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a randomized, placebo-controlled study**

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Efficacy and Safety of Omalizumab in Patients with Chronic Idiopathic/Spontaneous Urticaria Who Remain Symptomatic on H₁ Antihistamines: A Randomized, Placebo-Controlled Study

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ASTERIA I was a 40-week, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of subcutaneous omalizumab as add-on therapy for 24 weeks in patients with chronic idiopathic urticaria/spontaneous urticaria (CIU/CSU) who remained symptomatic despite H₁ antihistamine treatment at licensed doses. Patients aged 12–75 years with CIU/CSU who remained symptomatic despite treatment with approved doses of H₁ antihistamines were randomized (1:1:1:1) in a double-blind manner to subcutaneous omalizumab 75 mg, 150 mg, or 300 mg or placebo every 4 weeks for 24 weeks followed by 16 weeks of follow-up. The primary end point was change from baseline in weekly itch severity score (ISS) at week 12. Among randomized patients ($N=319$: placebo $n=80$, omalizumab 75 mg $n=78$, 150 mg $n=80$, 300 mg $n=81$), 262 (82.1%) completed the study. Compared with placebo ($n=80$), mean weekly ISS was reduced from baseline to week 12 by an additional 2.96 points (95% confidence interval (CI): -4.71 to -1.21 ; $P=0.0010$), 2.95 points (95% CI: -4.72 to -1.18 ; $P=0.0012$), and 5.80 points (95% CI: -7.49 to -4.10 ; $P<0.0001$) in the omalizumab 75-mg ($n=77$), 150-mg ($n=80$), and 300-mg groups ($n=81$), respectively. The omalizumab 300-mg group met all nine secondary end points, including a significant decrease in the duration of time to reach minimally important difference response (≥ 5 -point decrease) in weekly ISS ($P<0.0001$) and higher percentages of patients with well-controlled symptoms (urticaria activity score over 7 days (UAS7) ≤ 6 : 51.9% vs. 11.3%; $P<0.0001$) and complete response (UAS7=0: 35.8% vs. 8.8%; $P<0.0001$) versus placebo. During the 24-week treatment period, 2 (2.9%), 3 (3.4%), 0, and 4 (5.0%) patients in the omalizumab 75-mg, 150-mg, 300-mg, and placebo groups, respectively, experienced a serious adverse event. Omalizumab 300 mg administered subcutaneously every 4 weeks reduced weekly ISS and other symptom scores versus placebo in CIU/CSU patients who remained symptomatic despite treatment with approved doses of H₁ antihistamines.

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INTRODUCTION

Chronic idiopathic urticaria (CIU), also referred to as chronic spontaneous urticaria (CSU) (Zuberbier *et al.*, 2009a), is characterized by itchy wheals (hives), angioedema, or both that recur for >6 weeks and have no apparent external trigger. H₁ antihistamines are licensed as first-line treatment for CIU/

CSU (Zuberbier *et al.*, 2009b), although many patients continue to experience symptoms despite receiving these drugs at up to four times higher than the approved dose (Asero, 2007; Staevska *et al.*, 2010). Recommended add-on therapy for patients unresponsive to up-dosing of H₁ antihistamines includes leukotriene receptor antagonists (LTRAs) and

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Abbreviations: AE, adverse event; CIU, chronic idiopathic urticaria; CSU, chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; IgE, immunoglobulin E; ISS, itch severity score; LTRA, leukotriene receptor antagonist; MID, minimally important difference; UAS, urticaria activity score; UAS7, urticaria activity score over 7 days

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cyclosporine A (Zuberbier *et al.*, 2009b; Maurer *et al.*, 2013a). However, these agents have not received regulatory approval for this indication. Oral corticosteroids are used to treat CIU/CSU exacerbations, but they are not recommended for long-term treatment because of potential safety concerns with chronic use (Zuberbier *et al.*, 2009b).

Cutaneous mast cells, blood basophils, and immunoglobulin E (IgE) have been implicated in the pathophysiology of chronic urticaria (Vonakis and Saini, 2008). Omalizumab, a humanized IgE monoclonal antibody licensed for the treatment of moderate-to-severe (US; patients aged ≥ 12 years) and severe (Europe; patients aged ≥ 6 years) allergic asthma, recently received approval from the European Medicines Agency and the US FDA (Food and Drug Administration) for the treatment of CIU/CSU (European Medicines Agency, 2014; Genentech, Inc. and Novartis Pharmaceuticals Corporation, 2014). Omalizumab may have a beneficial role in CIU/CSU by reducing mast cell and basophil activation mediated by IgE and its high-affinity receptor (Fc ϵ RI) (Saini and MacGlashan, 2002; Beck *et al.*, 2004; Ong *et al.*, 2005). Data from proof-of-concept and phase II studies indicated that omalizumab improved symptoms and had an acceptable safety profile in patients with CIU/CSU (Gober *et al.*, 2008; Kaplan *et al.*, 2008; Maurer *et al.*, 2011; Saini *et al.*, 2011).

