



Angioedema in the omalizumab chronic idiopathic/spontaneous urticaria pivotal studies

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ABSTRACT

Background: Angioedema, present in some patients with chronic idiopathic/spontaneous urticaria (CIU/CSU), may have a negative effect on patient quality of life.

Objective: To describe patient-reported angioedema and its management in the pivotal omalizumab studies (ASTERIA I, ASTERIA II, GLACIAL).

Methods: Enrolled patients with CIU/CSU remained symptomatic despite treatment with histamine₁ (H₁)-antihistamines at licensed doses (ASTERIA I, ASTERIA II) or H₁-antihistamines at up to 4 times the approved dose plus H₂-antihistamines and/or a leukotriene receptor antagonist (GLACIAL). All studies administered omalizumab (75, 150, or 300 mg in ASTERIA I and ASTERIA II; 300 mg in GLACIAL) or placebo subcutaneously every 4 weeks for at least 12 weeks. Urticaria Patient Daily Diary entries were completed by patients and summarized.

Results: At baseline, angioedema prevalence was higher in GLACIAL (53.1%) than in ASTERIA I (47.5%) or ASTERIA II (40.7%). The mean proportion of angioedema-free days during weeks 4 to 12 was greater for patients treated with 300 mg of omalizumab than placebo in ASTERIA I (96.1% vs 88.2%, $P < .001$), ASTERIA II (95.5% vs 89.2%, $P < .001$), and GLACIAL (91.0% vs 88.7%, $P = .006$). Most patient-reported angioedema was managed by low-intensity interventions (doing nothing or taking medication).

Conclusion: Treatment with 300 mg of omalizumab was efficacious in reducing patient-reported angioedema. Low-intensity interventions were generally used to manage angioedema episodes.

Trial Registration: clinicaltrials.gov Identifiers: NCT01287117 (ASTERIA I), NCT01292473 (ASTERIA II), and NCT01264939 (GLACIAL).

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Introduction

Chronic idiopathic/spontaneous urticaria (CIU/CSU) is characterized by the spontaneous appearance of hives, angioedema, or

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both that recur without specific external stimuli for at least 6 weeks.^{1,2} Angioedema, which is the acute deeper swelling of the lower dermis or subcutaneous tissue, has been reported to occur in approximately 40% of patients with CIU/CSU.^{3–5} CIU/CSU, with and without angioedema, has a negative effect on health-related quality of life.⁶

Since the 1950s, antihistamines have been available to treat urticaria.² The non-sedating histamine₁ (H₁)-antihistamines were introduced decades later to address issues of sedation. For years, H₁-antihistamines were the only approved treatment for patients with CIU/CSU.² Even with H₁-antihistamine use at approved doses, many patients remain symptomatic.¹ Treatment with H₁-antihistamines at up to 4 times the approved dose has been used; however, many patients still remain symptomatic.^{1,7,8}

Omalizumab (Genentech Inc, South San Francisco, California, and Novartis Pharmaceuticals Corporation, East Hanover, New

Jersey) is a humanized anti-IgE monoclonal antibody that has been approved in Europe as add-on therapy for the treatment of CSU in adults and adolescents at least 12 years of age with inadequate response to H₁-antihistamines and in the United States for the treatment of CIU in adults and adolescents at least 12 years of age who remain symptomatic despite H₁-antihistamine treatment.^{9,10} The omalizumab phase 3 clinical trials included patients with CIU/CSU who remained symptomatic despite H₁-antihistamine treatment at licensed doses (ASTERIA I, ASTERIA II) or H₁-antihistamine treatment at up to 4 times the approved dose in combination with H₂-antihistamines and/or a leukotriene receptor antagonist (LTRA; GLACIAL).^{11–13} In these populations, treatment with omalizumab significantly improved CIU/CSU symptoms. Updated treatment guidelines and practice parameters now include a recommendation for omalizumab as add-on therapy to second-generation H₁-antihistamines for the treatment of CIU/CSU.^{2,14}

In all the omalizumab phase 3 studies in CIU/CSU, the presence of angioedema and its management were reported by patients via an electronic daily diary. This article describes patient-reported angioedema and its management from baseline to week 12 in ASTERIA I and II as well as GLACIAL. Data from ASTERIA I and GLACIAL from weeks 12 to 24 also are reported.

Methods

Omalizumab Phase 3 Studies

A summary of key pivotal study details is given in Table 1. ASTERIA I and ASTERIA II were phase 3, global, randomized, multicenter, double-blind, placebo-controlled clinical trials designed to assess the efficacy and safety of omalizumab in patients with CIU/CSU. In ASTERIA I, patients who remained symptomatic despite treatment with H₁-antihistamines at licensed doses were randomized 1:1:1:1 to receive omalizumab (75, 150, or 300 mg) or placebo subcutaneously every 4 weeks for 24 weeks (6 doses) with 16 weeks of additional observational follow-up. In ASTERIA II, patients who remained symptomatic despite treatment with H₁-antihistamines at licensed doses were randomized 1:1:1:1 to receive omalizumab (75, 150, or 300 mg) or placebo subcutaneously every 4 weeks for 12 weeks (3 doses) followed by an additional 16 weeks of observation. The primary end point in both studies was change in the weekly itch severity score from baseline to week 12. Further study details can be found elsewhere.^{12,13}

GLACIAL also was a phase 3, global, randomized, multicenter, double-blind, placebo-controlled clinical trial that assessed the safety and efficacy of omalizumab in patients with CIU/CSU. In contrast to ASTERIA I and II, patients were included in GLACIAL after combination therapy failed (H₁-antihistamines at up to 4 times the recommended dose plus H₂-antihistamines and/or LTRAs). Enrolled patients were randomized 3:1 to receive 300 mg of omalizumab or placebo subcutaneously every 4 weeks for 24 weeks (6 doses) with 16 weeks of follow-up. The primary objective of this

study was to evaluate the safety of 300 mg of omalizumab vs placebo. The key efficacy end point was change in the weekly itch severity score from baseline to week 12. Further study details can be found elsewhere.¹¹

All studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation Good Clinical Practice guidelines and all local regulatory requirements. This was a secondary analysis of clinical trials; detailed institutional review board approval and informed consent were not applicable.

