reduction) at week 12 in both the pooled ASTERIA I and II and GLACIAL populations (Table II). Significant treatment differences for omalizumab compared with placebo were observed across the other efficacy endpoints, and the magnitude of the differences was comparable in the ASTERIA I and II pooled and GLACIAL 300-mg treatment arms (Table II).

In terms of percentage change from baseline at week 12, the weekly ISS was reduced from baseline by an additional 38% and 36% over placebo in patients treated with 300-mg omalizumab in the pooled ASTERIA I and II and GLACIAL populations, respectively, and by an additional 25% over placebo in patients treated with 150-mg omalizumab in ASTERIA I and II (all $P < .0001$; Figure 3). Similar results were observed for

percentage reductions from baseline in UAS7 and weekly number of hives score at week 12 compared with placebo (Figure 3).

At week 12, the mean change in DLQI scores had improved from baseline by an additional 30% over placebo in the ASTERIA I and II populations and by an additional 50% in GLACIAL (both $P < .0001$; Figure 3). Percentage reductions in the selected endpoints were similar when ASTERIA I and II were evaluated separately (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

Safety

Omalizumab 150 mg and 300 mg were well tolerated as add-on therapy in patients with CIU/CSU who were symptomatic despite treatment with approved doses of H₁-antihistamines. Omalizumab 300 mg was also well tolerated in those who were taking standard combination therapies for CIU/CSU.

Baseline characteristics for the patient safety population were similar (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Overall, few patients discontinued treatment (4.0%) or the study (1.1%) because of an AE. The rates of treatment and study discontinuation as a result of an AE in the pooled dataset were 3.4% and 1.7% in the omalizumab 150-mg group, 3.6% and 1.2% in the 300-mg group, and 5.4% and 1.7% in the placebo group. During the treatment period from week 1 to week 12, the proportions of patients with ≥ 1 AE were

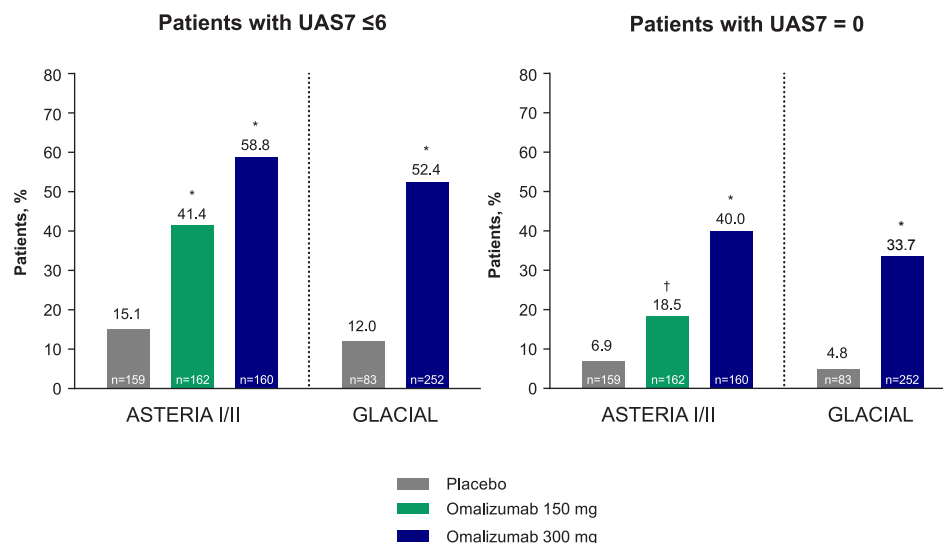


FIGURE 2. Proportion of responders by treatment group. * $P < .0001$. † $P = .002$. UAS7, urticaria activity score over 7 d. Results for the GLACIAL study from Kaplan et al.¹¹

similar in the omalizumab 150-mg and 300-mg groups, but higher than in the placebo group (Table III). During the 12-week treatment period, the rate of serious AEs (SAEs) was low; the rate of SAEs was higher in the placebo group than in either of the omalizumab treatment groups (Table III). SAEs reported in the placebo group included hemorrhoids, hypersensitivity, pneumonia, radius fracture, type 2 diabetes mellitus, hyperglycemia, cervical dysplasia, and chronic obstructive pulmonary disease. SAEs were hypertension reported in the omalizumab 150-mg group and melena, retroperitoneal infection, pelvic abscess, angioedema, and tonsillectomy in the omalizumab 300-mg group.

