Supplementary Material

MATERIALS AND METHODS

Randomization and allocation to treatment groups

Eligible patients were randomly assigned using a 1:1:1:1 ratio using an interactive voice and web response system to receive omalizumab 75 mg, 150 mg, or 300 mg or placebo by subcutaneous injection every 4 weeks during the 24-week double-blind treatment period. A hierarchical dynamic randomization scheme was used to achieve overall balance between the treatment groups and within strata. The hierarchy levels were overall study treatment balance, treatment balance within the baseline weekly itch severity score (ISS) strata, treatment balance within the body weight strata, and balance within each study center.

Protocol amendments

The protocol was amended once based on feedback from the US Food and Drug Administration, Genentech, Inc. staff, and external advisors. The key changes are detailed below. The eligibility criteria were revised as follows: the length of time that a patient must have had chronic idiopathic urticaria/chronic spontaneous urticaria (CIU/CSU) symptoms despite being treated with H_1-antihistamines was increased from 6 to 8 weeks, contraindications to diphenhydramine were added, the washout period required after regular doxepin use before enrollment was reduced from 6 weeks to 14 days, the criterion for women of childbearing potential and pregnancy was clarified, and nursing women were excluded from the study. The secondary objectives were clarified to indicate that a goal of the study was to provide information regarding the recurrence of disease/symptoms after withdrawal of omalizumab in patients with H_1-antihistamine–refractory CIU/CSU, and as a result, secondary and exploratory endpoints were modified. The start of the screening

period was modified from 14 to 18 days to 12 to 18 days before day 1. The in-clinic urticaria activity score (UAS) terminology was corrected. Procedures regarding the use of excluded therapy were modified in an effort to continue to follow patients for safety evaluation after they had discontinued study drug treatment. The difference between discontinuation from study drug treatment and discontinuation from the study was clarified. The medical monitor was replaced.

Study endpoints

Evaluation of patient-reported diary outcomes

The European Academy of Allergy and Clinical Immunology has proposed using the UAS, a combined score of itch severity and number of hives, as the official disease activity measure (Zuberbier *et al.*, 2009). The Urticaria Patient Daily Diary, developed according to the US Food and Drug Administration patient-reported outcome development guidelines, includes UAS as well as additional components (sleep interference, interference with daily activities, symptom occurrence and management) as part of a comprehensive assessment of symptoms in patients with CIU/CSU (Mathias *et al.*, 2010; Mathias *et al.*, 2012). Itch severity was measured on a scale of 0 to 3 (0=no itch; 1=mild; 2=moderate; 3=severe). Patients were instructed to ask for help in counting and measuring hives located on the back or in places that were hard to reach. Patients recorded the number of hives based on a scale of 0 to 3 (0=none; 1=1–6 hives; 2=7–12 hives; 3=>12 hives). Similarly, the size of the largest hive was recorded on a scale of 0 to 3 (0=none; 1=<1.25 cm; 2=1.25–2.5 cm; 3=>2.5 cm. For occurrence of angioedema (yes, no), if the response was yes, patients recorded how the angioedema was treated on a scale of 0 to 5 (0=no treatment; 1=took medication; 2=called doctor/nurse; 3=visited doctor/nurse; 4=visited the emergency department; 5=hospitalization).

Prespecified subgroup analyses

The following prespecified subgroup analyses were performed for the primary efficacy endpoints: sex (male, female); age (<18 years, 18–64 years, ≥65 years); race (white, black, all other races); region (United States, non-United States); baseline weekly ISS (<13, ≥13); baseline UAS over 7 days (UAS7; <median, ≥median); body weight (<80 kg, ≥80 kg); presence of basophil histamine releasing serum activity as detected by the CU® Index test (Viracor-IBT Laboratories, Inc., Lee's Summit, Missouri, USA; yes, no); presence of angioedema at baseline (yes, no); presence of thyroperoxidase antibody at baseline (high, normal); previous use of systemic steroids for CIU/CSU (yes, no); duration of disease before baseline (<2 years, 2–10 years, >10 years); and previous number of CIU/CSU medications (≤2, 3–5, >5).

Prespecified exploratory endpoints

The following exploratory endpoints were prespecified: change from baseline in weekly ISS at week 24, change from baseline in UAS7 at week 24, change from baseline in weekly number of hives score at week 24, change from baseline in weekly size of largest hive score at week 24, change from baseline in Chronic Urticaria Quality of Life Questionnaire overall score at weeks 12 and 40, change from baseline in overall Dermatology Life Quality Index at week 40, change from baseline in proportion of itch-free and/or hive-free days at weeks 12 and 24, change from baseline in number of tablets/week of sedating H_1-antihistamine (diphenhydramine) for itch relief at week 12, change from baseline in weekly sleep interference score at weeks 12 and 24, change from baseline in weekly interference with daily activities score at weeks 12 and 24, change from baseline in health utility (EuroQoL 5-Dimensions) at weeks 12 and 24, change from baseline in Medical Outcomes Study Sleep Scale scores at weeks 12 and 24, the proportion of patients with UAS7 ≤6 at

week 24, proportion of week 24 responders who maintained their response (UAS7 ≤6) at the week 40 visit, proportion of complete responders (UAS7=0) at weeks 24 and 40, time to UAS7 minimal important difference (MID) response by week 12, time to relapse in week 24 responders, health care utilization, actions taken in response to angioedema, and correlation between basophil high-affinity immunoglobulin E receptor density and change from baseline in weekly ISS at weeks 12, 24, and 40.