Data Collection

In all 3 studies, patients were given an electronic handheld device (eDiary) at day –14 and completed the components of the Urticaria Patient Daily Diary (UPDD)^{15,16} twice per day for the study duration. The UPDD questions included itch severity, number of hives, largest hive size, sleep interference, daily activities interference, diphenhydramine (rescue medication) use, angioedema episodes and management, and health care professional contact for CIU/CSU. The clinical trials collected angioedema status 2 weeks before randomization. Baseline angioedema status was defined as reporting angioedema 7 days before the randomization date and was obtained from patient-reported data in the eDiary (yes/no, rapid swelling [angioedema] of the face, mouth, or elsewhere in the last 24 hours). If they answered this question positively, they were further questioned about what they did in response to angioedema: (1) did nothing; (2) took medication; (3) called the health care professional; (4) went to see the health care professional; or (5) went to the emergency department (ED) at the hospital. Patients were able to select all responses that applied.

Angioedema End Points

The proportion of angioedema-free days from weeks 4 to 12 of therapy was a prespecified secondary end point for all 3 studies. The proportion of angioedema-free days from weeks 4 to 12 was calculated as a ratio. The numerator comprised the number of days for which the patient indicated a no response to a UPDD angioedema question described above. The denominator comprised the total number of patient days with a nonmissing diary entry, starting at the week 4 visit date and ending the day before the week 12 visit date. 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 and 12 study visits were not included in this analysis. No imputations were performed for missing data. Exploratory analyses in these 3 phase 3 studies included the proportion of patients reporting angioedema by study week and, for those patients reporting angioedema during a particular week, the number of days that angioedema was present in that week and how the angioedema was managed. We present data obtained during the full study period: active treatment (12

Table 1
Key study design features of ASTERIA I, ASTERIA II, and GLACIAL

Feature	ASTERIA I ¹³	ASTERIA II ¹²	GLACIAL ¹¹
Background therapy	Approved doses of H ₁ -antihistamines	Approved doses of H ₁ -antihistamines	Up to 4 times the approved dose of H ₁ -antihistamines plus LTRA or H ₂ -antihistamine or all 3 in combination
Study drugs	Placebo; 75, 150, 300 mg of omalizumab	Placebo; 75, 150, 300 mg of omalizumab	Placebo; 300 mg of omalizumab
No. of doses	6	3	6
Dosing weeks	0, 4, 8, 12, 16, 20	0, 4, 8	0, 4, 8, 12, 16, 20
Efficacy end point	Week 12	Week 12	Week 12
Follow-up period, wk	16	16	16
Total study duration, wk	40	28	40

Abbreviations: H₁, histamine₁; LTRA, leukotriene receptor antagonist.

weeks, ASTERIA I; 24 weeks, ASTERIA II and GLACIAL) and the 16-week posttreatment follow-up for all 3 studies.

Statistical Analysis

The proportion of angioedema-free days from weeks 4 to 12 was evaluated using a stratified Wilcoxon rank-sum test (van Elteren test) with the presence of angioedema at baseline (yes/no) and patient weight (<80 or ≥80 kg) as stratification variables in all 3 studies. Descriptive analysis of angioedema and angioedema management by study week from baseline to week 12 was performed on the data from ASTERIA II; for ASTERIA I and GLACIAL, data from baseline to week 24 were included. Data were summarized by proportion of reports of angioedema by study week, the number of days per week patients with angioedema reported angioedema, angioedema-free days, and reports of angioedema management (all prespecified in the statistical analysis plan for each study). The number of angioedema days were analyzed using Poisson regression. All statistical analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc, Cary, North Carolina).

Results

A total of 975 patients were randomized and received at least 1 dose of study drug in the 3 phase 3 studies: ASTERIA I (75 mg of omalizumab [n = 77], 150 mg of omalizumab [n = 80], 300 mg of omalizumab [n = 81], placebo [n = 80]), ASTERIA II (75 mg of omalizumab [n = 82], 150 mg of omalizumab [n = 82], 300 mg of omalizumab [n = 79], placebo [n = 79]), and GLACIAL (300 mg of omalizumab [n = 252], placebo [n = 83]). Patients had similar baseline characteristics and were more likely to be female (72.6% [ASTERIA I], 75.8% [ASTERIA II], and 71.9% [GLACIAL]) than male; most were white (82.7% [ASTERIA I], 84.5% [ASTERIA II], 89.0% [GLACIAL]), and the mean age was 41.2 years (ASTERIA I), 42.5 years (ASTERIA II), and 43.1 years (GLACIAL) (Table 2). At baseline, disease activity, as assessed by the weekly Urticaria Activity Score during 7 days (composite of itch severity and number of hives), was high in

all 3 studies (Table 2). Angioedema prevalence rates at baseline were 40.7% (ASTERIA II), 47.5% (ASTERIA I), and 53.1% (GLACIAL). Use of previous CIU/CSU medications was higher in GLACIAL than in ASTERIA I or II (Table 2).