Most AEs were mild or moderate in severity; 6.2% of patients in the placebo group, 1.7% of patients in the omalizumab 150-mg group, and 5.3% of patients in the omalizumab 300-mg group experienced a severe AE (Table III). From week 1 to week 12 of the treatment period, sinusitis (4.9% vs 2.1%), viral upper respiratory tract infection (0.5% vs 0%), arthralgia (2.9% vs 0.4%), headache (6.1% vs 2.9%), and cough (2.2% vs 1.2%) were more common in the omalizumab 300-mg group compared with the placebo group. Nasopharyngitis (9.1% vs 7.0%), viral upper respiratory tract infection (2.3% vs 0%), arthralgia (2.9% vs 0.4%), and headache (12.0% vs 2.9%) were more common in the omalizumab 150-mg group than in the placebo group. There was no evidence of dose-related AEs.

The profile of AEs during the longer 24-week treatment period in ASTERIA I⁹ and GLACIAL¹¹ was similar to that observed for the pooled data during the 12-week treatment period, which suggested that there were no observable late-onset events or any change in the rate of AEs with increased duration of exposure. The AE profile observed in the pooled phase III studies was consistent with that known for omalizumab in patients with allergic asthma,¹⁴⁻¹⁸ with the exception of AEs specific to the respective indications (eg, urticaria, pruritus). There were no events of anaphylaxis related to omalizumab reported. In subanalyses, the AE profile was similar regardless of background therapy for CIU/CSU.

Time to loss of response

The median time to loss of response in patients who had achieved a UAS7 ≤ 6 (well controlled) at the end of the treatment period (week 12: ASTERIA I; week 24: ASTERIA I and GLACIAL) was similar in all 3 studies. Median time to loss of response for the 150-mg and 300-mg doses of omalizumab was 3 weeks and 5 weeks, respectively, in both ASTERIA I and II. In GLACIAL, the median time to a loss of response was reported at 7 weeks for omalizumab 300 mg. Placebo patients reported a median time to loss of response at 7 weeks in ASTERIA I, 6 weeks in ASTERIA II, and 4.5 weeks for placebo-treated patients; this was most likely a reflection of the waxing and waning of the disease. No rebound effect following omalizumab discontinuation was noted.

DISCUSSION

Using data from the phase III studies for CIU, we sought to compare the efficacy, safety, and time to loss of response of omalizumab in patients with different background therapy. Despite differences in background therapy between studies, including triple therapy (H₁-antihistamines, H₂-antagonists, and LTRAs), we observed similar treatment effect sizes across multiple endpoints. This suggests that background therapies in patients with refractory disease do not affect response to omalizumab (ie, patients with more intense background therapy respond at the same level as those with less intense background treatment).

At baseline, mean DLQI scores were higher (ie, worse health-related quality of life [HRQoL]) than those observed in patients with atopic dermatitis, moderate to severe psoriasis, or psoriatic arthritis,^{19,20} which indicated considerable impact of CIU/CSU symptoms on HRQoL. Consistent treatment effects for omalizumab 300 mg versus placebo were observed across multiple efficacy endpoints in patients receiving different background therapies for CIU/CSU. After 12 weeks of treatment with omalizumab 300 mg, more than half of patients had

