

Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy

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Background: Patients with chronic idiopathic urticaria/ chronic spontaneous urticaria (CIU/CSU) often continue to

experience symptoms despite receiving standard-of-care therapy with H₁-antihistamines along with 1 or more add-on therapies.

Objectives: We sought to evaluate the safety and efficacy of 24 weeks of treatment with omalizumab in patients with persistent CIU/CSU despite treatment with H₁-antihistamines at up to 4 times the approved dose plus H₂-antihistamines, leukotriene receptor antagonists, or both.

Methods: In this phase III study patients were randomized to receive 6 subcutaneous injections at 4-week intervals of either 300 mg of omalizumab or placebo, followed by a 16-week observation period. The primary objective of the study was to evaluate the overall safety of omalizumab compared with placebo. Efficacy (itch severity, hive, and urticaria activity scores) was evaluated at weeks 12 and 24.

Results: The overall incidence and severity of adverse events and serious adverse events were similar between omalizumab and placebo recipients; the safety profile was consistent with omalizumab in patients with allergic asthma. At week 12, the mean change from baseline in weekly itch severity score was -8.6 (95% CI, -9.3 to -7.8) in the omalizumab group compared with -4.0 (95% CI, -5.3 to -2.7) in the placebo group ($P < .001$). Significant improvements were seen for additional efficacy end points at week 12; these benefits were sustained to week 24.

Conclusion: Omalizumab was well tolerated and reduced the signs and symptoms of CIU/CSU in patients who remained symptomatic despite the use of H₁-antihistamines (up to 4 times the approved dose) plus H₂-antihistamines, leukotriene receptor antagonists, or both. (J Allergy Clin Immunol 2013;132:101-9.)

Key words: Chronic idiopathic urticaria, chronic spontaneous urticaria, H₁-antihistamine, H₂-antihistamines, hive, itch, leukotriene receptor antagonist, omalizumab, pruritus, wheal

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Chronic idiopathic urticaria (CIU), also referred to as chronic spontaneous urticaria (CSU) in recent guidelines adopted by European and global allergy and dermatology associations, is characterized by itchy hives that occur for at least 6 weeks with or without angioedema but have no apparent trigger (eg, allergen, physical event, and drugs). The mainstay of treatment for patients with CIU/CSU is nonsedating H₁-antihistamine therapy.¹ However, in a significant proportion of patients, symptoms persist

Abbreviations used

AE:	Adverse event
CIU/CSU:	Chronic idiopathic urticaria/chronic spontaneous urticaria
CU-Q2oL:	Chronic Urticaria Quality-of-Life Questionnaire
DLQI:	Dermatology Life Quality Index
eDiary:	Electronic diary
ISS:	Itch severity score
LSM:	Least squares mean
LTRA:	Leukotriene receptor antagonist
MID:	Minimally important difference
UAS:	Urticaria activity score
UAS7:	Urticaria activity score over 7 days

despite treatment with H₁-antihistamines, even when administered at up to 4 times the approved dose.²⁻⁴ Should up dosing of H₁-antihistamines prove unsuccessful as second-line therapy, current European and global guidelines describe several alternative add-on therapies as third-line treatment options, including leukotriene receptor antagonists (LTRAs), cyclosporine, dapsone, H₂-antihistamines, omalizumab, and methotrexate.¹ Cyclosporine is effective but has the potential for severe side effects, necessitating monitoring of blood pressure and renal function. Most of the remaining alternatives are based on low-quality clinical evidence. Oral corticosteroids can be used to treat CIU/CSU exacerbations, and their use is sometimes unavoidable, but they are not recommended as a long-term treatment option given the potential for severe side effects associated with chronic use.¹

Omalizumab is a humanized anti-IgE mAb approved for the treatment of inadequately controlled moderate-to-severe (United States) or severe (Europe) allergic asthma.^{5,6} Initial studies suggested that omalizumab improved hives or wheals and pruritus in patients with CIU/CSU refractory to H₁-antihistamines.^{7,8} These findings were supported by a phase II study (MYSTIQUE), which included 90 patients with CIU/CSU,⁹ and an additional study involving a subgroup of patients with CIU/CSU (n = 49) with IgE antibodies against thyroperoxidase (X-QUISITE).¹⁰ Omalizumab demonstrated rapid and beneficial effects on the signs and symptoms of CIU/CSU in both studies.

Subsequently, a randomized, double-blind placebo-controlled trial (Q4882g; Astera-II; Clinicaltrials.gov identifier: NCT01292473) involving 323 patients was conducted as part of a series of phase III studies designed to assess the efficacy and tolerability of subcutaneous omalizumab in patients aged 12 to 75 years with CIU/CSU.¹¹ Patients with moderate-to-severe CIU/CSU who remained symptomatic despite receiving a licensed or approved dose of a second-generation H₁-antihistamine had significant improvement in their symptoms when treated with 150 or 300 mg of omalizumab over 12 weeks (dosing at 4-week intervals) compared with placebo. Efficacy was dose dependent, with the greatest effects seen with the 300-mg dose. No new safety issues or concerns were identified compared with the known safety profile of omalizumab in the allergic asthmatic patient population.

The primary objective of the current study was to assess the safety of omalizumab compared with placebo over 24 weeks when administered as an add-on therapy in patients with CIU/CSU whose signs and symptoms persisted despite treatment with H₁-antihistamines (including up to 4 times the approved dose) plus H₂-antihistamines, LTRAs, or both. The efficacy of omalizumab compared with that of placebo was also assessed.