Angioedema-Free Days on Weeks 4 to 12 (Prespecified Secondary End Point)

A significantly greater mean proportion of angioedema-free days from weeks 4 to 12 was observed with 300 mg of omalizumab vs placebo in ASTERIA I (96.1% vs 88.2%, $P < .001$), ASTERIA II (95.5% vs 89.2%, $P < .001$), and GLACIAL (91.0% vs 88.1%, $P < .001$) (Fig 1).

Proportion of Patients Reporting Angioedema During Active Treatment and Treatment Discontinuation

In all the phase 3 studies, for all treatment arms, the proportion of patients reporting angioedema decreased from baseline to week 12 (Fig 2). The number of patients reporting angioedema was lowest for 300 mg of omalizumab, evident after the first injection, and sustained through week 12. In ASTERIA I (Fig 2A) and GLACIAL (Fig 2C), fewer omalizumab-treated patients reported angioedema than placebo-treated patients throughout the entire active treatment period (to week 24). Figure 2 suggests that patients treated with 75 and 150 mg of omalizumab in ASTERIA I experienced an increase in angioedema events a week before the next treatment administration; however, further analyses revealed no clear trend such nature in other arms in the reported studies (data not shown). After treatment discontinuation (week 12, ASTERIA II; week 24, ASTERIA I and GLACIAL), the number of patients reporting angioedema increased in all treatment groups but did not return to the rates reported at baseline (Fig 2).

Number of Days With Angioedema

In patients with angioedema, the number of patient-reported days with angioedema remained constant or numerically decreased during the initial 12-week study period; this effect was observed in all study arms but was greatest for 300 mg of omalizumab (Fig 3). In ASTERIA I and II, a significant difference ($P < .001$) for 300 mg of omalizumab vs placebo beginning in weeks 1 to 4 and sustained through active treatment (weeks 21–24, ASTERIA I; weeks 9–12, ASTERIA II) was observed. A statistically significant difference was demonstrated in GLACIAL with the exception of weeks 5 to 8 ($P = .055$). In all 3 studies, after the active treatment periods were completed, there was a general trend of an increase in days with angioedema.

Angioedema Management

Overall, when angioedema occurred, there was generally no intervention or angioedema was managed by a low-intensity intervention, such as taking medication (eg, antihistamine). Patients reported few instances of calling or visiting their health care professional. There were no reports of visits to the ED or hospital because of angioedema during the first 12-week study period in ASTERIA I (Fig 4) or II (data not shown). During the first 12 weeks of GLACIAL (Fig 5), patients reported 2 visits to the ED to manage angioedema at weeks 1 (300 mg of omalizumab) and 7 (placebo and 300 mg of omalizumab) and 1 visit to the ED to manage angioedema at week 12 (300 mg of omalizumab). In addition, patients reported hospitalization for angioedema at weeks 3 and 6 (300 mg of omalizumab).

Similar to the initial 12-week period, management of angioedema generally required no intervention or a low-intensity intervention during weeks 13 to 24 of ASTERIA I and GLACIAL. During weeks 13 to 24 of ASTERIA I, 2 patients reported ED visits for angioedema: at weeks 21 (75 mg of omalizumab) and 24 (placebo).

Table 2
Baseline demographics and clinical characteristics^a

Characteristic	ASTERIA I (n = 318)	ASTERIA II (n = 322)	GLACIAL (n = 335)
Age, mean (SD), y	41.2 (14.5)	42.5 (13.7)	43.1 (14.1)
Female, No. (%)	231 (72.6)	244 (75.8)	241 (71.9)
White, No. (%)	263 (82.7)	272 (84.5)	298 (89.0)
Weight, mean (SD), kg	82.2 (21.0)	82.4 (21.9)	83.9 (22.5)
BMI, ^b mean (SD)	29.3 (6.8)	29.8 (7.3)	29.8 (7.8)
Duration of CIU/CSU, ^c mean (SD), y	6.9 (9.1)	6.5 (8.6)	7.4 (9.5)
Duration of CIU/CSU, ^b median (range), y	3.7 (0.5–50.5)	3.3 (0.5–66.4)	3.6 (0.5–54.1)
IgE level, ^d mean (SD), IU/mL	182.8 (387.8)	168.2 (231.9)	158.5 (287.7)
IgE level, ^d median (range), IU/mL	83.0 (1–5,000)	78.0 (1–1,450)	78.0 (1–3,050)
UAS7, ^e mean (SD)	31.1 (6.6)	30.7 (6.8)	30.9 (6.6)
Angioedema present, No. (%) ^f	151 (47.5)	131 (40.7)	178 (53.1)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); CIU/CSU, chronic idiopathic/spontaneous urticaria; UAS7, Urticaria Activity Score 7 (a clinically validated composite symptom scoring system in which patients rate both wheals and pruritus during a 7-day period).

^aDose-specific demographics can be found in the primary publications: ASTERIA I,¹³ ASTERIA II,¹² GLACIAL.¹¹

^bASTERIA I (n = 316).

^cASTERIA I (n = 313), ASTERIA II (n = 314), and GLACIAL (n = 329).

^dASTERIA I (n = 306), ASTERIA II (n = 308), and GLACIAL (n = 326).

^eDefined as the largest value from the day –14 screening visit, day –7 screening visit, and the day 1 visit.

^fBased on data collected in an Urticaria Patient Daily Diary in the week before randomization.