The phase III clinical trial program for omalizumab consisted of three randomized, double-blind, placebo-controlled studies in patients with moderate-to-severe H₁ antihistamine-refractory CIU/CSU: ASTERIA I (ClinicalTrials.gov number: NCT01287117), ASTERIA II (NCT01292473), and GLACIAL (NCT01264939). ASTERIA I and ASTERIA II evaluated the efficacy and safety of omalizumab 75 mg, 150 mg, and 300 mg versus placebo in patients with CIU/CSU who remained symptomatic despite treatment with approved doses of H₁ antihistamines. These studies were similar in design, except that the double-blind treatment period was twice as long in ASTERIA I (24 weeks) than in ASTERIA II (12 weeks; Supplementary Table S1 online). ASTERIA I was conducted to evaluate the potential effects of treatment over a longer duration, in part because the symptoms of CIU/CSU wax and wane over time. In this study, the introduction of an additional H₁ antihistamine was allowed after week 12 with the aim to reduce patient dropout over the longer treatment period. The GLACIAL study was conducted to evaluate the safety and efficacy of omalizumab 300 mg versus placebo in patients with CIU/CSU who remained symptomatic despite receiving up to four times the approved dosage of H₁ antihistamines and either an H₂ antihistamine or LTRA, or all three in combination. The primary objective of GLACIAL was to assess the safety of omalizumab in patients who were receiving different add-on therapies for CIU/CSU, although efficacy end points from ASTERIA I and II were also evaluated as secondary end points. Background CIU therapies in the GLACIAL population were reflective of the standard-of-care treatments typically used in clinical practice for patients who were refractory to approved dosages of H₁ antihistamines. Results for the GLACIAL safety study and the shorter ASTERIA II study have been reported (Kaplan *et al.*, 2013; Maurer *et al.*, 2013b).

Here, we report results from the longer ASTERIA I study that evaluated the efficacy and safety of three doses of omalizumab over a 24-week treatment period in patients with CIU/CSU who remained symptomatic despite treatment with approved dosages of H₁ antihistamines.

RESULTS

Figure 1 shows the study profile. A total of 319 patients were randomized and 318 received at least one dose of the study drug. Overall, 262 (82.1%) patients completed the 40-week study and 265 (83.1%) patients completed the 24-week treatment period (Figure 1). Baseline characteristics were generally similar across groups (Table 1). Diary compliance was high (>90%) throughout the 40-week study and was similar among groups (Supplementary Table S2 online).

At week 12, mean weekly itch severity score (ISS) decreased from baseline (primary end point) by 6.46, 6.66, and 9.40 points in the omalizumab 75-mg, 150-mg, and 300-mg groups, respectively, versus the placebo group (3.63 points; Table 2). The difference between each omalizumab group and placebo was significant in favor of omalizumab (75 mg, $P=0.0010$; 150 mg, $P=0.0012$; 300 mg, $P<0.0001$). Reductions from baseline in weekly ISS were observed as early as week 1 in all groups (placebo, 2.02 points; omalizumab 75 mg, 3.07 points; omalizumab 150 mg, 3.24 points; omalizumab 300 mg, 5.34 points; Figure 2). Median time to reach the minimally important difference (MID) in weekly ISS was 3, 2, and 1 weeks in the omalizumab 75-mg, 150-mg, and 300-mg groups, respectively, versus 4 weeks in the placebo group (Table 2). Improvements in urticaria activity score (UAS) over 7 days (UAS7; Supplementary Figure S1 online) and weekly number of hives score (Supplementary Figure S2 online) over time were similar to those observed for weekly ISS (Figure 2). Proportions of patients who achieved well-controlled disease (UAS7 ≤ 6) and those with complete response (UAS7=0) at week 12 were more than four times higher in the omalizumab 300-mg group than in the placebo group (Figure 3; both $P<0.0001$). Significant improvements compared with placebo were observed on all nine end points in the omalizumab 300-mg group, six of nine end points in the omalizumab 150-mg group, and two of nine end points in the omalizumab 75-mg group (Table 2; Supplementary Table S3 online). Sensitivity analyses of the primary end point using different methods for handling missing data confirmed those of the primary analysis (see Supplementary Material online).

Magnitudes of mean changes from baseline to week 24 for weekly ISS, UAS7, weekly number of hives score, and weekly size of largest hive score for each omalizumab group (Supplementary Table S3 online) were similar to those observed at week 12 (Table 2 and Supplementary Table S2 online). However, in the placebo group, magnitudes of mean changes in these outcomes were greater from baseline to week 24 than to week 12, resulting in generally smaller treatment effects at week 24. The omalizumab 300-mg group showed sustained improvements from baseline in symptom scores at week 24 (Supplementary Table S3 online). After week 24 (follow-up period), mean weekly ISS in the omalizumab groups increased to values similar to those in the placebo