Safety

Verbatim descriptions of adverse events (AEs) were coded with the use of the Medical Dictionary for Regulatory Activities version 15.1 and analyzed with the use of appropriate thesaurus terms.

Statistical analysis

Baseline demographic and clinical characteristics were summarized using descriptive statistics. Secondary endpoints that measured change from baseline at week 12 were evaluated using analysis of covariance (ANCOVA) models similar to those used for the primary efficacy endpoint analysis, adjusted for baseline score strata of the respective endpoint (<median, ≥median) and baseline weight (<80 kg, ≥80 kg). Treatment comparisons were performed using the Cox proportional hazards model stratified by baseline weekly ISS (<13, ≥13) and baseline weight (<80 kg, ≥80 kg). For the proportions of patients with UAS7 ≤6, MID response for weekly ISS, and complete response (UAS7=0), treatment comparisons were performed using the Cochran–Mantel–Haenszel test stratified by baseline scores for the respective endpoint (<median, ≥median) and baseline weight (<80 kg, ≥80 kg). The treatment comparison for the proportion of angioedema-free days from weeks 4 to 12 was conducted using a Wilcoxon rank-sum test, stratified by presence of angioedema at baseline (yes, no) and baseline weight (<80 kg, ≥80 kg).

Type I error control plan

In order to maintain an overall type I error rate of 0.05 (two-sided) across the three omalizumab dose groups, testing of the primary endpoint was conducted in the following hierarchical order: stage 1, omalizumab 300-mg group versus the placebo group; if there was no statistically significant difference found between the omalizumab 300-mg group and the placebo group at the significance level of 0.05, then the test for the next stage was not considered statistically significant regardless of the *P*-value. Stage 2, omalizumab 150-mg group versus the placebo group; if there was no statistically significant difference found between the omalizumab 150-mg group and the placebo group at the significance level of 0.05, then the test for the next stage was not be considered statistically significant regardless of the *P*-value. Stage 3, omalizumab 75-mg group versus the placebo group; the statistical test was conducted at a significance level of 0.05. For secondary efficacy endpoints, a hierarchical analysis, detailed below, was performed for each omalizumab dose found to be significant for the primary endpoint. All tests were conducted at a significance level of 0.05. A *P*-value <0.05 could only be claimed as statistically significant if statistical significance had been claimed at the previous stage. The hierarchical analysis of the secondary endpoints was independent between the different omalizumab dose levels. Failure to claim statistical significance for a secondary endpoint at a particular dose of omalizumab did not affect the test of a secondary endpoint at another omalizumab dose level. The hierarchical order was as follows: stage 1, change from baseline in UAS7 at week 12; stage 2, change from baseline in the weekly number of hives score at week 12; stage 3, time to weekly ISS MID response (≥5-point decrease) at week 12; stage 4, proportion of patients with UAS7 ≤6 at week 12; stage 5, proportion of weekly ISS MID responders at week 12; stage 6, change from baseline in weekly size of the largest hive score at week 12;

stage 7, change from baseline in health-related quality of life as measured by the Dermatology Life Quality Index at week 12; stage 8, proportion of angioedema-free days from weeks 4 to 12 of therapy; and stage 9, proportion of complete responders (UAS7=0) at week 12.

RESULTS

Study population

Baseline demographic and disease characteristics

Patients were predominantly female, white, and had a mean age of 41 years, elevated immunoglobulin E levels (median 83.0), and moderate-to-severe symptom scores. There were no major imbalances in baseline disease characteristics across treatment groups. Some differences were noted and included that the placebo group had a higher percentage of patients with a positive CU Index test (31.3%) compared with the other treatment groups (23.4%, 20.3%, and 25.9% of patients in the omalizumab 75-mg, 150-mg, and 300-mg groups, respectively). The placebo group also had a higher percentage of patients reporting the presence of angioedema at baseline (55.0%) compared with the other treatment groups (45.5%, 47.5%, and 42.0% of patients in the omalizumab 75-mg, 150-mg, and 300-mg groups, respectively). The omalizumab 75-mg group had a higher percentage of patients with high levels of thyroperoxidase antibody (21.6%) than the other three groups (12.5%, 11.1%, and 15.2% of patients in the omalizumab 150-mg, omalizumab 300-mg, and placebo groups, respectively). The omalizumab 75-mg group also had a higher (53.2%) percentage of patients who had previously used systemic steroids for CIU/CSU compared with the other three groups (40.0%, 44.4%, and 38.8% of patients in the omalizumab 150-mg, omalizumab 300-mg, and placebo groups, respectively).