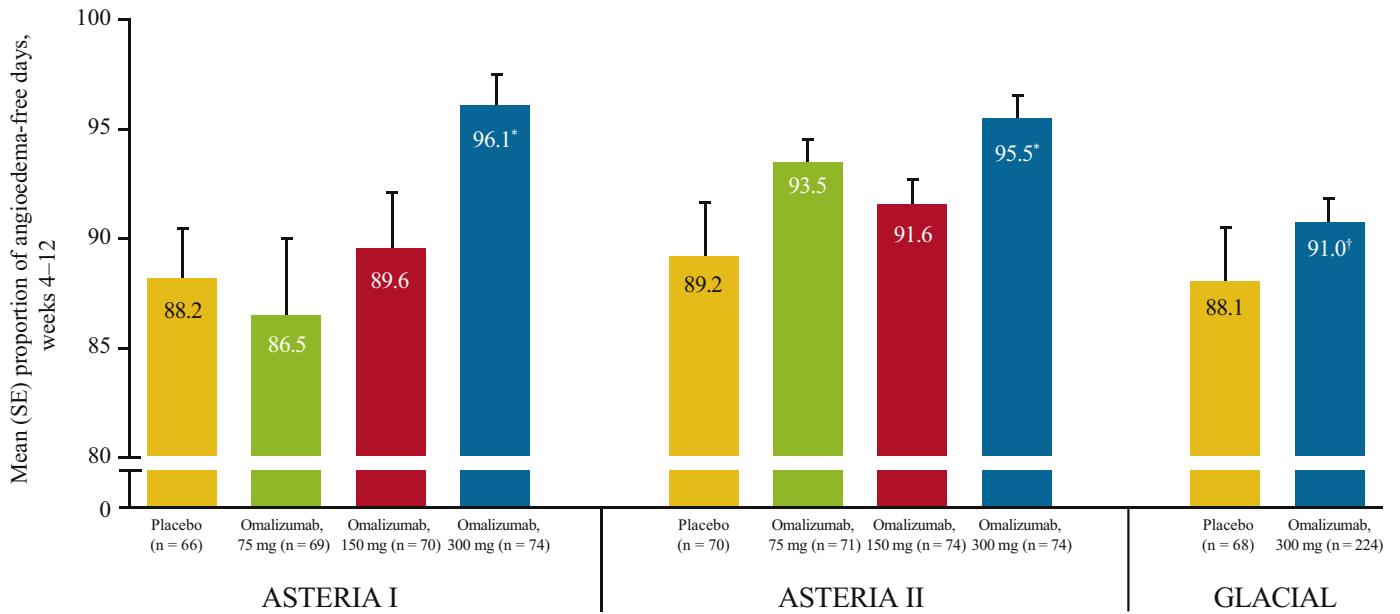


Figure 1. Mean proportion of angioedema-free days from weeks 4 to 12 in the omalizumab chronic idiopathic/spontaneous urticaria phase 3 trials. Results cannot be compared across study populations. * $P < .0001$ vs placebo. † $P = .0006$ vs placebo.

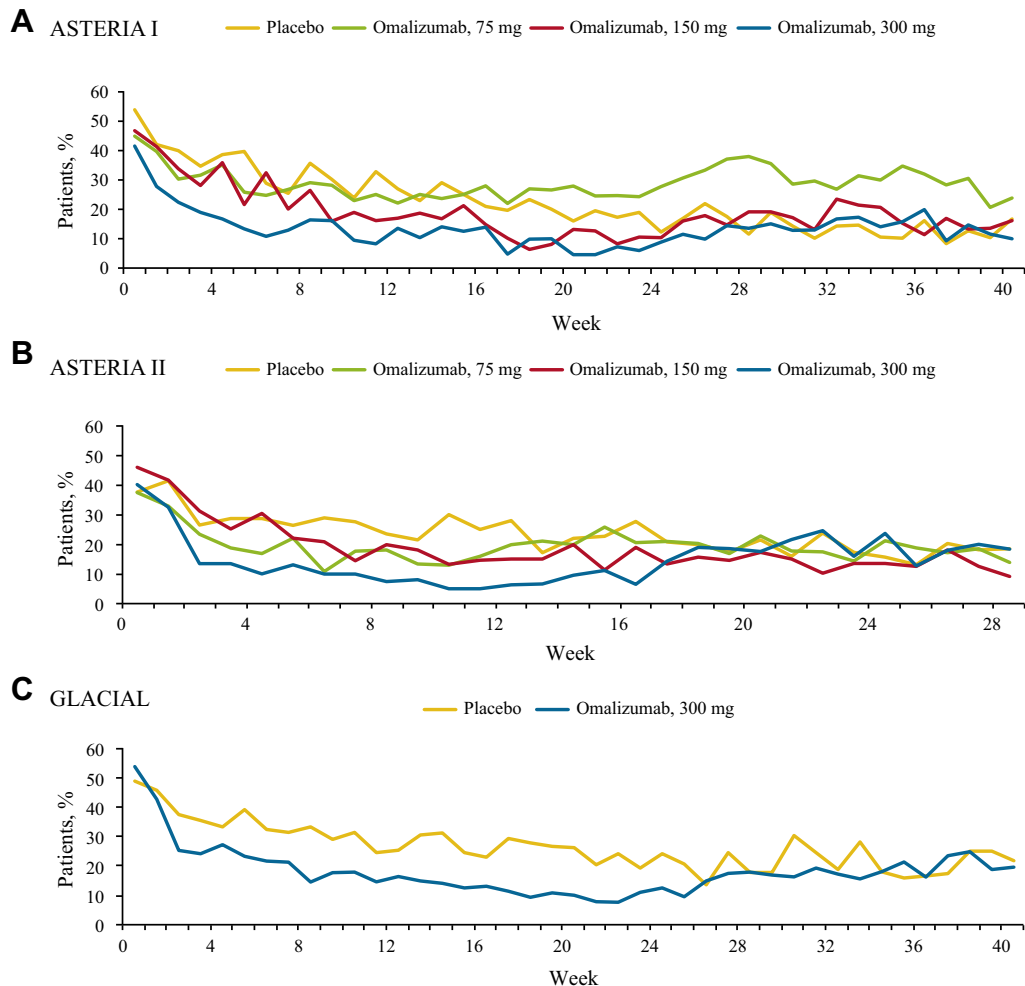
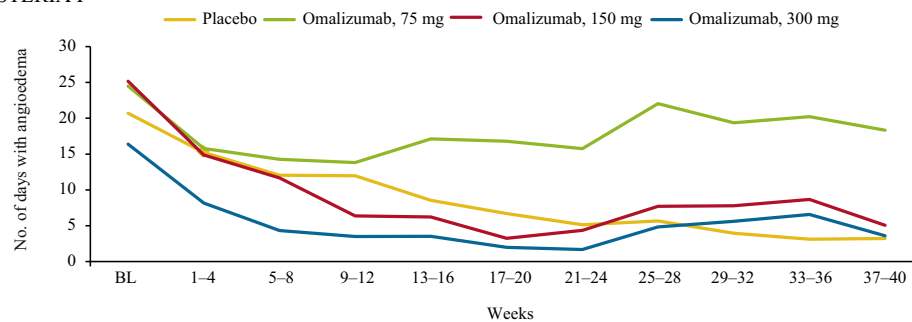
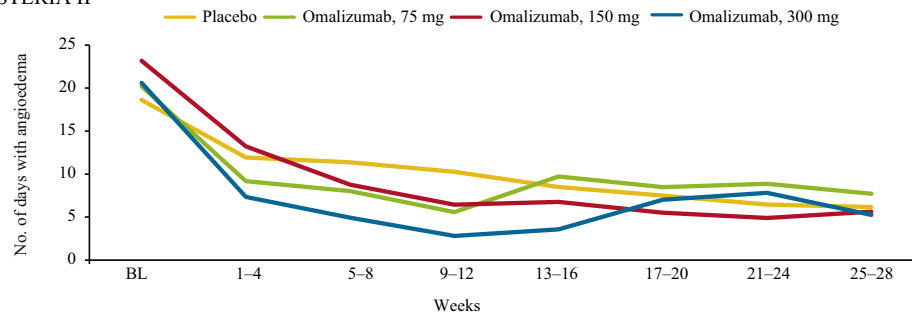