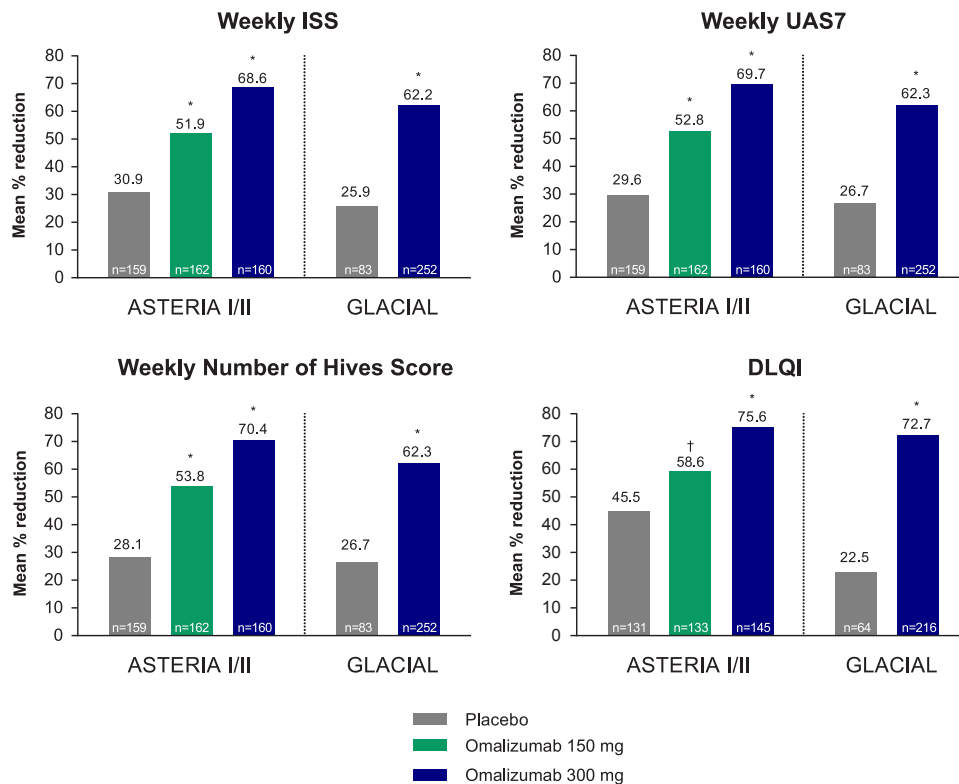


FIGURE 3. Percent reductions in key endpoints from baseline to week 12. * $P < .0001$. † $P = .034$. *DLQI*, Dermatology Life Quality Index; *ISS*, itch severity score; *UAS7*, urticaria activity score over 7 d.

well-controlled symptoms ($UAS7 \leq 6$) and more than one third were completely itch- and hive-free ($UAS7 = 0$).

The European/World Allergy Organization (EAACI/GA² LEN/EDF/WAO) published guidelines for the management of CIU/CSU suggest that omalizumab should be used as the third line of therapy (ie, on top of increased dosage up to 4-fold of modern second generation antihistamines) in the algorithm of treatment of urticaria (strong recommendation/high level evidence).¹ However, the US published guidelines for the management of CIU/CSU suggest that omalizumab should be used as the fourth step of therapy.²¹ Yet, there are limited to no robust clinical data that demonstrate incremental response rates for therapies other than omalizumab after using step 2 therapies. Whether or not omalizumab should also be considered as a third-step treatment in the United States (after up-dosing of second generation H₁-antihistamines) remains to be determined. A systematic review of omalizumab in patients with CIU determined that the 300 mg dose has the most compelling data supporting its use.⁶ The more recently published omalizumab phase III results, including this pooled analysis, will likely be of importance to include in such assessments.

There were few serious AEs and the rate of serious AEs was lower in the omalizumab 300-mg group than in the placebo group. With the exception of urticaria-specific AEs, the most common AEs were consistent with those known for omalizumab in allergic asthma with no instances of anaphylaxis. Most AEs were mild to moderate in severity. Taken together with the efficacy results, the totality of the data suggests a favorable benefit-risk profile for omalizumab in the treatment of CIU.

The loss of response after discontinuation of therapy was similar despite the length of treatment received by the patient, which suggested that disease modification does not occur at these treatment durations. Rebound did not occur following omalizumab discontinuation. The return of symptoms on a consistent basis highlights the need for more prolonged therapy and a continued unmet need in this population of patients for disease modification. Treatment with omalizumab offers a fast onset of relief from symptoms for many patients with difficult-to-manage symptoms, yet the nature of the disease requires treatments that can reduce symptomatology on a chronic basis. Although efficacy over a 6-month treatment period has been demonstrated,^{9,11} further studies that evaluate long-term treatment with omalizumab in CIU/CSU are needed to examine benefits with chronic therapy.