METHODS**Study design**

This global phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study investigated the safety, tolerability, and efficacy of 300 mg of omalizumab in patients aged 12 to 75 years (18-75 years in Germany) with CIU/CSU who remained symptomatic despite treatment with H₁-antihistamines at up to 4 times the approved dose plus H₂-antihistamines, LTRAs, or both. The study involved a 2-week screening period, a 24-week treatment period, and a 16-week follow-up period (during which omalizumab was not administered). Patients from 65 centers were randomized in a 3:1 ratio to receive subcutaneous injections of either omalizumab (n = 252) or placebo (n = 84) at intervals of 4 weeks for a total of 24 weeks (6 doses). Randomization was stratified according to baseline weekly itch severity score (ISS), baseline weight, and study site (see the [Methods](#) section in this article's Online Repository at www.jacionline.org for further details on the randomization process). Throughout the treatment period, participants were required to maintain stable doses of their prerandomization combination therapy with H₁-antihistamine treatment plus H₂-antihistamines, LTRAs, or both. For the duration of the study, patients were provided with 25 mg of diphenhydramine as rescue medication for symptom relief (up to a maximum of 3 doses per 24-hour period or fewer depending on local regulations).

The study protocol was approved by the institutional review board or ethics committee at each center, and the study was 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 national laws. An independent data-monitoring committee monitored the study conduct and reviewed blinded and unblinded safety data every 6 months for the duration of the study.

Study population

Patients were eligible for inclusion if they met the following criteria: 12 to 75 years old (18-75 years old in Germany); CIU/CSU for 6 months or longer; itch and hives for more than 6 consecutive weeks before enrollment despite therapy with H₁-antihistamines plus H₂-antihistamines, LTRAs, or both; an urticaria activity score (UAS) over 7 days (UAS7) of 16 or greater (on a scale ranging from 0-42, with higher scores indicating greater activity)¹² and a weekly ISS of 8 or greater (range, 0-21) during 7 days before randomization obtained from a daily symptom electronic diary (eDiary) completed by the patient^{13,14}; an in-clinic physician-assessed UAS (range, 0-6) of 4 or greater on one of the screening visit days (days -14, -7, or 1); treatment with a regimen that included an H₁-antihistamine (up to 4 times the approved dosage) plus H₂-antihistamines, LTRAs, or both H₂-antihistamines and LTRAs for CIU/CSU for 3 or more consecutive days immediately before day -14; willingness and ability to complete a daily symptom eDiary throughout the study; and no missing eDiary entries in the 7 days before randomization.

Key exclusion criteria comprised the following: a clearly defined underlying cause for chronic urticaria (eg, physical urticaria); doses administered daily or every other day for 5 or more consecutive days of systemic or topical corticosteroids, hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, or intravenous immunoglobulin within 30 days before day -14; history of malignancy; hypersensitivity to omalizumab; treatment with omalizumab within the previous year; evidence of parasitic infection; history of anaphylactic shock; or women who are pregnant, breast-feeding, or of childbearing potential and not using acceptable contraception.

Written informed consent was obtained from each participant or the participant's parent or legal guardian (if participant was <18 years of age) before they were included in the study.

Assessments

Each patient completed the Urticaria Patient Daily Diary^{13,14} by using an eDiary for the duration of the study, recording ISSs (0, none; 1, mild; 2, moderate; and 3, severe), number of hives (0, none; 1, 1-6 hives; 2, 7-12 hives; and 3, >12 hives), and size of the largest hive (0, none; 1, <1.25 cm; 2, 1.25-2.5 cm; and 3, >2.5 cm) twice daily; sleep and daily activity interference