Figure 2. Percent of patients reporting angioedema per week in ASTERIA I, ASTERIA II, and GLACIAL. Study drug given at 0, 4, 8, 12, 16, and 20 weeks in ASTERIA I and GLACIAL and at 0, 4, and 8 weeks in ASTERIA II. The number of patients who completed their angioedema questionnaire at each visit for each study and each week are found in eTables 1 and 2.

A ASTERIA I

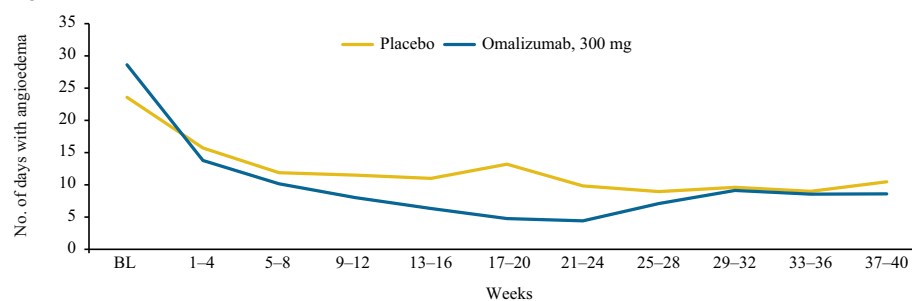
Total patient days by study week

	BL	1–4	5–8	9–12	13–16	17–20	21–24	25–28	29–32	33–36	37–40
Placebo	560	2,128	1,890	1,764	1,568	1,540	1,484	1,351	1,253	1,246	1,176
Omalizumab, 75 mg	539	2,044	1,897	1,806	1,764	1,673	1,715	1,631	1,463	1,316	1,288
Omalizumab, 150 mg	560	2,191	1,988	1,778	1,680	1,645	1,533	1,442	1,372	1,372	1,351
Omalizumab, 300 mg	567	2,177	2,051	1,981	1,925	1,883	1,883	1,883	1,680	1,505	1,365
<i>P</i> value*	.094	<.001	<.001	<.001	<.001	<.001	<.001	.23	.023	<.001	.98

B ASTERIA II

Total patient days by study week

	BL	1–4	5–8	9–12	13–16	17–20	21–24	25–28
Placebo	553	2,205	2,044	1,869	1,848	1,827	1,729	1,603
Omalizumab, 75 mg	574	2,198	1,953	1,876	1,764	1,554	1,512	1,435
Omalizumab, 150 mg	574	2,212	2,058	1,974	1,925	1,743	1,596	1,498
Omalizumab, 300 mg	553	2,191	2,128	2,030	1,960	1,813	1,596	1,393
<i>P</i> value*	.45	<.001	<.001	<.001	<.001	.96	.12	.25

C GLACIAL

Total patient days by study week

	BL	1–4	5–8	9–12	13–16	17–20	21–24	25–28	29–32	33–36	37–40
Placebo	581	2,156	1,988	1,848	1,743	1,652	1,652	1,575	1,477	1,358	1,288
Omalizumab, 300 mg	1,764	6,615	6,237	5,957	5,649	5,544	5,523	5,495	4,956	4,606	4,137
<i>P</i> value*	.044	.046	.055	<.001	<.001	<.001	<.001	.021	.27	.65	.083

Figure 3. Number of angioedema days from baseline through the end of the trial (observed data). Study drug given at 0, 4, 8, 12, 16, and 20 weeks in ASTERIA I and GLACIAL and at 0, 4, and 8 weeks in ASTERIA II. Sum of all patients in the 4-week period, including the active treatment and observation periods, is shown. Angioedema days were averaged during a week when diary days were missing, but no last observation carried forward was performed from week to week. **P* value compares 300 mg of omalizumab angioedema days with placebo angioedema days using Poisson regression. BL indicates baseline.