Previous treatments for CIU/CSU

Patients had been previously treated with a mean (standard deviation) of 4.7 (2.8) medications for CIU/CSU. All but one patient in the study was previously treated with H_1-antihistamines for CIU/CSU. This patient (in the omalizumab 150-mg group) did not meet the study's inclusion criteria. Besides H_1-antihistamines, the most frequently used previous medications for CIU/CSU were corticosteroids (50.0%), H_2-antihistamines (29.2%), leukotriene receptor antagonists (26.1%), and hydroxyzine hydrochloride (30.5%), with similar percentages, in general, across treatment groups. In addition, there were two patients (one in the placebo group, one in the omalizumab 150-mg group) who received previous treatment with omalizumab for CIU/CSU >1 year before screening.

Treatment discontinuations

Among the 319 randomized patients, 54 (16.9%) were discontinued from study drug treatment and one of these patients never received assigned study drug treatment. The most common reasons for study drug treatment discontinuation across the four treatment groups were disease progression (6.3% [*n*=20]), AE (4.7% [*n*=15]), and patient/legal guardian's decision (3.8% [*n*=12]). The omalizumab 300-mg group had the lowest (9.9% [*n*=9]) treatment discontinuation rate. The placebo group had larger percentages of patients discontinuing treatment owing to disease progression (12.5% [*n*=10]) and AEs (8.8% [*n*=7]) compared with any of the other treatment groups. Six patients in the placebo group, four in the omalizumab 75-mg group, seven in the omalizumab 150-mg group, and one in the omalizumab 300-mg group withdrew from study drug treatment but remained in the study and completed the 16-week follow-up period.

Diary compliance

The diary compliance rates during the treatment and follow-up periods are shown in Table S2.

Efficacy

Prespecified subgroup analyses

Subgroup analyses for the change from baseline in ISS at week 12 (the primary efficacy endpoint) were performed (Figure S3). For some subgroups (age <18 years, age ≥65 years, black race, other race) no meaningful interpretation of results could be made owing to small sample sizes. Across all treatment groups, patients with higher baseline weekly ISS (≥13) had larger absolute reductions from baseline in weekly ISS compared with patients with lower baseline weekly ISS (<13; Figure S3). The observed treatment effect of omalizumab versus placebo for all three doses of omalizumab was larger in patients with higher baseline weekly ISS versus patients with lower weekly ISS (Figure S3).

Sensitivity analyses

Sensitivity analyses were performed on the primary endpoint to assess the robustness of the primary analysis results. ANCOVA models were used to evaluate the impact of using the last observation carried forward method of imputing missing data on the primary analysis, with similar results to those obtained using the reported baseline observation carried forward (BOCF) method. Fitting a mixed-effects model, which included all observed weekly ISS from baseline to week 12, also showed similar results to those obtained using the reported BOCF method. Finally, an ANCOVA model was fitted, which was similar to the primary analysis but imputed the week 12 weekly ISS by carrying forward the baseline weekly ISS for the three patients in the study with non-missing weekly ISS at week 12 who received systemic

steroids during the 2 weeks before the week 12 visit (days 71–84) but for whom the duration of steroid therapy did not meet the criteria for excluded medication. Again, the results were similar to those obtained using the reported BOCF method.

Safety

AEs, severe AEs, and serious AEs were infrequent across the treatment groups (Tables S6–S8).The majority of AEs were mild or moderate in intensity (Table S7). During the treatment period, 21 (6.6%) patients experienced a severe AE: five (7.1%) patients in the omalizumab 75-mg group, five (5.7%) patients in the omalizumab 150-mg group, three (3.7%) patients in the omalizumab 300-mg group, and eight (10.0%) patients in the placebo group. During the follow-up period, 18 (5.7%) patients experienced a severe AE: three (4.3%) patients in the omalizumab 75-mg group, four (4.6%) patients in the omalizumab 150-mg group, 10 (12.3%) patients in the omalizumab 300-mg group, and one (1.3%) patient in the placebo group. The most common severe AE reported during the follow-up period (by Medical Dictionary for Regulatory Activities system organ class high-level term) was urticaria (*n*=12 [3.8%]), which was reported in two (2.9%) patients in the omalizumab 75-mg group, three (3.4%) patients in the omalizumab 150-mg group, seven (8.6%) patients in the omalizumab 300-mg group, and no patients in the placebo group. No patients had evidence of an antibody response against omalizumab during the study.

One female patient randomized to placebo with a history of uterine fibromas was diagnosed with severe cervical dysplasia on day 10 (9 days after the receipt of the last dose of study drug before this event). The pathology report, which determined that this patient had experienced cervical adenocarcinoma *in situ*, was received post-database lock. The patient underwent elective excision of the entire cervix and the event was considered resolved. The investigator assessed the event as serious and not related to the study drug but related to the concurrent illness.

Three patients with suspected anaphylaxis during omalizumab therapy were referred for blinded external adjudication. In one patient in the omalizumab 75-mg group, an event originally reported as an exacerbation of urticaria was assessed as anaphylaxis owing to concomitant gastrointestinal symptoms and was not attributed to study drug. In another patient in the omalizumab 150-mg group, it was determined that this event was not anaphylaxis. During follow-up (weeks 24–40), one patient in the omalizumab 300-mg group experienced a serious anaphylactic reaction (142 days after receiving the final dose of omalizumab). The adjudication committee confirmed this event as a reaction to dipyrone and unrelated to study drug.