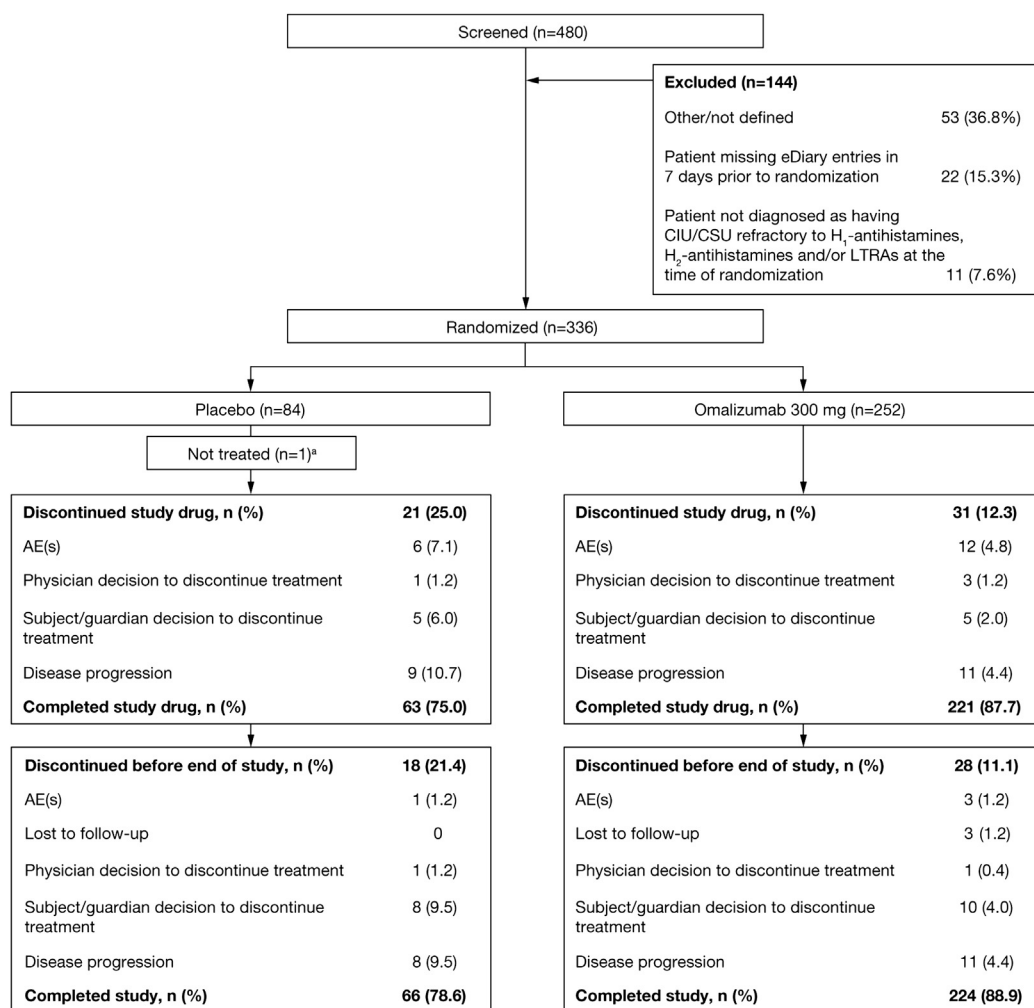


FIG 1. Patient disposition. ^aOne patient, who was randomized to the placebo group, was subsequently withdrawn before receiving the first dose of study treatment because of a clinically significant creatinine value.

(scored 0 = none to 3 = substantial), rescue medication use (number of tablets of 25 mg of diphenhydramine over 24 hours), presence of angioedema (yes or no), angioedema management, and contact with a health care provider because of CIU/CSU (see the [Methods](#) section in this article's Online Repository for further details) were assessed once daily. For weekly symptom scores (ISS, number of hives, and size of largest hive), average daily scores from the morning and evening assessments were totaled to produce a value in the range of 0 to 21. Compliance with the eDiary was assessed throughout the study.

Patients completed the Dermatology Life Quality Index (DLQI)^{15,16} and the Chronic Urticaria Quality-of-Life Questionnaire (CU-Q2oL, in regions where translations were available).¹⁷ The DLQI was completed at baseline and weeks 12 and 40; the CU-Q2oL was completed at baseline and weeks 4, 12, 24, and 40. The 10 items of the DLQI are rated to produce a total score of 0 to 30,^{15,16} with higher scores indicating a reduced quality of life, whereas the 23 items on the CU-Q2oL result in a score of 0 to 100, with higher scores indicating improved quality of life.

Study end points

The primary objective of the study was to evaluate the safety of 300 mg of omalizumab compared with placebo by assessing the following over the 24-week treatment period: the incidence and severity of adverse events (AEs) and serious AEs and changes in vital signs and clinical laboratory evaluations (see the [Methods](#) section in this article's Online Repository for the definition of

serious AEs). Anti-omalizumab antibody data were evaluated at the end of the study (week 40). Safety analyses for the 16-week follow-up period were also performed.

The key efficacy end point was the change from baseline in mean weekly ISSs at week 12. Additional efficacy end points evaluated at week 12 included the following: changes from baseline in the UAS7 (itch severity and number of hives scores averaged each day and then totaled each week were used to determine the UAS7),¹² weekly number of hives score, weekly size of largest hive score, and health-related quality of life, as measured by using the DLQI; time to achieve a minimally important difference (MID) in weekly ISS (reduction from baseline of ≥ 5 points)¹²; proportion of patients with UAS7s of 6 or less; proportion of patients with change from baseline in mean ISSs of 5 or greater (MID); proportion of angioedema-free days from weeks 4 to 12; and proportion of patients who were hive and itch free (UAS7 = 0) at week 12.

Exploratory end points evaluated at week 12 included the following: change from baseline in rescue medication use (diphenhydramine); change from baseline in health-related quality of life, as measured by using the CU-Q2oL; time to achieve an MID on the UAS7 (reduction from baseline of ≥ 11 points); daily activity and sleep interference; and 13 prespecified subgroup analyses (including sex, age, race, region, baseline weekly ISS, baseline UAS7, body weight, positive chronic urticaria index test result for anti-FcεRI autoantibody at baseline, angioedema at baseline, previous use of CIU/CSU therapies, and duration of disease). Exploratory end points were also evaluated at week 24 (see the [Methods](#) section in this article's Online Repository for details).