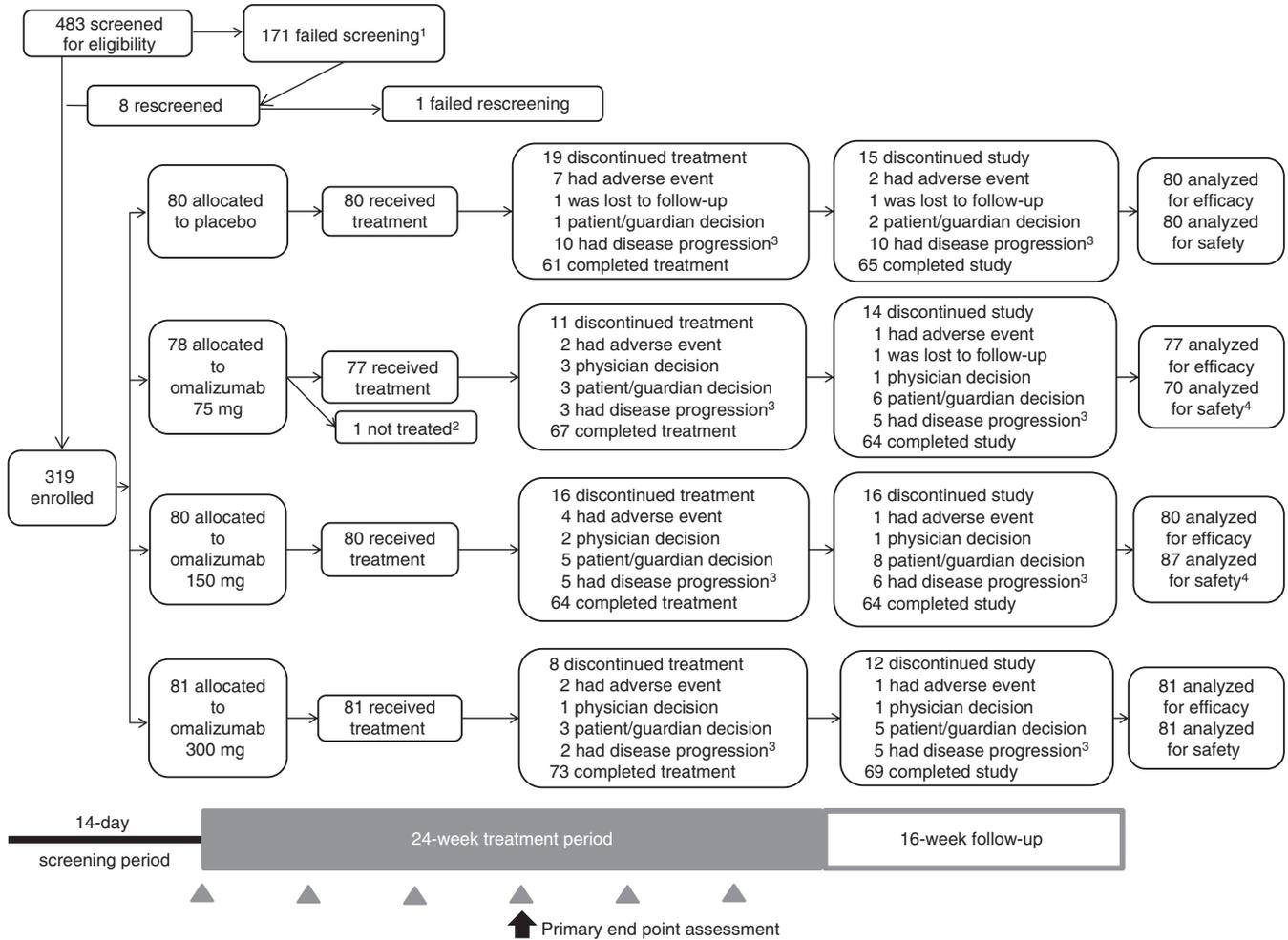


Figure 1. Patient disposition and study. Gray arrowheads denote study drug treatment on day 1 and at weeks 4, 8, 12, 16, and 20. Black arrow indicates primary end point assessment at week 12. ¹Reasons for screen failure: 14.0% of patients were unwilling to give written informed consent, adhere to the visit schedules, and meet study requirements; 10.5% of patients were not diagnosed with chronic idiopathic urticaria/spontaneous urticaria refractory to H₁ antihistamines at the time of randomization; and 27.5% of patients were categorized as “Other, not defined.” ²Patient did not receive study drug as a result of not meeting all study eligibility criteria and was therefore not included in the modified intention-to-treat population. ³Defined as either the worsening of or no improvement in symptoms. ⁴Seven patients randomized to the omalizumab 75-mg group received at least one dose of omalizumab 150 mg during the treatment period and were included in the omalizumab 150-mg group for the safety and pharmacokinetic analyses.

group, but did not return to baseline mean values for the duration of follow-up (Figure 2).

During the treatment period, the percentage of patients with a new onset of antihistamine was numerically lower in the omalizumab 300-mg group (6.2%, $n=5$) than in the placebo (13.8%, $n=11$), omalizumab 75-mg (16.9%, $n=13$), or omalizumab 150-mg (12.5%, $n=10$) groups. At week 12, a reduction in rescue medication use from baseline was observed in the omalizumab 150- and 300-mg groups versus placebo ($P<0.03$; Supplementary Table S3 online).

At baseline, mean Dermatology Life Quality Index (DLQI) scores ranged from 12.8 to 14.0 across groups (Table 1; higher score = greater impairment). At week 12, mean (standard deviation) DLQI score decreased from baseline by 10.29 (7.23) points in the omalizumab 300-mg group versus 6.13 (6.25) points in the placebo group (Supplementary Table S3

online). The difference between these groups was significant in favor of omalizumab ($P<0.0001$). Improvement in the Chronic Urticaria Quality-of-Life Questionnaire overall score at week 12 was consistent with that observed for the DLQI (Supplementary Table S3 online). Patients in the omalizumab 300-mg group experienced a greater mean proportion of angioedema-free days during weeks 4 to 12 (96.1% (95% confidence interval (CI): 93.5–98.7)) versus the placebo group (88.2% (95% CI: 83.5–93.0); $P<0.0001$; Supplementary Table S3 online). The proportion of patients with angioedema decreased in all groups over the 24-week treatment period (Supplementary Table S5 online). Overall, results of the prespecified subgroup and exploratory analyses (Supplementary Figure S3 online; Supplementary Table S4 online) were generally consistent with those of the primary analyses.