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Table S1. ASTERIA I, ASTERIA II, and GLACIAL Study Designs

Study	Background therapy for CIU/CSU	Treatment groups	DB treatment period (FU period)	Primary endpoint
ASTERIA I	• Approved doses of H_1-antihistamines	• Omalizumab 75 mg, 150 mg, 300 mg vs placebo	• 24 weeks (16 weeks)	• Change from baseline to Week 12 in Weekly ISS
ASTERIA II*	• Approved doses of H_1-antihistamines	• Omalizumab 75 mg, 150 mg, 300 mg vs placebo	• 12 weeks (16 weeks)	• Change from baseline to Week 12 in Weekly ISS
GLACIAL†	• Up to 4X approved dose of H_1-antihistamines plus H_2-antihistamines or LTRAs, or all 3 in combination	• Omalizumab 300 mg vs placebo	• 24 weeks (16 weeks)	• Safety

CIU, chronic idiopathic urticaria; CSU, chronic spontaneous urticaria; DB, double-blind; FU, follow-up; ISS, itch severity score.

*Maurer, Rosen, *et al* 2013.

†Kaplan *et al*., 2013.

Table S2. Diary compliance rate[1]

Proportion of days with ≥1 diary entry	Placebo (*n*=80)	Omalizumab 75 mg (*n*=77)	Omalizumab 150 mg (*n*=80)	Omalizumab 300 mg (*n*=81)
Treatment period (up to week 12)				
n	80	77	80	81
Mean (SD) days	97.8% (8.8%)	96.5% (14.5%)	98.8% (5.0%)	98.9 (3.7%)
Range (%)	31.0%–100.0%	4.8%–100.0%	58.3%–100.0%	78.6%–100.0%
>85% of days, n (%)	77 (96.3%)	74 (96.1%)	79 (98.8%)	79 (97.5%)
Treatment period (up to week 24)				
n	80	77	80	81
Mean (SD) days	97.6% (7.5%)	95.8% (14.2%)	98.4% (4.7%)	98.2% (5.0%)
Range (%)	47.7%–100.0%	13.8%–100.0%	65.9%–100.0%	69.8%–100.0%
>85% of days, *n* (%)	76 (95.0%)	72 (93.5%)	78 (9.5%)	78 (96.3%)
Follow-up period (after week 24)				
n	77	73	80	78
Mean (SD) days	91.9% (18.2%)	93.1% (12.7%)	94.3% (10.2%)	94.0% (15.2%)
Range (%)	0.8%–100.0%	36.4%–100.0%	33.3%–100.0%	11.1%–100.0%
>85% of days, *n* (%)	70 (87.5%)	62 (80.5%)	69 (86.3%)	69 (85.2%)

Abbreviation: SD, standard deviation.

[1]Analyses for all periods are based on modified intention-to-treat population. Proportions are based on number of non-missing daily diary entries for a patient within the total number of days during a period that the patient was active.

Table S3. Summary of additional secondary endpoints[1]

Endpoint	Placebo (*n*=80)	Omalizumab 75 mg (*n*=77)	Omalizumab 150 mg (*n*=80)	Omalizumab 300 mg (*n*=81)
Change from baseline to week 12 in weekly number of hives				
Mean (SD)	−4.37 (6.60)	−7.36 (7.52)	−7.78 (7.08)	−11.35 (7.25)
Median (range)	−1.8 (−21.0 to 7.3)	−5.8 (−21.0 to 5.5)	−7.3 (−21.0 to 2.1)	−11.8 (−21.0 to 3.0)
LSM treatment difference versus placebo (95% CI)	–	−2.75 (−4.95 to −0.54)	−3.44 (−5.57 to −1.32)	−6.93 (−9.10 to −4.76)
P-value versus placebo	–	0.0149	0.0017	<0.0001
Change from baseline to week 12 in weekly size of largest hive score				
Mean (SD)	−3.93 (5.44)	−6.20 (6.29)	−6.96 (6.68)	−9.79 (6.66)
Median (range)	−2.8 (−21.0 to 4.0)	−4.5 (−21.0 to 2.0)	−6.0 (−21.0 to 2.5)	−10.5 (−21.0 to 3.0)
LSM treatment difference versus placebo (95% CI)	–	−2.34 (−4.17 to −0.51)	−3.16 (−5.05 to −1.27)	−5.73 (−7.59 to −3.87)
P-value versus placebo	–	0.0124[2]	0.0012	<0.0001
Change from baseline to week 12 in overall DLQI score[3]				
Mean (SD)	−6.13 (6.25)	−6.33 (6.08)	−8.00 (7.24)	−10.29 (7.23)
Median (range)	−5.0 (−24.0 to 9.0)	−5.0 (−24.0 to 8.0)	−8.0 (−30.0 to 9.0)	−10.5 (−26.0 to 5.0)
LSM treatment difference *vs* placebo (95% CI)	–	0.26 (−1.76 to 2.28)	–1.31 (−3.46 to 0.84)	–4.08 (−5.96 to –2.20)
P-value versus placebo	–	0.7956[2]	0.2286	<0.0001
Proportion of angioedema-free days from weeks 4 to 12[4]				
Mean (SD)	88.2% (19.4%)	86.5% (28.4%)	89.6% (20.6%)	96.1% (11.3%)
Median (range)	98.1%	100.0%	100.0%	100.0%