TABLE I. Patients' demographics and baseline characteristics (mITT)*

	Omalizumab, 300 mg (n = 252)	Placebo (n = 83)	All patients (n = 335)
Age (y)	42.7 (13.9)	44.3 (14.7)	43.1 (14.1)
Female sex, no. (%)	186 (73.8)	55 (66.3)	241 (71.9)
BMI (kg/m ²)	29.4 (7.1)	31.0 (9.6)	29.8 (7.8)
Race (white), no. (%)	223 (88.5)	75 (90.4)	298 (89.0)
Total IgE level (IU/mL)			
Mean (SD)	162.3 (306.4)	147.2 (224.4)	158.5 (287.7)
Median (range)	79.0 (1-3050)	71.0 (1-1230)	78.0 (1-3050)
Time since diagnosis of CIU/CSU (y)			
Mean (SD)	7.0 (8.8)	8.8 (11.2)	7.4 (9.5)
Median (range)	3.4 (0.5-50.3)	4.1 (0.6-54.1)	3.6 (0.5-54.1)
No. of previous CIU/CSU medications	5.9 (2.5)	6.4 (2.9)	6.0 (2.6)
CIU/CSU medication history, no. (%)			
H ₁ -antihistamines	252 (100)	83 (100)	335 (100)
H ₂ -antihistamines	221 (87.7)	76 (91.6)	297 (88.7)
LTRAs	145 (57.5)	50 (60.2)	195 (58.2)
CIU/CSU medication use on study day 1, no. (%)			
H ₁ -antihistamines + H ₂ -antihistamines	141 (56.0)	45 (54.2)	186 (55.5)
H ₁ -antihistamines + H ₂ -antihistamines + LTRAs	64 (25.4)	25 (30.1)	89 (26.6)
H ₁ -antihistamines + LTRAs	36 (14.3)	11 (13.3)	47 (14.0)
Other combinations	11 (4.4)	2 (2.4)	13 (3.9)
H ₁ -antihistamine dose on study day 1, no. (%)			
Standard† dose	98 (39.7)	25 (30.5)	123 (37.4)
Standard dose ×2	80 (32.4)	36 (43.9)	116 (35.3)
Standard dose ×3	30 (12.1)	7 (8.5)	37 (11.2)
Standard dose ×4	39 (15.8)	14 (17.1)	53 (16.1)
Previous use of systemic steroids for CIU/CSU, no. (%)	146 (57.9)	48 (57.8)	194 (57.9)
Previous use of immunosuppressant medications for CIU/CSU, no. (%)	24 (9.5)	10 (12.0)	34 (10.1)
In-clinic UAS	5.2 (0.8)	5.2 (0.8)	5.2 (0.8)
UAS7	31.2 (6.6)	30.2 (6.7)	30.9 (6.6)
Weekly ISS	14.0 (3.6)	13.8 (3.6)	14.0 (3.6)
Weekly no. of hive score	17.1 (4.2)	16.4 (4.6)	16.9 (4.3)
Presence of angioedema, no. (%)	137 (54.4)	41 (49.4)	178 (53.1)

BMI, Body mass index; mITT, modified intention-to-treat.

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

†Licensed or approved dose.

Statistical analyses

The safety analyses were conducted in all patients who were randomized and received at least 1 dose of the study treatment, with patients analyzed according to the treatment actually received (safety evaluable population). The intention-to-treat population comprised all randomized patients, regardless of whether they received the study drug. The efficacy analyses for the treatment period were conducted in all patients who were randomized and received at least 1 dose of study drug (ie, the modified intention-to-treat population), according to the treatment the patient was assigned to receive.

For the key efficacy end point, differences between the omalizumab and placebo groups were analyzed by using an analysis of covariance (ANCOVA) model stratified according to baseline weekly ISS (<13 vs ≥13) and baseline weight (<80 vs ≥80 kg). The strata were predefined based on the medians reported in a phase II clinical study.⁹ Missing data at week 12 were imputed with the baseline score (baseline observation carried forward); sensitivity analyses with 2 multiple imputation methods were also conducted. Details of the sensitivity analyses are provided in the [Methods](#) section in this article's Online Repository. Treatment differences were presented as least squares means (LSMs), along with corresponding 95% CIs and *P* values. Analysis of additional end points evaluating change from baseline was similar to that of the key efficacy end point, with treatment differences derived from ANCOVA models stratified by baseline score for the respective end point (less than the median vs median or greater) and baseline weight (<80 vs ≥80 kg). Additional details on the statistical methods and sample size calculation are provided in the [Methods](#) section in this article's Online Repository.

RESULTS

Patients

Of 480 patients screened, 336 were randomized to treatment, although 1 patient did not receive the study drug. As a result, safety and efficacy were evaluated in 335 patients (modified intention-to-treat population). In total, 290 (86.3%) completed the study ([Fig 1](#)). Mean duration of drug exposure was 22.4 weeks (SD, 4.7 weeks) in the omalizumab-treated group and 20.6 weeks (SD, 6.4 weeks) in the placebo-treated group. Patients in the omalizumab and placebo groups received a mean of 5.6 (SD, 1.2) and 5.1 (SD, 1.6) doses, respectively.

Study discontinuation (patient stopped receiving study drug before completing the protocol-defined study schedule: 11.1% vs 21.4%) and treatment discontinuation (patient stopped receiving study drug before completing the protocol-defined treatment schedule: 12.3% vs 25.0%) rates were approximately 2-fold lower in omalizumab versus placebo recipients. Over the 40-week study period, the most common reasons for study discontinuation were disease progression (4.4% vs 9.5%) and subject/legal guardian decision to discontinue treatment (4.0% vs 9.5%). The most common reasons for treatment discontinuation were disease progression (4.4% vs 10.7%) and AEs (4.8% vs 7.1%, with idiopathic urticaria being the most common).

TABLE II. AEs during the study: overall profile (safety evaluable)*

	Omalizumab, 300 mg (n = 252)	Placebo (n = 83)	All patients (n = 335)
Patients with ≥1 AE	211 (83.7)	65 (78.3)	276 (82.4)
Patients with ≥1 AE suspected to be caused by study drug	28 (11.1)	11 (13.3)	39 (11.6)
Patient withdrawals because of AEs	3 (1.2)	1 (1.2)	4 (1.2)
Patients with ≥1 serious AE	18 (7.1)	5 (6.0)	23 (6.9)

*Data are presented as numbers (percentages).