Table 1. Patient demographic and baseline characteristics at randomization¹

Characteristic	Placebo (n = 80)	Omalizumab		
		75 mg (n = 77)	150 mg (n = 80)	300 mg (n = 81)
Age (years)	40.4 (15.6)	40.7 (15.2)	41.1 (14.0)	42.4 (13.2)
Age group, n (%)				
12–17 years	4 (5.0)	5 (6.5)	7 (8.8)	2 (2.5)
18–40 years	41 (51.3)	33 (42.9)	29 (36.3)	34 (42.0)
41–64 years	30 (37.5)	35 (45.5)	41 (51.3)	42 (51.9)
≥65 years	5 (6.3)	4 (5.2)	3 (3.8)	3 (3.7)
Female, n (%)	52 (65.0)	55 (71.4)	64 (80.0)	60 (74.1)
Race, n (%)				
White	64 (80.0)	62 (80.5)	63 (78.8)	74 (91.4)
Black	10 (12.5)	9 (11.7)	9 (11.3)	5 (6.2)
Other	6 (7.5)	6 (7.8)	8 (10.0)	2 (2.5)
Weight (kg)	83.0 (20.5)	81.1 (19.2)	83.2 (24.4)	81.6 (19.7)
<80 kg, n (%)	35 (43.8)	38 (49.4)	40 (50.0)	45 (55.6)
Body mass index (kg m ⁻²)	28.7 (6.2)	29.4 (6.5)	29.8 (7.7)	29.3 (6.9)
Time since diagnosis of CIU/CSU (years) ²	7.0 (9.7)	7.0 (9.7)	7.6 (9.2)	6.2 (8.0)
CU index test, n (%) ³	25 (31.3)	18 (23.4)	16 (20.3)	21 (25.9)
No. of previous CIU/CSU medications	5.0 (2.8)	4.7 (2.8)	4.5 (3.2)	4.5 (2.3)
Median (range) total IgE level (IU ml ⁻¹) ⁴	92.0 (1–1,010)	91.0 (1–2,030)	71.0 (1–5,000)	85.5 (1–2,330)
In-clinic UAS ⁵	5.3 (0.8)	5.3 (0.8)	5.3 (0.7)	5.3 (0.8)
UAS ⁶	31.1 (6.7)	31.7 (6.7)	30.3 (7.3)	31.3 (5.8)
Weekly ISS ⁶	14.4 (3.5)	14.5 (3.6)	14.1 (3.8)	14.2 (3.3)
≥13, n (%)	54 (67.5)	49 (63.6)	54 (67.5)	53 (65.4)
Weekly number of hives score ⁶	16.7 (4.4)	17.2 (4.2)	16.2 (4.6)	17.1 (3.8)
Overall DLQI score ⁷	14.0 (6.6)	12.8 (6.1)	13.6 (7.1)	13.0 (6.7)
Angioedema present, n (%) ⁶	44 (55.0)	35 (45.5)	38 (47.5)	34 (42.0)

Abbreviations: CIU/CSU, chronic idiopathic urticaria/chronic spontaneous urticaria; CU, chronic urticaria; DLQI, Dermatology Life Quality Index; IgE, immunoglobulin E; ISS, itch severity score; UAS, urticaria activity score; UAS7, urticaria activity score over 7 days.

¹Analyses are based on the modified intention-to-treat population. Data are presented as mean (standard deviation) unless otherwise stated.

²Placebo, n = 78; omalizumab 75 mg, n = 76; omalizumab 150 mg, n = 78; omalizumab 300 mg, n value as stated.

³Determined using the CU index test (Viracor-IBT Laboratories, Lee's Summit, MO); n values reflect those for the modified intention-to-treat population except for omalizumab 150 mg, n = 79.

⁴Placebo, n = 77; omalizumab 75 mg, n = 75; omalizumab 150 mg, n = 74; omalizumab 300 mg, n = 80.

⁵Defined as the largest value from the day – 14 screening visit, day – 7 screening visit, and day 1 visit.

⁶Based on data collected in a patient daily diary in the 7 days before the first treatment date.

⁷n values reflect those for the modified intention-to-treat population except for placebo, n = 79, and omalizumab 75 mg, n = 75.

Safety

During the 24-week treatment period, the proportions of patients who experienced one or more treatment-emergent adverse events (AEs) ranged from 57 to 69% in the omalizumab groups versus 51% in the placebo group (Table 3; Supplementary Table S6 online). Headaches, arthralgia, and injection-site reactions were more common in the omalizumab groups than in the placebo group. The majority of AEs were mild or moderate in intensity (Supplementary Table S7 online).

The proportion of patients with AEs reported as suspected to be caused by study drug increased as the dose of omalizumab

increased (Table 3). The dose-dependent trend was not clustered by a specific AE type. The largest numerical differences occurred between the omalizumab 300-mg and placebo groups for headache (4 vs. 0 patients) and injection-site reactions (3 vs. 1 patient). The majority of AEs suspected to be caused by study drug were mild (34/50) or moderate in intensity (14/50); 10 of the moderate events were in the omalizumab 300-mg group. Two severe events were reported, one each in the omalizumab 150-mg and 300-mg groups. During the treatment period, 2 (2.9%), 3 (3.4%), and 0 patients in the omalizumab 75-mg, 150-mg, and 300-mg groups, respectively, experienced a serious AE compared with