	(2.0%–100.0%)	(0%–100.0%)	(0%–100.0%)	(23.2%–100.0%)
P-value versus placebo	–	0.4867[2]	0.1747[2]	<0.0001

Abbreviations: CI, confidence interval; DLQI, Dermatology Life Quality Index; LSM, least-squares mean; SD, standard deviation.

[1]Analyses are based on modified intention-to-treat population. Missing week 12 scores were imputed using the baseline weekly score (except for DLQI, for which there was no imputation).

[2]Not evaluated for statistical significance in accordance with the type I error control plan.

[3]Placebo, *n*=62; omalizumab 75 mg, *n*=66; omalizumab 150 mg, *n*=63; omalizumab 300 mg, *n*=72.

[4]Placebo, *n*=66; omalizumab 75 mg, *n*=69; omalizumab 150 mg, *n*=70; omalizumab 300 mg, *n*=74.

Defined as the number of days for which the patient responded no to the angioedema question in the daily diary divided by the total number of days with a non-missing diary entry starting on 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 >40% of the daily diary entries between the weeks 4 and 12 study visits were not included in this analysis.

Table S4. Summary of selected exploratory endpoints up to the end of treatment (week 24) and at the end of the follow-up period (week 40)

		Omalizumab		
Endpoint	**Placebo (*n*=80)**	**75 mg (*n*=77)**	**150 mg (*n*=80)**	**300 mg (*n*=81)**
Median time to UAS7 MID response (≥5-point decrease) by week 12	6.0	3.0	3.0	1.5
Hazard ratio versus placebo (95% CI)	–	1.52[1] (1.03–2.24)	1.67[1] (1.15–2.44)	2.69[2] (1.86–3.90)
Change from baseline in CU-Q2oL at week 12	−19.7 (19.7)	−19.2 (19.0)	−23.1 (18.6)	−30.5[1] (19.1)
Change from baseline in weekly ISS at week 24	−5.41 (5.76)	−6.98 (6.42)	−6.47 (6.50)	−9.84[2] (5.95)
Change from baseline in UAS7 at week 24	−11.73 (12.53)	−14.92 (13.77)	−14.21 (13.33)	−22.11[2] (12.46)
Change from baseline in weekly no. of hives score at week 24	−6.32 (7.24)	−7.95 (7.73)	−7.75 (7.26)	−12.28[2] (7.33)
Change from baseline in weekly size of largest hive score at week 24	−5.25 (6.69)	−6.33 (7.14)	−6.81 (6.94)	−10.74[2] (7.00)
Patients with UAS7 ≤6, n (%)				
At week 24	20 (25.0%)	23 (29.9%)	29 (36.3%)	50[2] (61.7%)
At week 40	18 (22.5%)	12 (15.6%)	15 (18.8%)	13 (16.0%)
Week 24 responders[3] who maintained response (UAS7 ≤6) at week 40, *n* (%)	5 (6.3%)	5 (6.5%)	2 (2.5%)	6 (7.4%)
Patients with a complete response (UAS7=0), n (%)				

At week 24	10 (12.5%)	18 (23.4%)	16 (20.0%)	39[2] (48.1%)
At week 40	11 (13.8%)	7 (9.1%)	9 (11.3%)	8 (9.9%)
Change from baseline in overall DLQI score at week 40	−7.9 (8.0)	−7.0 (5.8)	−5.2 (6.7)	−4.9 (8.1)
Median time to relapse[4] after week 24 in week 24 responders (weeks)	7.0	3.0	3.0	5.0
Change from baseline in rescue medication use (tablets/week of diphenhydramine)	−1.0 (5.2)	−2.3 (6.9)	−2.9 (7.1)[5]	−4.2 (6.4)[5]

Abbreviations: CI, confidence interval; CU-Q2oL, Chronic Urticaria Quality-of-Life Questionnaire; DLQI, Dermatology Life Quality Index; ISS, itch severity score; MID, minimal important difference; SD, standard deviation; UAS7, urticaria activity score over 7 days.

[1]*P*<0.05 versus placebo at weeks 12 or 24 (no statistical analyses were performed for week 40 exploratory endpoints).

[2]*P*<0.0001 versus placebo at weeks 12 or 24 (no statistical analyses were performed for week 40 exploratory endpoints).

[3]Week 24 responders (defined as patients who achieved an absolute UAS7 ≤6 at week 12) who discontinued before week 40 who had not relapsed were censored at the week of their last non-missing UAS7.

[4]Time to relapse is defined as the date of the week 24 visit to the date where UAS7 >6.