TABLE III. Treatment-emergent AEs occurring in 3% or more of patients during the treatment period (safety evaluable)

	Omalizumab, 300 mg (n = 252)	Placebo (n = 83)	All patients (n = 335)
Gastrointestinal disorders, no. (%)			
Overall	40 (15.9)	12 (14.5)	52 (15.5)
Nausea	10 (4.0)	5 (6.0)	15 (4.5)
Diarrhea	9 (3.6)	5 (6.0)	14 (4.2)
Abdominal pain	8 (3.2)	2 (2.4)	10 (3.0)
General disorders and administration-site conditions, no. (%)			
Overall	30 (11.9)	8 (9.6)	38 (11.3)
Fatigue	8 (3.2)	3 (3.6)	11 (3.3)
Infections and infestations, no. (%)			
Overall	93 (36.9)	25 (30.1)	118 (35.2)
Nasopharyngitis	22 (8.7)	7 (8.4)	29 (8.7)
Sinusitis	19 (7.5)	5 (6.0)	24 (7.2)
Upper respiratory tract infection	18 (7.1)	2 (2.4)	20 (6.0)
Injury, poisoning, and procedural complications, no. (%)			
Overall	20 (7.9)	7 (8.4)	27 (8.1)
Ligament sprain	4 (1.6)	3 (3.6)	7 (2.1)
Musculoskeletal and connective tissue disorders, no. (%)			
Overall	24 (9.5)	6 (7.2)	30 (9.0)
Back pain	2 (0.8)	3 (3.6)	5 (1.5)
Nervous system disorders, no. (%)			
Overall	39 (15.5)	10 (12.0)	49 (14.6)
Headache	22 (8.7)	3 (3.6)	25 (7.5)
Migraine	4 (1.6)	3 (3.6)	7 (2.1)
Respiratory, thoracic, and mediastinal disorders, no. (%)			
Overall	35 (13.9)	9 (10.8)	44 (13.1)
Cough	10 (4.0)	3 (3.6)	13 (3.9)
Oropharyngeal pain	6 (2.4)	3 (3.6)	9 (2.7)
Sinus congestion	3 (1.2)	4 (4.8)	7 (2.1)
Skin and subcutaneous tissue disorders, no. (%)			
Overall	42 (16.7)	12 (14.5)	54 (16.1)
Idiopathic urticaria	7 (2.8)	6 (7.2)	13 (3.9)

Baseline demographics and clinical characteristics were similar across treatment groups (Table I). For the overall population, mean age was 43.1 years (SD, 14.1 years), 71.9% were female, mean body mass index was 29.8 kg/m² (SD, 7.8 kg/m²), and mean and median IgE levels were 158.5 IU/mL (SD, 287.7 IU/mL) and 78.0 IU/mL (range, 1-3050 IU/mL), respectively. Mean time since diagnosis of CIU/CSU was 7.4 years (SD, 9.5 years), and the mean number of previous CIU/CSU medications was 6.0 (SD, 2.6). At baseline, most patients were receiving either dual therapy with H₁-antihistamines and H₂-antihistamines (55.5%) or triple therapy with H₁-antihistamines plus H₂-antihistamines plus LTRAs (26.6%); a minority of patients were receiving H₁-antihistamines plus LTRAs. H₁-antihistamines were being administered at 1 to

TABLE IV. Treatment-emergent serious AEs occurring during the treatment period (safety evaluable)

	Omalizumab, 300 mg (n = 252)	Placebo (n = 83)
Treatment period		
Total, no. (%)	7 (2.8)	3 (3.6)
Per patient	1. Cholelithiasis and viral gastroenteritis	1. Unstable angina
	2. Gastroenteritis	2. Hypersensitivity*
	3. Retroperitoneal infection	3. Hyperglycemia
	4. Pelvic abscess	
	5. Lower respiratory tract infection	
	6. Angioedema	
	7. Intermittent claudication	
Follow-up		
Total, no. (%)	11 (4.4)	2 (2.4)
Per patient	1. Angioedema and idiopathic urticaria	1. Angioedema and respiratory distress
	2. Angioedema and urticaria	2. Urticaria
	3. Angioedema	
	4. Blood glucose increase and blood pressure increase	
	5. Depression	
	6. Gastric ulcer	
	7. Gastritis erosive and intervertebral disc protrusion	
	8. Multiple drug overdose	
	9. Urinary tract infection	
	10. Urticaria	
	11. Viral infection	

Serious AEs are presented per patient (some patients reported >1 serious AE). Serious AEs were collected according to International Conference on Harmonisation guidelines.

*Allergic reaction to nonsteroidal anti-inflammatory drugs mapped to the MedDRA term "hypersensitivity."

2 times the licensed or approved dose in the majority of patients (72.6%), but 27.4% were receiving H₁-antihistamines at 3 to 4 times the standard dose.

Mean eDiary compliance rates were high (>97%, which was defined as ≥1 daily entry) during the treatment period (see Table E1 in this article's Online Repository at www.jacionline.org). The percentages of days with a diary entry were similar between the treatment groups.

Safety

During the 40-week study period (24-week treatment and 16-week follow-up period), the incidence and severity of AEs and serious AEs were similar between omalizumab and placebo recipients, with no new omalizumab safety issues identified. In omalizumab and placebo recipients the percentages of patients experiencing at least 1 AE, AEs reported as suspected to be caused by study drug, and serious AEs were 83.7% versus 78.3%, 11.1% versus 13.3%, and 7.1% versus 6.0%, respectively (Table II).