Table 2. Primary and selected secondary efficacy end points¹

	Omalizumab			
	Placebo (n = 80)	75 mg (n = 77)	150 mg (n = 80)	300 mg (n = 81)
<i>Primary end point</i>				
<i>Change from baseline in ISS to week 12</i>				
Mean (SD)	-3.63 (5.22)	-6.46 (6.14)	-6.66 (6.28)	-9.40 (5.73)
Median (range)	-2.3 (-18.5 to 7.5)	-6.0 (-21.0 to 4.0)	-6.0 (-21.0 to 5.0)	-10.0 (-19.5 to 0)
LSM treatment difference versus placebo (95% CI)	-	-2.96 (-4.71 to -1.21)	-2.95 (-4.72 to -1.18)	-5.80 (-7.49 to -4.10)
P-value versus placebo ²	-	0.0010	0.0012	<0.0001
<i>Selected secondary end points</i>				
<i>Change from baseline in UAS7 to week 12</i>				
Mean (SD)	-8.01 (11.47)	-13.82 (13.26)	-14.44 (12.95)	-20.75 (12.17)
Median (range)	-4.0 (-39.0 to 14.5)	-13.0 (-42.0 to 7.0)	-14.8 (-40.0 to 4.5)	-22.0 (-40.0 to 1.0)
LSM treatment difference versus placebo (95% CI)	-	-5.75 (-9.59 to -1.92)	-6.54 (-10.33 to -2.75)	-12.80 (-16.44 to -9.16)
P-value versus placebo ²	-	0.0035	0.0008	<0.0001
<i>Time to MID in weekly ISS (weeks)</i>				
Median (95% CI)	4.0 (2.0-6.0)	3.0 (2.0-5.0)	2.0 (2.0-3.0)	1.0 (1.0-2.0)
Minimum, maximum	1.0, 12.0+	0+, 12.0+	1.0, 12.0+	0+, 12.0+
Hazard ratio versus placebo (95% CI) ³	-	1.39 (0.95-2.03)	1.49 (1.04-2.14)	2.34 (1.63-3.36)
P-value versus placebo	-	0.0879	0.0301	<0.0001
<i>Patients with MID in weekly ISS at week 12, n (%)</i>				
	29 (36.3)	43 (55.8)	45 (56.3)	61 (75.3)
P-value versus placebo	-	0.0118 ⁴	0.0226	<0.0001

Abbreviations: CI, confidence interval; ISS, itch severity score; LSM, least-squares mean; MID, minimally important difference; SD, standard deviation; UAS7, urticaria activity score over 7 days.

¹Analyses are based on the modified intention-to-treat population with missing week 12 scores imputed using the baseline weekly score.

²Derived from an analysis of covariance *t*-test.

³In this analysis, the hazard ratio represents the likelihood that a patient in a given omalizumab dose group will achieve MID response in weekly ISS relative to patients in the placebo group at any point in time up to week 12.

⁴Not evaluated for statistical significance in accordance with the type 1 error control plan.

4 (5.0%) patients in the placebo group (Table 3; Supplementary Table S8 online). None of these was assessed by the investigator to be related to the study drug. There were no deaths during the study.

There were no observations of treatment-emergent AEs considered to be malignancies in the omalizumab groups. At database lock, an event of cervical dysplasia was reported in one patient (placebo group); however, after receiving the pathology report for this patient post-database lock, it was determined that the patient experienced cervical adenocarcinoma *in situ* (see Supplementary Material online). Three patients with suspected anaphylaxis (two during omalizumab treatment and one 142 days post final dose of study drug) were referred for blinded external adjudication. The two events during omalizumab treatment were judged to be not anaphylaxis and anaphylaxis not attributed to study drug, respectively. The event 142 days post treatment was judged to be dipryone-induced anaphylaxis (see Supplementary Material online).

DISCUSSION

ASTERIA I is one of the largest clinical studies in patients with H₁ antihistamine-refractory CIU/CSU to date. Strengths of this study include its size and high rates of diary compliance; the main results were confirmed by the pre-planned sensitivity analyses. Efficacy results in ASTERIA I were consistent with those from ASTERIA II and GLACIAL (Kaplan *et al.*, 2013; Maurer *et al.*, 2013b). The baseline characteristics of patients were generally similar among the three studies except for the number of previous medications used for CIU/CSU, which was slightly higher in GLACIAL (median, 6) than in ASTERIA I and ASTERIA II (median, 4 for both). In ASTERIA II, significant improvements from baseline in weekly ISS at week 12 compared with placebo were observed in the omalizumab 150-mg and 300-mg groups, but not in the 75-mg group, which differs from the results of the current study. It is possible that this difference may have resulted from the higher placebo effect in ASTERIA II compared with ASTERIA I (placebo mean change from baseline: -5.1 and -3.6, respectively). In both