On a practical level, the population of patients in the GLACIAL study, in which patients were taking multiple concomitant therapies for CIU/CSU, may be more reflective of patients with H₁-antihistamine-refractory CIU/CSU encountered in clinical practice. These patients with refractory symptoms continued the background therapies once they entered the trial and demonstrated similar responses to omalizumab as patients receiving less intense background treatment (ie, approved doses of H₁-antihistamines) indicating that the response to omalizumab is not appreciably influenced by background therapies.

Because the placebo-controlled period in the ASTERIA II study was 12 weeks, the current pooled analyses were limited to evaluating changes up to week 12. However, 2 of the 3 studies, ASTERIA I⁹ and GLACIAL,¹¹ also provide safety and efficacy information for the longer treatment period of 24 weeks.

TABLE III. Patients with treatment-emergent adverse events during weeks 1 to 12 of treatment in ASTERIA I, ASTERIA II, and GLACIAL combined

Adverse event, n (%)	Placebo (n = 242)	Omalizumab 150 mg (n = 175)	Omalizumab 300 mg (n = 412)
Any AE	103 (42.6)	96 (54.9)	210 (51.0)
Serious AEs	8 (3.3)	1 (0.6)	5 (1.2)
AEs by severity			
Mild	41 (16.9)	50 (28.6)	94 (22.8)
Moderate	47 (19.4)	42 (24.0)	91 (22.1)
Severe	15 (6.2)	3 (1.7)	22 (5.3)
AEs with incidence $\geq 3\%$			
Infections and infestations	44 (18.2)	40 (22.9)	94 (22.8)
Upper respiratory tract infections	30 (12.4)	23 (13.1)	63 (15.3)
Nasopharyngitis	17 (7.0)	16 (9.1)	27 (6.6)
Sinusitis	5 (2.1)	2 (1.1)	20 (4.9)
Upper respiratory tract infection	5 (2.1)	2 (1.1)	14 (3.4)
Nervous system disorders	14 (5.8)	26 (14.9)	42 (10.2)
Headache	7 (2.9)	21 (12.0)	25 (6.1)
Respiratory, thoracic, and mediastinal disorders	11 (4.5)	9 (5.1)	29 (7.0)
Coughing and associated symptoms	3 (1.2)	2 (1.1)	12 (2.9)
Cough	3 (1.2)	2 (1.1)	9 (2.2)
Skin and subcutaneous tissue disorders	23 (9.5)	12 (6.9)	45 (10.9)
Urticarias	12 (5.0)	5 (2.9)	16 (3.9)
Idiopathic urticaria	6 (2.5)	1 (0.6)	9 (2.2)

AE, adverse event.

Additional studies in real-world populations will provide additional information on the efficacy and safety of omalizumab. One limitation of the UAS7 is that non-urticaria-related itch is captured and this may result in underestimation of the rate of complete response (ie, UAS7 = 0) to omalizumab. The analyses were based on clinical studies with strict eligibility criteria, and, thus, the results may not be generalizable to all patients encountered in clinical practice. The indirect comparisons across different studies and the *post hoc* nature of the analyses are further limitations of note.

In summary, the findings from this *post hoc* analysis indicate that omalizumab 300 mg had similar efficacy in CIU/CSU patients regardless of the background therapy for urticaria used in the trials, and the safety profile in CIU was generally similar to that in allergic asthma. There was no evidence of dose-related safety issues.