The incidence of AEs was similar for the omalizumab and placebo groups during the 24-week treatment period (65.1% vs 63.9%). Across both treatment groups, treatment-emergent AEs in the following MedDRA system organ classes occurred most frequently (≥3% in any group): infections and infestations, skin and subcutaneous disorders, and gastrointestinal disorders (Table III). Headache and upper respiratory tract infections were

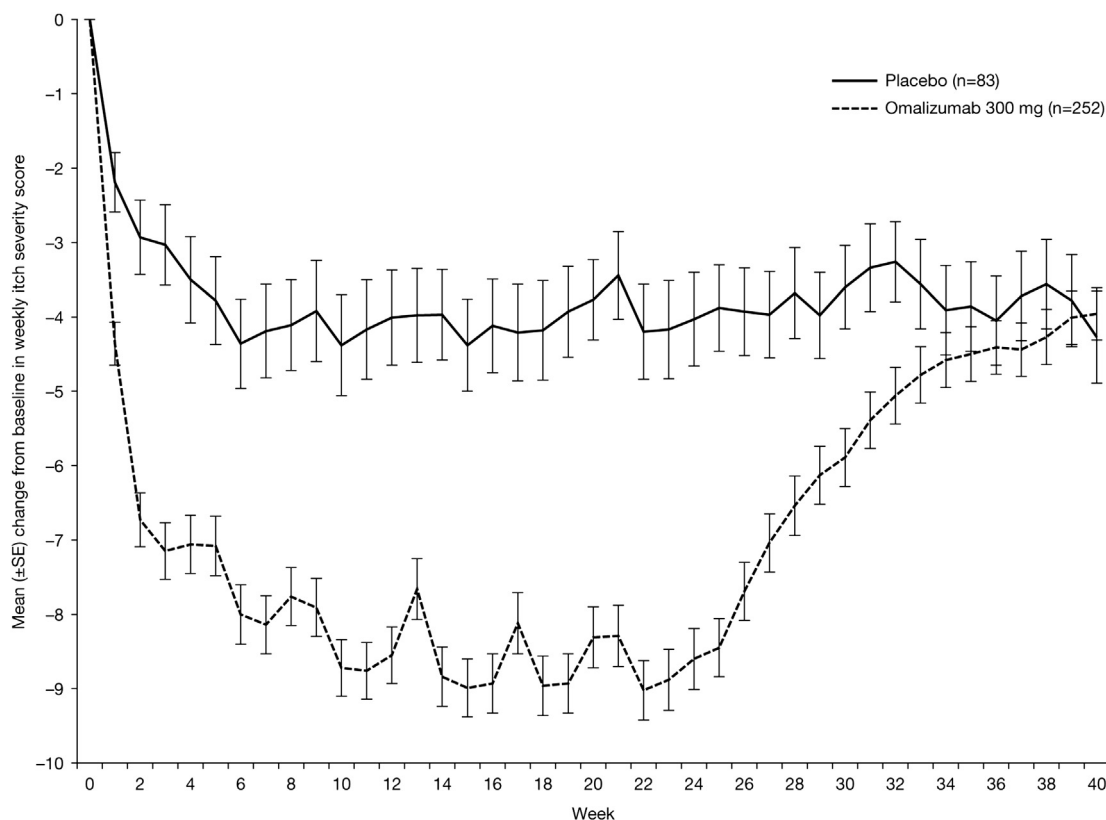


FIG 2. Mean change from baseline in weekly ISS by study week (baseline observation carried forward method, modified intention-to-treat population).

more common in the omalizumab group, whereas sinus congestion, migraine, and idiopathic urticaria were more common in the placebo group. The incidence of AEs was also similar for the omalizumab and placebo groups during the 16-week follow-up period (52.0% vs 47.0%). During the 16-week follow-up period, upper respiratory tract infections, urinary tract infections, and idiopathic urticaria were reported more frequently in the omalizumab group, whereas nasal congestion was more common with placebo.

Serious AEs were reported by 23 (6.9%) patients during the 40-week study period (18 [7.1%] patients in the omalizumab group and 5 [6.0%] patients in the placebo group). No serious AEs were suspected to be caused by the study drug. During the treatment period, serious AEs occurred in 7 (2.8%) omalizumab recipients and 3 (3.6%) placebo recipients (Table IV). During follow-up (after study drug withdrawal), treatment-emergent serious AEs occurred in 11 (4.4%) patients in the omalizumab group and 2 (2.4%) in the placebo group (Table IV).

No anaphylactic reactions, malignancies, or deaths occurred during the whole study, and there was no evidence of any clinically meaningful trends in laboratory parameters or vital signs associated with omalizumab therapy. No patients had anti-omalizumab antibodies, levels of which were measured at week 40.

Efficacy

The mean change from baseline in weekly ISS at week 12 (key efficacy end point) was significantly improved in the omalizumab group compared with that in the placebo group (-8.6 vs -4.0 , $P < .001$, Fig 2 and Table V). This significant efficacy benefit with