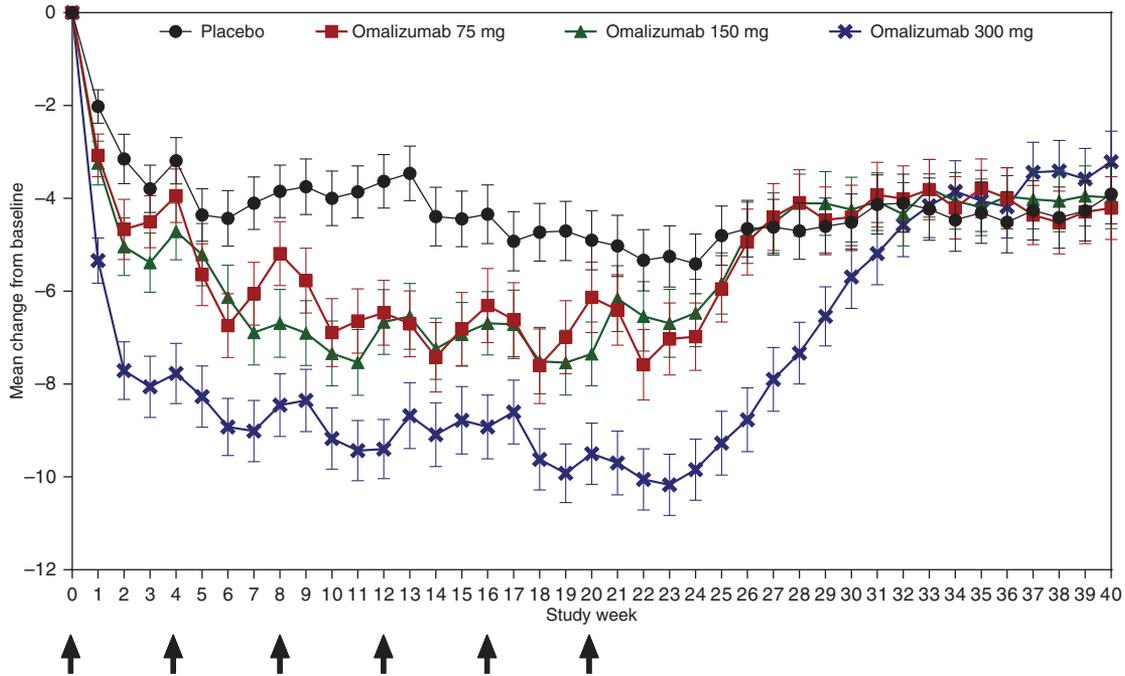


Figure 2. Mean weekly itch severity score by study week. Error bars represent standard error of the mean. Arrows indicate study drug injection day. Analyzed on the basis of the modified intention-to-treat population with missing weekly scores imputed using baseline weekly itch severity scores.

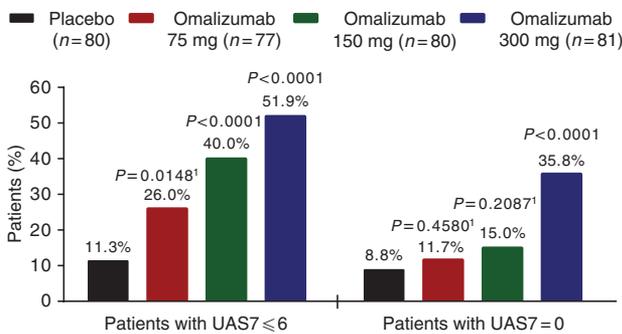


Figure 3. Responder analysis. P-value versus placebo derived from the Cochran–Mantel–Haenszel χ^2 -test stratified by baseline UAS7 (<median, \geq median) and baseline weight (<80 kg, \geq 80 kg). ¹Not evaluated for statistical significance in accordance with the type I error control plan. UAS7, urticaria activity score over 7 days.

studies, dose-dependent effects were observed for most of the prespecified secondary end points, with omalizumab 300 mg affording greatest efficacy (Maurer *et al.*, 2013b). A return of symptoms was observed in both the current study and ASTERIA II (Maurer *et al.*, 2013b) during follow-up, reaching mean values similar to those in the placebo group but not returning to baseline values. One possible explanation for this observation that occurred in all treatment groups is that some patients may have experienced spontaneous remission of their disease. The safety data in ASTERIA I confirm those observed in ASTERIA II (Maurer *et al.*, 2013b) and were consistent with the established profile of omalizumab in allergic asthma (Maurer *et al.*, 2011; Saini *et al.*, 2011; Maurer *et al.*, 2013b; European Medicines Agency, 2014; Genentech, Inc. and Novartis Pharmaceuticals Corporation, 2014).

Improvements across all end points for the omalizumab 300-mg group were maintained to week 24 in both ASTERIA I and GLACIAL, and similar safety data were observed in these studies (Kaplan *et al.*, 2013).

The results of this study may not be generalizable to all patients with CIU/CSU encountered in clinical practice or to patients with inducible urticaria. One limitation is that safety and efficacy have not been studied in patients with treatment longer than 24 weeks; however, the long-term safety profile of omalizumab has been well established in allergic asthma (Tan and Corren, 2011).

In this study, omalizumab significantly reduced symptoms after 12 weeks of treatment in patients with CIU/CSU who remained symptomatic despite treatment with approved doses of H₁ antihistamines. Median time to MID in weekly ISS was shortest in the omalizumab 300-mg group and suggests a relationship between omalizumab dose and time to onset. Our current findings not only confirm those from ASTERIA II, but also extend them beyond 12 weeks of treatment and show a sustained treatment effect of omalizumab 300 mg for up to 24 weeks on CIU/CSU symptom scores in patients with H₁ antihistamine-refractory CIU/CSU. The safety profile for omalizumab over 24 weeks of treatment in patients with CIU/CSU receiving approved doses of H₁ antihistamines was consistent with the established safety profile in allergic asthma and with previous observations in CIU/CSU.