Analyses are based on the modified intention-to-treat population. None of these analyses were part of the type 1 error control plan. Data are presented as mean (SD) unless otherwise noted.

[5]*P*<0.03 based on treatment difference in least square means relative to the placebo group.

Table S5. Summary of angioedema occurrences at baseline, week 12, and week 24

Endpoint	Placebo (*n*=80)	Omalizumab 75 mg (*n*=77)	Omalizumab 150 mg (*n*=80)	Omalizumab 300 mg (*n*=81)
Baseline				
n	80	77	80	81
Patients with angioedema, *n* (%)[1]	44 (55.0%)	35 (45.5%)	38 (47.5%)	34 (42.0%)
Mean (SD) no. of days a patient had angioedema (all patients)	1.45 (1.83)	1.71 (2.43)	1.76 (2.31)	1.15 (1.77)
Week 12				
n	64	65	62	72
Patients with angioedema, *n* (%)[1]	17 (26.6%)	14 (21.5%)	10 (16.1%)	9 (12.5%)
Mean (SD) no. of days a patient had angioedema (all patients)	0.76 (1.58)	0.88 (2.01)	0.58 (1.64)	0.33 (1.01)
Week 24				
n	54	62	55	67
Patients with angioedema, *n* (%)[1]	6 (11.1%)	17 (27.4%)	5 (9.1%)	5 (7.5%)
Mean (SD) no. of days a patient had angioedema (all patients)	0.27 (0.86)	1.16 (2.22)	0.24 (0.90)	0.21 (1.00)

Abbreviation: SD, standard deviation.

[1]Percentage of patients who had angioedema is based on the number of patients who had non-missing data.

Analyses are based on the modified intention-to-treat population.

Table S6. Summary of treatment-emergent AEs according to study group (≥3% in any group)[1]

MedDRA SOC preferred term, *n* (%)	Placebo (*n*=80)	Omalizumab 75 mg (*n*=70)	Omalizumab 150 mg (*n*=87)	Omalizumab 300 mg (*n*=81)
Any AEs	41 (51.3%)	41 (58.6%)	60 (69.0%)	46 (56.8%)
General disorders and administration site conditions				
Overall	2 (2.5%)	3 (4.3%)	7 (8.0%)	7 (8.6%)
Pyrexia	1 (1.3%)	1 (1.4%)	3 (3.4%)	0
Infections and infestations				
Overall	22 (27.5%)	20 (28.6%)	32 (36.8%)	16 (19.8%)
Nasopharyngitis	10 (12.5%)	3 (4.3%)	11 (12.6%)	9 (11.1%)
Sinusitis	4 (5.0%)	5 (7.1%)	4 (4.6%)	3 (3.7%)
Bronchitis	5 (6.3%)	4 (5.7%)	2 (2.3%)	1 (1.2%)
URTI	3 (3.8%)	3 (4.3%)	3 (3.4%)	1 (1.2%)
UTI	2 (2.5%)	1 (1.4%)	4 (4.6%)	1 (1.2%)
Fungal infection	0	0	3 (3.4%)	0
Musculoskeletal and connective tissue disorders				
Overall	2 (2.5%)	7 (10.0%)	12 (13.8%)	9 (11.1%)
Arthralgia	0	1 (1.4%)	5 (5.7%)	3 (3.7%)
Pain in extremity	0	1 (1.4%)	3 (3.4%)	0
Nervous system disorders				
Overall	4 (5.0%)	7 (10.0%)	14 (16.1%)	8 (9.9%)
Headache	2 (2.5%)	4 (5.7%)	8 (9.2%)	5 (6.2%)
Migraine	0	0	3 (3.4%)	0
Respiratory, thoracic, and mediastinal disorders				
Overall	10 (12.5%)	5 (7.1%)	12 (13.8%)	4 (4.9%)
Oropharyngeal pain	4 (5.0%)	2 (2.9%)	5 (5.7%)	0
Cough	2 (2.5%)	3 (4.3%)	2 (2.3%)	0
Skin and subcutaneous tissue disorders				
Overall	13 (16.3%)	13 (18.6%)	10 (11.5%)	9 (11.1%)
Urticaria	6 (7.5%)	5 (7.1%)	4 (4.6%)	2 (2.5%)

Idiopathic urticaria	2 (2.5%)	5 (7.1%)	1 (1.1%)	1 (1.2%)
Angioedema	3 (3.8%)	0	0	3 (3.7%)

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class; URTI, upper respiratory tract infection; UTI, urinary tract infection.

[1]Data are for the safety population. Multiple occurrences of a specific AE for a patient were counted once in the frequency for the AE. Similarly, multiple occurrences of AEs within a specific SOC for a patient were counted once in the frequency for the SOC.

Table S7. Summary of treatment-emergent AEs according to study group by severity[1]

		Omalizumab		
Severity, *n* (%)	**Placebo (*n*=80)**	**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%)
Mild	23 (28.8%)	21 (30.0%)	31 (35.6%)	18 (22.2%)
Moderate	22 (27.5%)	27 (38.6%)	33 (37.9%)	26 (32.1%)
Severe	8 (10.0%)	7 (10.0%)	8 (9.2%)	13 (16.0%)

Abbreviation: AE, adverse event.