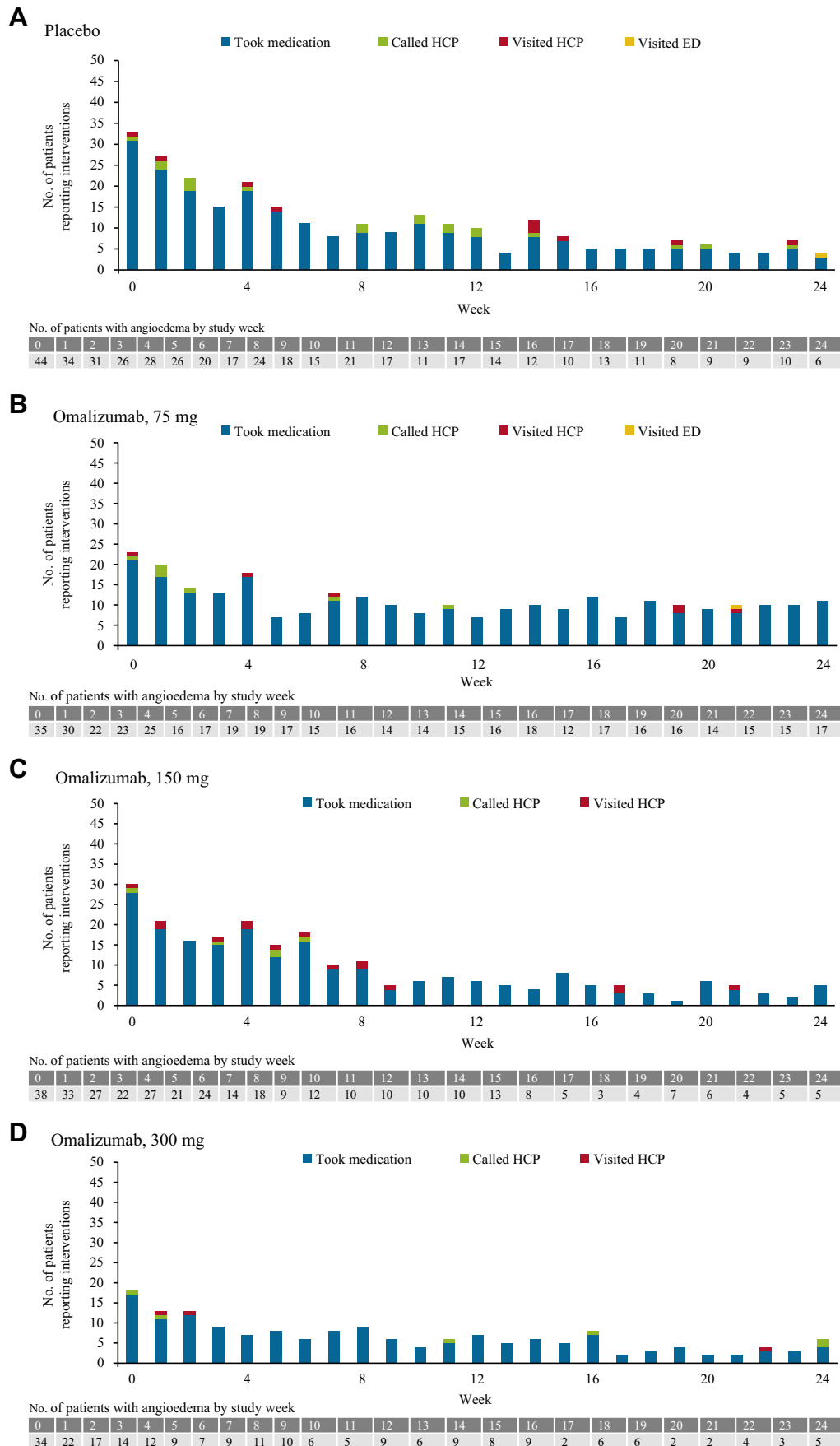


Figure 4. Number of patients reporting interventions used to manage angioedema during weeks 0 to 24 in ASTERIA I (patients could select all that applied). Study drug was given at 0, 4, 8, 12, 16, and 20 weeks in ASTERIA I. ED indicates emergency department; HCP, health care professional.