MATERIALS AND METHODS

Study design and participants

This was a global phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to investigate the efficacy and safety of omalizumab in adult and adolescent patients with

Table 3. Summary of AEs according to study group over the 40-week study period¹

Patients, n (%)	Placebo (n=80)	Omalizumab		
		75 mg (n=70)	150 mg (n=87)	300 mg (n=81)
Any AE	53 (66.3)	55 (78.6)	72 (82.8)	57 (70.4)
Any AE during treatment period	41 (51.3)	41 (58.6)	60 (69.0)	46 (56.8)
Any AE during follow-up period	32 (40.0)	36 (51.4)	45 (51.7)	38 (46.9)
Any AE leading to discontinuation of study drug	7 (8.8)	2 (2.9)	4 (4.6)	2 (2.5)
Early discontinuation from study owing to AE	2 (2.5)	0	2 (2.3)	1 (1.2)
Any serious AE	5 (6.3)	2 (2.9)	5 (5.7)	2 (2.5)
Serious AE during treatment period	4 (5.0)	2 (2.9)	3 (3.4)	0
Serious AE during follow-up period	1 (1.3)	0	2 (2.3)	2 (2.5)
Death	0	0	0	0
Any AE suspected to be caused by study drug	4 (5.0)	6 (8.6)	9 (10.3)	14 (17.3)
Any severe AE	8 (10.0)	7 (10.0)	8 (9.2)	13 (16.0)
Severe AE during treatment period	8 (10)	5 (7.1)	5 (5.7)	3 (3.7)
Severe AE during follow-up period	1 (1.3)	3 (4.3)	4 (4.6)	10 (12.3)

Abbreviation: AE, adverse event.

¹Data are for the safety population.

CIU/CSU who remained symptomatic despite treatment with approved doses of H₁ antihistamines. It was carried out at 53 centers in Denmark, France, Germany, Italy, Poland, Spain, Turkey, and the US between February 2011 and October 2012. The study comprised a 14-day screening period, 24-week double-blind treatment period, and 16-week follow-up period during which omalizumab was not administered (Figure 1). For the first 12 weeks of the treatment period, participants were required to maintain stable doses of their prerandomization H₁ antihistamine treatment. During weeks 13 to 24 of the treatment period, patients were allowed to add one additional H₁ antihistamine. Patients were permitted to take diphenhydramine 25 mg as needed for itch relief (up to a maximum of three doses per 24 hours, or less if required by local regulations) throughout the entire study period.

Patients aged 12–75 years (18–75 years in Germany) with a diagnosis of CIU/CSU for ≥6 months who had hives and itching for ≥8 consecutive weeks at any time before enrollment despite H₁ antihistamine treatment were eligible for study inclusion. Participants were required to meet the following criteria during the screening period: the use of an approved dosage of an H₁ antihistamine for CIU/CSU for ≥3 consecutive days immediately before day –14 with documented use on the day of the initial screening visit; in-clinic physician-assessed UAS ≥4 (range 0–6; see Procedures) on one or more screening days (day –14, –7, or 1); UAS7 (range 0–42) of ≥16 and itch component of UAS7 (range 0–21) of ≥8 during the 7 days before randomization; willing and able to complete a symptom diary with an electronic hand-held device (eDiary; Urticaria Patient Daily Diary) twice daily during the study; and no missing eDiary entries during the 7 days before randomization. Exclusion criteria included the following: clearly defined underlying etiology for chronic urticaria (e.g., cold, pressure); the presence of a disease with symptoms of urticaria or angioedema, including hereditary or acquired angioedema; routine doses (daily or every other day for ≥5 consecutive days) of systemic steroids, hydroxychloroquine,

methotrexate, cyclosporine, cyclophosphamide, or intravenous immunoglobulin ≤30 days of day –14; use of H₂ antihistamines or LTRAs ≤7 days of day –14; use of H₁ antihistamines at greater than approved doses ≤3 days of day –14; history of malignancy; weight <20 kg; hypersensitivity to omalizumab; or previous treatment with omalizumab within the previous year.

The study protocol was approved by the institutional review board or ethics committee at each center. The study was conducted in accordance with US FDA regulations, the International Conference on Harmonization E6 Guideline for Good Clinical Practice, Declaration of Helsinki, and any other applicable country laws. The study is registered with ClinicalTrials.gov, NCT01287117. There was one amendment to the protocol based on feedback from the US FDA, Genentech, Inc. staff, and external advisors. The protocol was amended before the study began and registration at ClinicalTrials.gov (see Supplementary Material online). An independent data monitoring committee was established to monitor study conduct and to review blinded and unblinded safety data at 6-month intervals. A blinded external anaphylaxis review committee adjudicated suspected cases of anaphylaxis. Written informed consent was obtained from each participant or, if the participant was aged <18 years, their parent or legal guardian.

Randomization and masking

On day 1, patients were randomized in a 1:1:1:1 ratio using an interactive voice and web response system to receive subcutaneous doses of omalizumab 75 mg, 150 mg, or 300 mg or placebo at intervals of 4 weeks during the 24-week treatment period (six doses). Randomization to treatment group was stratified by baseline weekly ISS (<13, ≥13), baseline weight (<80 kg, ≥80 kg), and study site (see Supplementary Material online). All patients, evaluating physician(s), the sponsor and its agents, and study personnel were masked to treatment assignment, except for the site pharmacist(s) who prepared the study drug but who did not interact with the patients.