[1]Safety population.

Table S8. Summary of treatment-emergent serious AEs occurring during the study according to preferred term[1]

MedDRA SOC preferred term, *n* (%)	Placebo (*n*=80)	Omalizumab 75 mg (*n*=70)	Omalizumab 150 mg (*n*=87)	Omalizumab 300 mg (*n*=81)
During treatment (up to week 24)				
Any serious AEs	4 (5.0%)	2 (2.9%)	3 (3.4%)	0
Specific events				
Angina unstable	0	0	1 (1.1%)	0
GERD	0	1 (1.4%)	0	0
Appendicitis	0	0	1 (1.1%)	0
Radius fracture	1 (1.3%)	0	0	0
Type 2 diabetes mellitus	1 (1.3%)	0	0	0
Pain in extremity	0	0	1 (1.1%)	0
Cervical dysplasia	1 (1.3%)[2]	0	0	0
COPD	1 (1.3%)	0	0	0
Urticaria	0	1 (1.4%)	0	0
Hypertension	0	0	1 (1.1%)	0
During follow-up (weeks 24 to 40)				
Any serious AEs	1 (1.3%)	0	2 (2.3%)	2 (2.5%)
Specific events				
Urticaria	0	0	1 (1.1%)	0
Idiopathic urticaria	1 (1.3%)	0	0	0
Angioedema	0	0	1 (1.1%)	0
Abortion induced	0	0	1 (1.1%)	0
Anaphylactic reaction	0	0	0	1 (1.2%)[3]
Hypoglycemic shock	0	0	0	1 (1.2%)

Abbreviations: AE, adverse event; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class.

[1]Data are for the safety population. Multiple occurrences of a specific AE for a patient were counted once in the frequency for the AE. Similarly, multiple occurrences of AEs within a specific SOC for a patient were counted

once in the frequency for the SOC. A treatment-emergent AE was defined as any AE reported at the time of or after the first dose of study drug.

[2]In the pathology report received post-database lock, the cervical dysplasia event was found to be a cervical adenocarcinoma *in situ*.

[3]Serious anaphylactic reaction. The investigator confirmed this event, which occurred during follow-up at 142 days after the last dose of study drug, as a reaction to dipyrone and assessed the event as not related to the study drug.

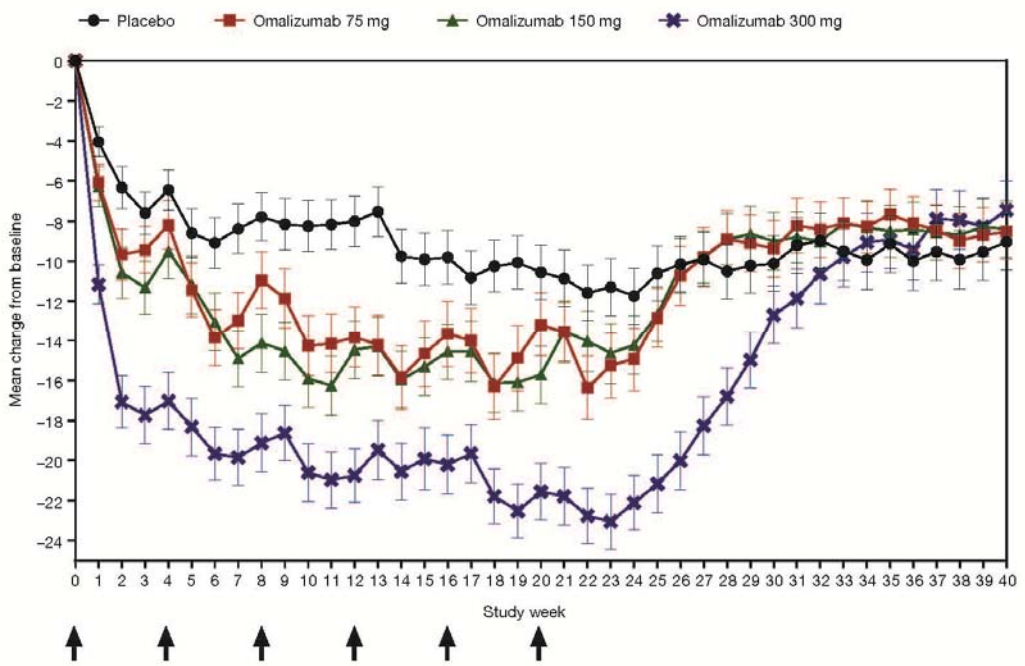

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Figure S1. Mean change from baseline in UAS7 by study week.[1] Errors bars represent standard error of the mean. Arrows indicate study drug injection day.[1]Analyses are based on the modified intention-to-treat population with missing weekly scores imputed using baseline UAS7 scores. UAS7, urticaria activity score over 7 days.