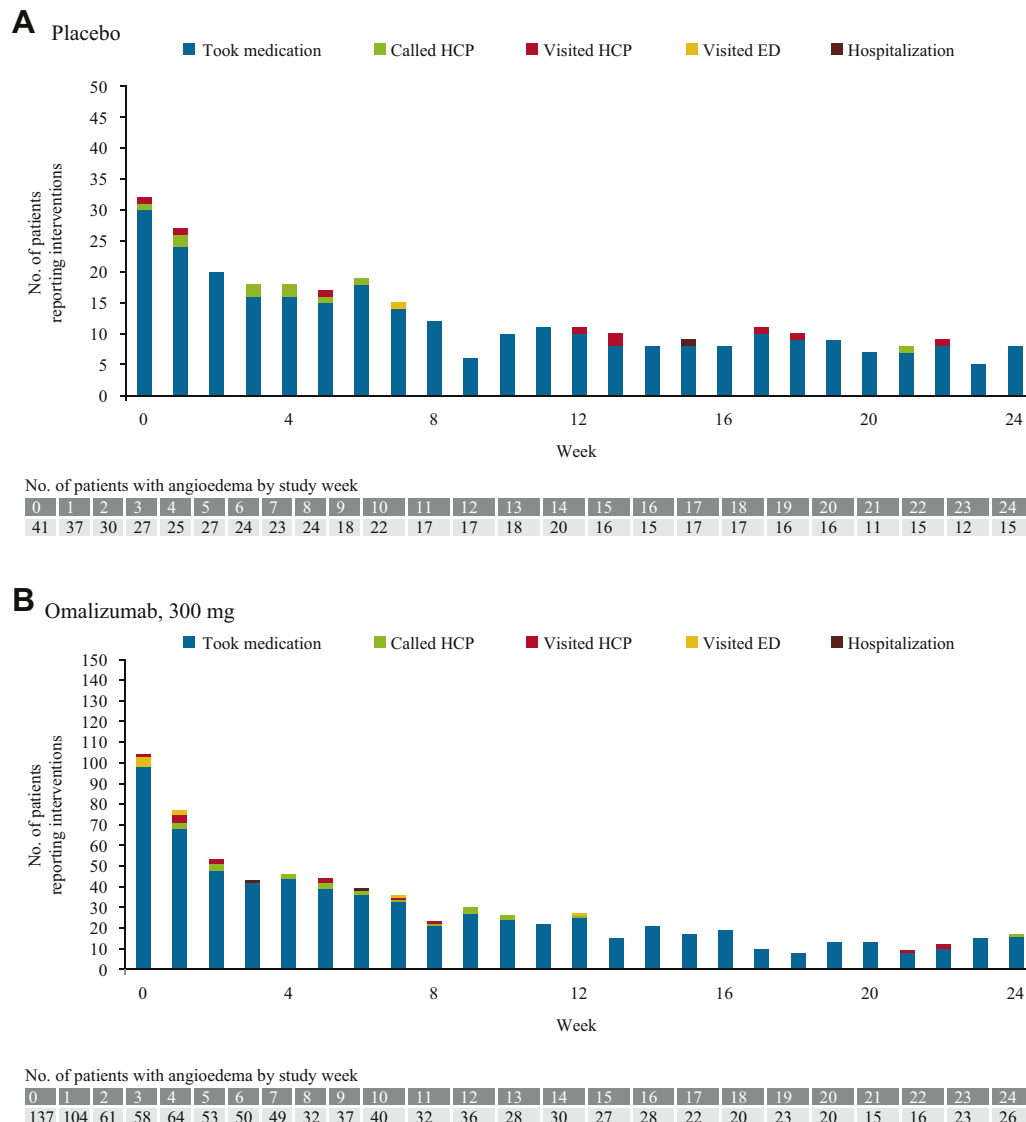


Figure 5. Number of patients reporting interventions used to manage angioedema during weeks 0 to 24 in GLACIAL. Study drug was given at 0, 4, 8, 12, 16, and 20 weeks in GLACIAL. In the GLACIAL trial, patients were randomized 3:1 to receive omalizumab or placebo. Graphs displaying angioedema management also follow the 3:1 ratio to allow for comparison of the number of interventions across treatment arms. ED indicates emergency department; HCP, health care professional.

In GLACIAL, during weeks 13 to 24, there were no visits to the ED and only 1 hospitalization (placebo).

Discussion

Angioedema was a prevalent symptom in patients with CIU/CSU in the phase 3 studies of omalizumab and occurred in 44% to 53% of patients at baseline. These rates are slightly higher than the 40% of patients with CIU/CSU who have been reported to have angioedema.³ Approximately 40% to 50% of patients reported angioedema at baseline. Disease activity at baseline was similar in all 3 studies. However, previous CIU/CSU medication use was higher in patients in GLACIAL, as expected based on the enrollment criteria, than that in ASTERIA I or II. During the active treatment period, use of 300 mg of omalizumab resulted in a reduction in the percentage of patients with angioedema and a reduction in overall angioedema days. Results from ASTERIA I and GLACIAL provide evidence that reductions in the occurrence of angioedema with 300 mg of omalizumab were sustained with continued treatment to week 24.

Although phase 3 randomized, double-blind, placebo-controlled trials remain the gold standard for establishing efficacy, the results

of this study should be interpreted in light of its limitations. Angioedema and angioedema management were patient reported rather than physician assessed, and severity was not assessed. The etiology of self-reported angioedema was not investigated, and it is possible that the angioedema was not related to CIU/CSU. However, patients with diseases who may have symptoms of urticaria or angioedema, such as urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary or acquired angioedema, lymphoma, leukemia, or generalized cancer, were excluded.^{11–13} We did not control for rescue medication use because the omalizumab and placebo arms had the same baseline and background treatment allowed. However, even with the same allowed background therapy, patients receiving placebo might have used more rescue medications than their counterparts in the active treatment arms. Had this happened, this fact would have contributed to narrowing the gap between the active treatment and placebo arms. Patients tended to choose low-intensity (ie, did nothing or took medication, such as an antihistamine) interventions to manage their angioedema. These experienced patients (median duration of CIU/CSU, 3–4 years) may have knowledge about angioedema that nonexperienced patients may not possess, and

the intensity of intervention in a nonexperienced population might differ from what was observed in these 3 trials. In addition, patients with CIU/CSU and angioedema but without hives were not included in these trials. Further evaluation of this subpopulation of patients with CIU/CSU is needed to determine whether their responses parallel what was observed in these phase 3 trials. These trials should include recently developed angioedema-specific tools for measuring disease activity and effect.^{17,18}

Treatment with 300 mg of omalizumab was efficacious in reducing patient-reported angioedema in patients with CIU/CSU who were symptomatic despite a variety of treatments. Most patients reported that they did nothing or took H₁-antihistamine medication to manage their angioedema. There were only a few reports of high-intensity interventions (ie, calling a health care professional or going to the ED or hospital) for angioedema management. In summary, treatment with 300 mg of omalizumab can help patients with CIU/CSU with angioedema in whom H₁-antihistamine treatment is failing by reducing the number of days with angioedema they experience.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2016.06.024>.