Procedures

Patient-reported outcomes were recorded in the Urticaria Patient Daily Diary using an electronic hand-held device. Itch severity, number of hives, and size of largest hive (all scored 0–3) were recorded every morning and evening. Sleep interference (range 0–3), activity interference (range 0–3), rescue medication use (range 0–9), angioedema (yes, no), angioedema treatment, and healthcare contacts were recorded once daily (see Supplementary Material online). Urticaria Patient Daily Diary compliance was evaluated throughout the study. The UAS is a composite eDiary-recorded score with severity intensity ratings (range: 0 = none to 3 = intense/severe) for the number of hives and intensity of itch, measured twice daily (morning and evening). The daily UAS is the average of the morning and evening scores (range 0–6 points per day), and the UAS7 is the sum of the daily UAS scores over 7 days (total score 0–42) (Mathias *et al.*, 2010). Health-related quality of life was assessed using the DLQI questionnaire (range 0–30; higher score represents greater impairment) (Finlay and Khan, 1994).

The primary end point was change from baseline in weekly ISS (i.e., sum of the daily ISS for 7 days; range 0–21) at week 12. Secondary end points, all evaluated at week 12, included changes from baseline in UAS7 and weekly number of hives score; time to MID response (≥ 5 -point decrease) in weekly ISS; the proportion of patients with UAS7 ≤ 6 ; the proportion of weekly ISS MID responders; changes from baseline in weekly size of largest hive score and overall DLQI score; the proportion of angioedema-free days during weeks 4 to 12; and the proportion of patients with complete response (UAS7 = 0). Subgroup analyses were performed based on demographic and baseline variables to evaluate the consistency of the primary efficacy results. Exploratory end points included the assessment of efficacy end points at week 24, the proportion of itch-free days and/or hive-free days at weeks 12 and 24, and change from baseline to week 12 in Chronic Urticaria Quality-of-Life Questionnaire score (see Supplementary Material online). In addition, time to relapse (loss of UAS7 ≤ 6) during the follow-up period was assessed in patients with UAS7 response ≤ 6 at week 24. The proportion of patients with UAS7 ≤ 6 at week 24 who maintained their response at week 40 also was evaluated. Safety was evaluated by recording and monitoring incidence and severity of AEs and serious AEs and changes in vital signs and clinical laboratory values. The presence of antibodies against omalizumab was evaluated from blood samples at week 40.

Statistical analysis

For the primary end point, analysis of covariance models stratified by baseline weekly ISS (< 13 , ≥ 13) and baseline weight (< 80 kg, ≥ 80 kg) were used to generate least-squares means of the differences between each of the omalizumab groups and the placebo group. Similar models were used for the secondary end points that measured change from baseline. Efficacy analyses were conducted using data from the modified intention-to-treat population (i.e., randomized patients who received one or more doses of study drug). Missing data at week 12 were imputed with the baseline observation carried forward in analyses of end points evaluating change from baseline to week 12 (except for the DLQI, for which no imputation was performed). All statistical tests were two-sided with an overall significance level of 0.05. Adjustments for multiple comparisons

were performed according to the type I error control plan (see Supplementary Material online).

The sample size for this study was based on safety and regulatory considerations. The estimation of power for efficacy assumed a mean change from baseline to week 12 in weekly ISS of 9 points in the omalizumab groups and 3.5 points in the placebo group, with a common standard deviation of 6 points and an early discontinuation rate of 15% by week 12; enrollment of 300 patients (75 in each group) would yield $\sim 98\%$ power to detect a treatment effect for the primary end point.

CONFLICT OF INTEREST

SSS has received research support from Astra-Zeneca, Genentech, Inc., the National Institutes of Health, and Novartis, and has served as a consultant to Array, Genentech, Inc., Kendle, Medimmune, Novartis, and Pharmacyclics. SSS also serves as an interest section leader for American Academy of Allergy, Asthma & Immunology, section editor for UpToDate, and section editor for the *Journal of Investigative Dermatology*. CB-J has received research funding from Genentech, Inc., Meda, MSD, Novartis, Schering-Plough, Shire, Stallergenes, and Termo Fisher and has served as a speaker for Faes Farma, MSD, and Termo Fisher. MM has received research funding from Almirall, Faes Farma, Novartis, MSD, UCB, and Uriach and has served as a speaker and/or advisor for Almirall, Genentech, Inc., Merckle Recordati, Moxie, MSD, Novartis, Sanofi-Aventis, Schering-Plough, UCB, and Uriach. J-JG has received funding and/or honoraria for advisor or speaker functions from Almirall, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, Meda, Merck, and Roche. SS has received research funding from Array, Astra-Zeneca, Forest, Genentech, Inc., GlaxoSmithKline, Johnson & Johnson, KaloBios, Merck, Mylan, Novartis, Revalesio, Rigol, Roxane, Sanofi-Aventis, Teva, and Vectura. KR is employed by Genentech, Inc. and receives stock/stock options from Roche. AR is employed by Genentech, Inc. and receives stock/stock options from Roche. MSB is employed by Genentech, Inc. and receives stock options from Roche. JC is employed by and receives stock/stock options from Novartis Pharma. PG is employed by and receives stock/stock options from Novartis Pharma AG. The remaining authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

SSS, MM, SS, CB-J, MSB, JC, and KR participated in the design of the study. SSS, CB-J, MM, J-JG, EBB, OA, and SS participated in patient accrual and data collection. All authors analyzed and interpreted the data. MSB was the study biostatistician responsible for the statistical analyses. All authors were members of the writing group and participated in the development of the report, agreed on the content, reviewed drafts, and approved the final version.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at <http://www.nature.com/jid>

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