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TABLE E1. Percentage reductions from baseline in key endpoints at week 12 in ASTERIA I and ASTERIA II

Endpoint	ASTERIA I			ASTERIA II		
	Placebo (n = 80)	Omalizumab 150 mg (n = 80)	Omalizumab 300 mg (n = 81)	Placebo (n = 79)	Omalizumab 150 mg (n = 82)	Omalizumab 300 mg (n = 79)
Weekly ISS*	25.5% (38.1)	47.7% (42.5)	66.6% (36.3)	36.2% (38.9)	56.0% (43.2)	70.6% (41.3)
Difference vs placebo (95% CI)†	-	21.8% (9.7, 34.0)‡	40.5% (28.4, 52.6)‡	-	19.9% (6.6, 33.2)§	34.5% (21.1, 48.0)‡
UAS7*	25.5% (38.5)	48.8% (41.4)	67.0% (36.6)	33.7% (39.2)	56.6% (40.1)	72.6% (40.6)
Difference vs placebo (95% CI)†	-	23.2% (11.1, 35.2)§	40.8% (28.7, 52.9)‡	-	23.0% (10.4, 35.6)§	38.7% (25.9, 51.5)‡
Weekly no. of hives score*	25.0% (41.3)	50.2% (41.7)	67.0% (39.2)	31.3% (42.8)	57.3% (40.2)	73.8% (43.3)
Difference vs placebo (95% CI)†	-	24.8% (12.2, 37.4)‡	41.3% (28.7, 54.0)‡	-	26.3% (13.2, 39.4)‡	42.1% (28.8, 55.3)‡
DLQI score*,	47.2% (41.1)	50.9% (72.5)	73.6% (40.6)	44.0% (54.1)	65.5% (36.4)	77.6% (34.0)
Difference vs placebo (95% CI)†	-	2.9% (15.3, 21.1)¶	26.2% (8.6, 43.8)§	-	22.1% (6.2, 37.9)§	33.3% (17.6, 48.9)‡

CI, confidence interval; DLQI, Dermatology Life Quality Index; ISS, itch severity score; UAS7, urticaria activity score over 7 days.

*Mean (SD) percentage reduction from baseline to week 12.

†Treatment difference in least-squares means relative to placebo.

‡ $P < .0001$.

§ $P < .05$.

||Number of patients: ASTERIA I, placebo, n = 62, omalizumab 150 mg, n = 63 and 300 mg, n = 72; ASTERIA II, placebo, n = 69, omalizumab 150 mg, n = 70 and omalizumab 300 mg, n = 73.

¶Not significant.

TABLE E2. Patient characteristics at baseline (safety data)*

	ASTERIA I/II & GLACIAL	
	Placebo (n = 242)	Omalizumab 300 mg (n = 412)
Age (y)	42.6 (14.4)	42.9 (13.7)
Female sex, n (%)	162 (66.9)	309 (75.0)
Race, n (%)		
White	209 (86.4)	365 (88.6)
Weight (kg)	84.9 (23.9)	82.1 (20.9)
<80 kg, n (%)	116 (47.9)	214 (51.9)
Body mass index (kg/m ²)	29.9 (8.0)	29.3 (6.9)
Time since diagnosis of CIU/CSU (y)†	7.7 (10.5)	6.7 (8.3)
Positive CU Index test, n (%)	75 (31.0)	115 (28.1)
Number of previous CIU/CSU medications, mean (median)	5.3 (3.0)	5.3 (2.6)
Previous use of systemic steroids, n (%)	112 (46.3)	187 (45.4)
Total IgE level (IU/mL), median (range)‡	80.0 (1-1230)	79.0 (1-3050)
In-clinic UAS§	5.3 (0.7)	5.2 (0.8)
UAS7	30.8 (6.6)	30.9 (6.5)
Weekly ISS	14.1 (3.5)	14.0 (3.5)
≥13, n (%)	149 (61.6)	249 (60.4)
Weekly number of hives score	16.7 (4.4)	16.9 (4.2)
Angioedema present, n (%)	115 (47.5)	203 (49.3)

CIU/CSU, chronic idiopathic urticaria/chronic spontaneous urticaria; CU, chronic urticaria; ISS, itch severity score; UAS, urticaria activity score; UAS7, urticaria activity score over 7 d.

*Data are presented as means (standard deviation) unless otherwise stated.

†Number of patients: placebo, n = 238, omalizumab 300 mg, n = 403.

‡Placebo, n = 236; omalizumab 300 mg, n = 396.

§Defined as the largest value from the day -14 screening visit, day -7 screening visit, and day 1 visit.

||Based on data collected in a patient daily diary in the 7 d before the first treatment date.