References

- [1] Maurer M, Weller K, Bindslev-Jensen C, et al. Unmet clinical needs in chronic spontaneous urticaria: a GA²LEN task force report. *Allergy*. 2011;66:317–330.
- [2] Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA²LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69:868–887.
- [3] Kaplan AP, Greaves M. Pathogenesis of chronic urticaria. *Clin Exp Allergy*. 2009;39:777–787.
- [4] Kaplan AP. Angioedema. *World Allergy Organ J*. 2008;1:103–113.
- [5] Saini SS. Chronic spontaneous urticaria: etiology and pathogenesis. *Immunol Allergy Clin North Am*. 2014;34:33–52.
- [6] Staubach P, Eckhardt-Henn A, Dechene M, et al. Quality of life in patients with chronic urticaria is differentially impaired and determined by psychiatric comorbidity. *Br J Dermatol*. 2006;154:294–298.
- [7] Asero R. Chronic unremitting urticaria: is the use of antihistamines above the licensed dose effective? A preliminary study of cetirizine at licensed and above-licensed doses. *Clin Exp Dermatol*. 2007;32:34–38.
- [8] Staevska M, Popov TA, Kralimarkova T, et al. The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. *J Allergy Clin Immunol*. 2010;125:676–682.
- [9] Xolair (omalizumab) prescribing information. http://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed February 5, 2015.
- [10] Summary of product characteristics [omalizumab (Xolair)]. <http://www.medicines.org.uk/emc/medicine/24912/SPC/Xolair+150mg+Solution+for+In+jection/#INDICATIONS>. Accessed February 5, 2015.
- [11] Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol*. 2013;132:101–109.
- [12] Maurer M, Rosén K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368:924–935.
- [13] Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H₁ antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol*. 2015;135:67–75.
- [14] Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;133:1270–1277.
- [15] Mathias SD, Dreskin SC, Kaplan A, Saini SS, Spector S, Rosén KE. Development of a daily diary for patients with chronic idiopathic urticaria. *Ann Allergy Asthma Immunol*. 2010;105:142–148.
- [16] Mathias SD, Tschosik EA, Zazzali JL. Adaptation and validation of the Urticaria Patient Daily Diary for adolescents. *Allergy Asthma Proc*. 2012;33:186–190.
- [17] Weller K, Groffik A, Magerl M, et al. Development and construct validation of the angioedema quality of life questionnaire. *Allergy*. 2012;67:1289–1298.
- [18] Weller K, Groffik A, Magerl M, et al. Development, validation, and initial results of the Angioedema Activity Score. *Allergy*. 2013;68:1185–1192.

eTable 1

Number of patients who completed their angioedema questionnaire at each visit during active treatment

Group	Week																								
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
ASTERIA I																									
Placebo	80	80	77	75	72	65	70	68	67	60	64	64	64	49	59	57	59	53	57	57	53	48	55	55	54
Omalizumab, 75 mg	77	75	73	73	71	63	70	72	66	61	67	65	65	57	65	65	65	56	64	61	58	58	62	63	62
Omalizumab, 150 mg	80	79	80	79	75	69	74	72	69	60	66	66	62	56	63	63	58	56	61	60	58	52	58	54	55
Omalizumab, 300 mg	81	80	78	77	76	73	73	76	71	66	73	72	72	66	69	70	70	63	70	69	67	66	69	67	67
ASTERIA II																									
Placebo	79	79	78	79	79	71	75	75	71	64	69	67	67	No active treatment											
Omalizumab, 75 mg	82	81	80	78	75	71	71	72	65	65	67	67	69												
Omalizumab, 150 mg	82	81	79	78	78	71	75	74	74	65	73	73	71												
Omalizumab, 300 mg	79	79	79	79	76	74	77	77	76	71	73	73	73												
GLACIAL																									
Placebo	83	80	79	75	74	68	73	72	71	61	69	68	66	58	63	64	64	57	60	59	60	53	61	61	61
Omalizumab, 300 mg	252	241	237	236	231	224	226	226	215	204	219	214	214	183	207	210	207	186	207	206	193	184	201	202	202

eTable 2

Number of patients who completed their angioedema questionnaire at each visit during follow-up

	Follow-up week															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
ASTERIA I (weeks 25–40)																
Placebo	50	47	48	48	44	45	45	45	44	43	45	46	43	43	44	38
Omalizumab, 75 mg	59	60	59	55	56	53	51	49	48	47	46	47	50	46	45	43
Omalizumab, 150 mg	53	53	51	49	49	49	50	48	48	50	49	49	50	49	48	46
Omalizumab, 300 mg	68	70	67	64	64	60	59	57	55	54	54	52	50	51	48	46
ASTERIA II (weeks 13–28)																
Placebo	68	67	65	64	66	64	67	64	61	62	62	62	59	58	59	53
Omalizumab, 75 mg	65	64	61	62	56	58	52	56	55	56	54	51	52	51	53	49
Omalizumab, 150 mg	71	69	68	67	65	62	60	62	58	56	57	57	54	54	54	52
Omalizumab, 300 mg	70	70	69	71	68	67	63	61	59	60	55	54	53	49	49	48
GLACIAL (weeks 25–40)																
Placebo	57	57	56	55	55	52	52	52	49	49	49	47	45	47	47	45
Omalizumab, 300 mg	202	196	196	191	185	180	173	170	162	168	165	163	155	150	146	140