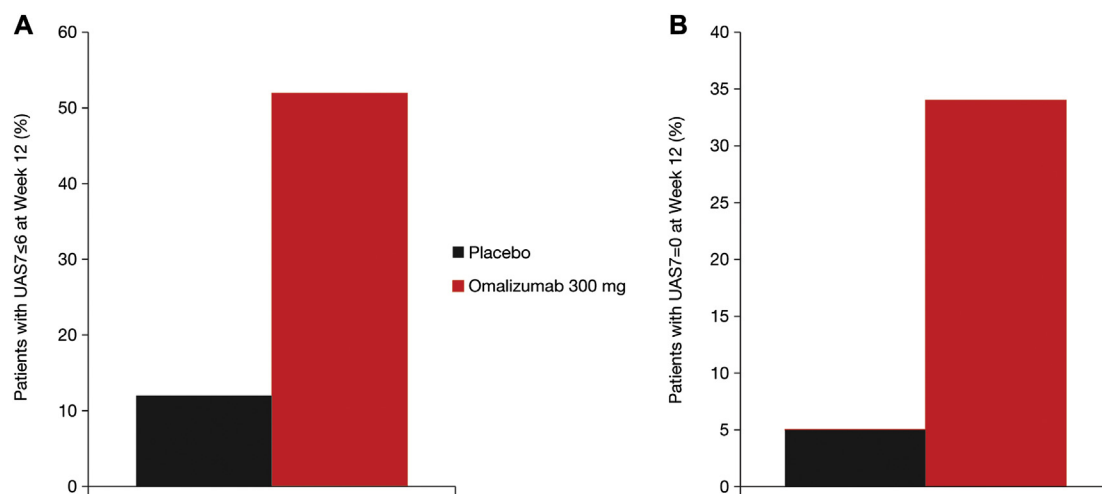
omalizumab was sustained to week 24 (-8.6 vs -4.0 ; LSM treatment difference, -4.5 [95% CI, -6.1 to -3.0]; $P < .001$). After week 24 and until week 40 (ie, during the follow-up period), the mean weekly ISS in the omalizumab group gradually increased to values similar to those in the placebo group but did not return to baseline values throughout the follow-up period; however, there were no statistical differences between the omalizumab and placebo groups at week 40. Sensitivity analyses conducted for the key efficacy end point were consistent with the primary analyses (see Table E2 in this article's Online Repository at www.jacionline.org).

Significant improvements with omalizumab versus placebo were seen for all additional efficacy end points (changes from baseline in UAS7; weekly number of hives score; weekly size of largest hive score; DLQI; time to achieve the MID response in weekly ISS; proportion of patients with a UAS7 ≤ 6 ; proportion of patients with change from baseline in mean ISS of ≥ 5 [MID]; proportion of angioedema-free days from weeks 4 to 12; and proportion of patients who were itch and hive free [UAS7 = 0]; Fig 3 and Table V and Figs E1 and E2 in this article's Online Repository at www.jacionline.org). A significantly greater number of patients in the omalizumab group were completely itch and hive free (UAS7 = 0) at week 12 compared with the placebo group (34% vs 5%, $P < .001$, Table V). Similar to the key efficacy end point, significant improvements in additional efficacy end points seen with omalizumab at week 12 were maintained at week 24; however, after discontinuation of omalizumab, improvements observed during the treatment period decreased such that values were similar to placebo values by week 40 (data not shown).

TABLE V. Summary of efficacy end points

	Omalizumab, 300 mg (n = 252)	Placebo (n = 83)	LSM treatment difference (95% CI)	P value
Key efficacy end point				
Change from baseline in weekly ISS at week 12 (BOCF method), mean (95% CI)	−8.6 (−9.3 to −7.8)	−4.0 (−5.3 to −2.7)	−4.5 (−6.0 to −3.1)	<.001
Additional efficacy end points				
Change from baseline in UAS7 at week 12 (BOCF method), mean (95% CI)	−19.0 (−20.6 to −17.4)	−8.5 (−11.1 to −5.9)	−10.0 (−13.2 to −6.9)	<.001
Change from baseline in weekly no. of hive score at week 12 (BOCF method), mean (95% CI)	−10.5 (−11.4 to −9.5)	−4.5 (−5.9 to −3.1)	−5.9 (−7.7 to −4.1)	<.001
Time to achieve MID response in weekly ISS, median (wk)	2.0	5.0	—	<.001
Patients with a UAS7 ≤6 at week 12, no. (%)	132 (52.4)	10 (12.0)	—	<.001
Patients with change from baseline in mean ISS of ≤−5 (MID), no. (%)	176 (69.8)	33 (39.8)	—	<.001
Change from baseline in overall DLQI score at week 12 (observed data), mean (95% CI)	−9.7 (−10.6 to −8.8)	−5.1 (−7.0 to −3.2)	−4.7 (−6.3 to −3.1)	<.001
Proportion of angioedema-free days from weeks 4 to 12, % (95% CI)	91.0 (88.2 to 93.8)	88.1 (83.6 to 92.7)	—	<.001
Change from baseline in weekly size of largest hive score at week 12, mean (95% CI)	−8.8 (−9.7 to −7.9)	−3.1 (−4.3 to −1.9)	−5.6 (−7.3 to −4.0)	<.001
Patients itch and hive free (UAS7 = 0) at week 12, no. (%)	85 (33.7)	4 (4.8)	—	<.001
Exploratory end points				
Change from baseline in rescue medication use at week 12, mean (95% CI)	−3.9 (−4.9 to −3.0)	−2.7 (−3.8 to −1.6)	−1.2 (−2.7 to 0.4)	.15
Change from baseline in CU-Q ₂ OL score at week 12, mean (95% CI)	−29.3 (−31.8 to −26.7)	−16.3 (−21.1 to −11.5)	−13.4 (−18.2 to −8.6)	<.001

BOCF, Baseline observation carried forward.

**FIG 3.** Responder analysis. Patients with a UAS7 of 6 or less (A) or a UAS7 of 0 (B) at week 12.

In the exploratory analyses the reduction from baseline in the mean CU-Q₂OL score was significantly greater with omalizumab versus placebo at week 12 (−29.3 vs −16.3; LSM treatment difference, −13.4 [95% CI, −18.2 to −8.6]; $P < .001$) and week 24 (−30.9 vs −16.3; LSM treatment difference, −14.6 [95% CI, −19.7 to −9.5]; $P < .001$). At week 12, mean change from baseline in rescue medication was numerically reduced with omalizumab, but the difference versus placebo did not reach statistical significance (−3.9 vs −2.7; LSM treatment difference, −1.2 [95% CI, −2.7 to 0.42]; $P = .150$).

Overall, the prespecified subgroup analyses for the key end point demonstrated that the efficacy of omalizumab was maintained across patient subgroups (see Fig E3 in this article's Online

Repository at www.jacionline.org). Of note, omalizumab was effective, irrespective of the combination of protocol-approved concomitant CIU/CSU medications. Small sample sizes precluded meaningful interpretation of the results in some subgroups (patients who were aged <18 years, were nonwhite, or received 2 or less previous CIU/CSU medications).

DISCUSSION

The safety and tolerability of omalizumab in patients with CIU/CSU has been observed in this phase III study. Patients with CIU/CSU who remained symptomatic despite treatment with H₁-antihistamines (up to 4 times approved or licensed dose) plus either

H₂-antihistamines, LTRAs, or both had 300 mg of omalizumab administered subcutaneously every 4 weeks, and the incidences of AEs and serious AEs were similar in both the omalizumab- and placebo-treated groups. No new safety issues or concerns were identified. AEs of headache and upper respiratory tract infections were reported more frequently with omalizumab than placebo; AEs of idiopathic urticaria were reported more frequently with placebo than omalizumab. Omalizumab was well tolerated. Study discontinuation and drug withdrawal were approximately 2-fold lower in the omalizumab group compared with the placebo group.

There was statistically significant efficacy with 300 mg of omalizumab. This was observed compared with placebo by the change from baseline in weekly ISS (key efficacy end point) and in all other efficacy end points at week 12, including an improvement in days free from angioedema. These significant improvements were sustained throughout the 24-week treatment period. Furthermore, omalizumab was associated with consistent improvements in the key efficacy end point across a number of prespecified subgroups, including those defined according to concomitant CIU/CSU medication use. After discontinuation of omalizumab, symptoms gradually recurred over a period of about 10 weeks to levels similar to those observed with placebo.

These results support those of another placebo-controlled phase III study, which investigated the efficacy and safety of 3 doses of omalizumab compared with placebo in patients with CIU/CSU who remained symptomatic despite the use of approved doses of H₁-antihistamines.¹¹ Patients receiving 150 or 300 mg of omalizumab administered every 4 weeks experienced significant and dose-dependent reductions in symptoms over 12 weeks compared with those receiving placebo, with gradual symptom recurrence after omalizumab discontinuation, and the incidence of AEs was similar across the treatment groups. However, it is important to note that the present study has a longer duration (24 weeks) and includes patients who remain symptomatic despite H₁-antihistamine therapy at up to 4 times the approved dose plus an H₂-antihistamine, an LTRA, or both, a combination of treatments that is frequently used in the clinical setting. It should also be noted that the efficacy of omalizumab was similar regardless of therapy at baseline.

Several studies suggest that the quality of life in patients with CIU/CSU remains measurably impaired, despite the presence of only moderate ISSs.^{18,19} Thus to achieve a meaningful treatment response from the perspective of patients, symptoms must be reduced to a minimum or be absent entirely. In fact, current treatment guidelines explicitly state that "the goal of treatment is to achieve the absence of and complete protection from symptoms."²⁰ Symptoms discussed in treatment guidelines include not only itch severity but also the presence of hives, angioedema, or both. In that regard treatment response as measured based on the UAS7, which includes numbers of hives in addition to itch severity, might be a particularly relevant efficacy end point. To assess completeness of response, 2 responder definitions (UAS7 ≤ 6 and UAS7 = 0) were included as efficacy end points in this study. A UAS7 of 6 or less reflects minimal symptoms and might be useful in identifying those patients with a good clinical response. A UAS7 of 0 reflects complete resolution of symptoms, which represents the most desirable outcome. This study shows that approximately half of the patients who received add-on omalizumab achieved UAS7s of 6 or less, and one third were completely itch and hive free (UAS7 = 0). A limitation of the UAS7 is that non-urticaria-related itch might be recorded, and as such, a greater number of

patients might have achieved a complete reduction of symptoms while receiving omalizumab.

Apart from reducing free IgE levels, the additional mechanisms by which omalizumab works in patients with CIU/CSU remains unclear. Reports describe patients with CIU/CSU as having abnormal basophil function, including decreased responsiveness to stimuli acting through the IgE receptor (50% of patients), blood basopenia, and recruitment of basophils into skin lesions.²¹ With successful therapy, blood basopenia and FcεRI function began to return to normal levels.²¹ In previous studies the binding of circulating IgE by omalizumab reduces free IgE levels within hours after administration and downregulates FcεRI on blood basophils within 2 weeks; in nasal mast cells reduction in FcεRI expression and degranulation typically occurs after 8 weeks,²²⁻²⁴ whereas a study of human cutaneous mast cells indicates a downregulatory effect in 3 to 4 weeks.²⁵ However, in individual patients the time course of symptom control does not necessarily follow these parameters. Although this study was not designed to further elucidate the mechanism of action of omalizumab on basophils or cutaneous mast cells, ongoing research aims to provide a better understanding of how omalizumab treatment alleviates the symptoms of CIU/CSU.

In conclusion, the results support omalizumab as a well-tolerated and effective treatment option for patients with CIU/CSU who remain symptomatic despite treatment with multiple background therapies of H₁-antihistamines and H₂-antihistamines, LTRAs, or both.

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Clinical implications: Omalizumab is well tolerated and efficacious in the treatment of patients with CIU/CSU who remain symptomatic despite receiving H₁-antihistamines at up to 4 times the approved dose plus H₂-antagonists, LTRAs, or both.

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