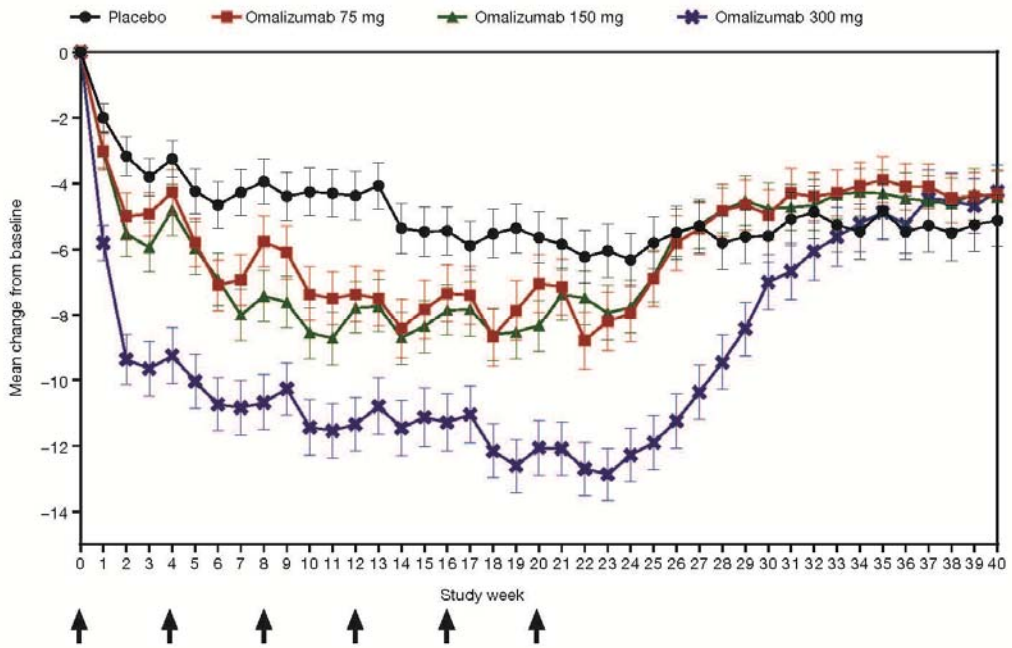
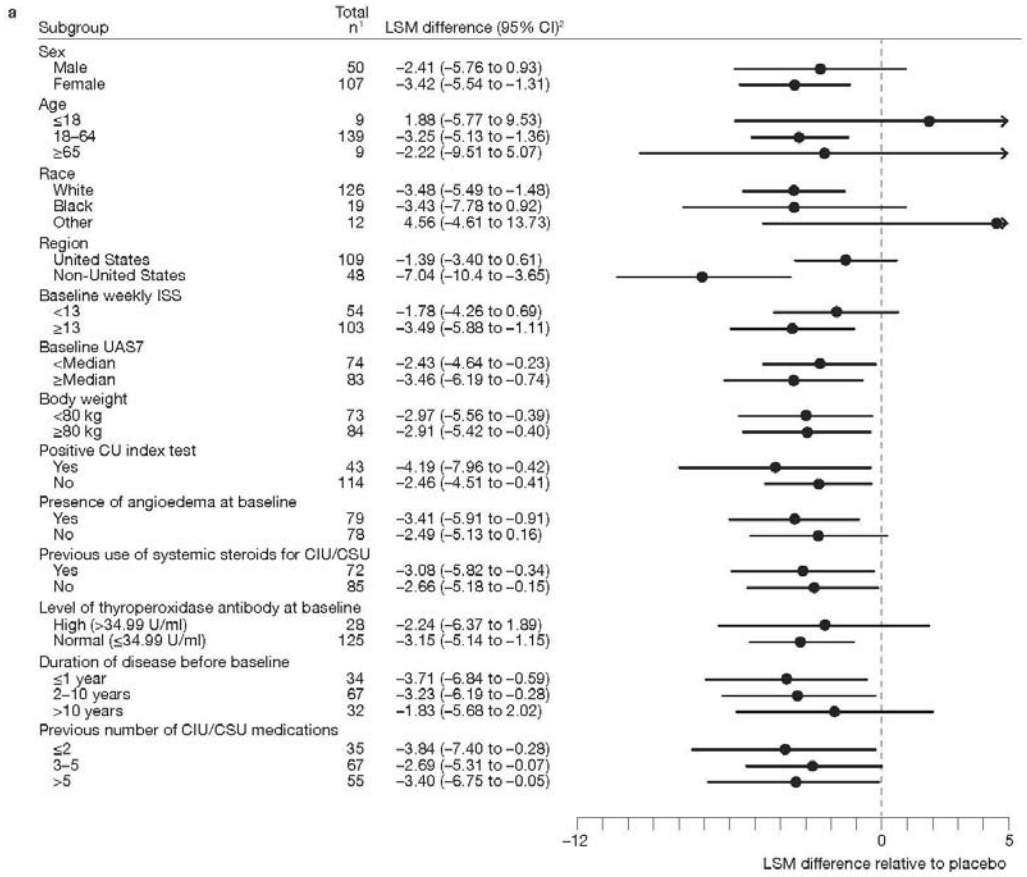
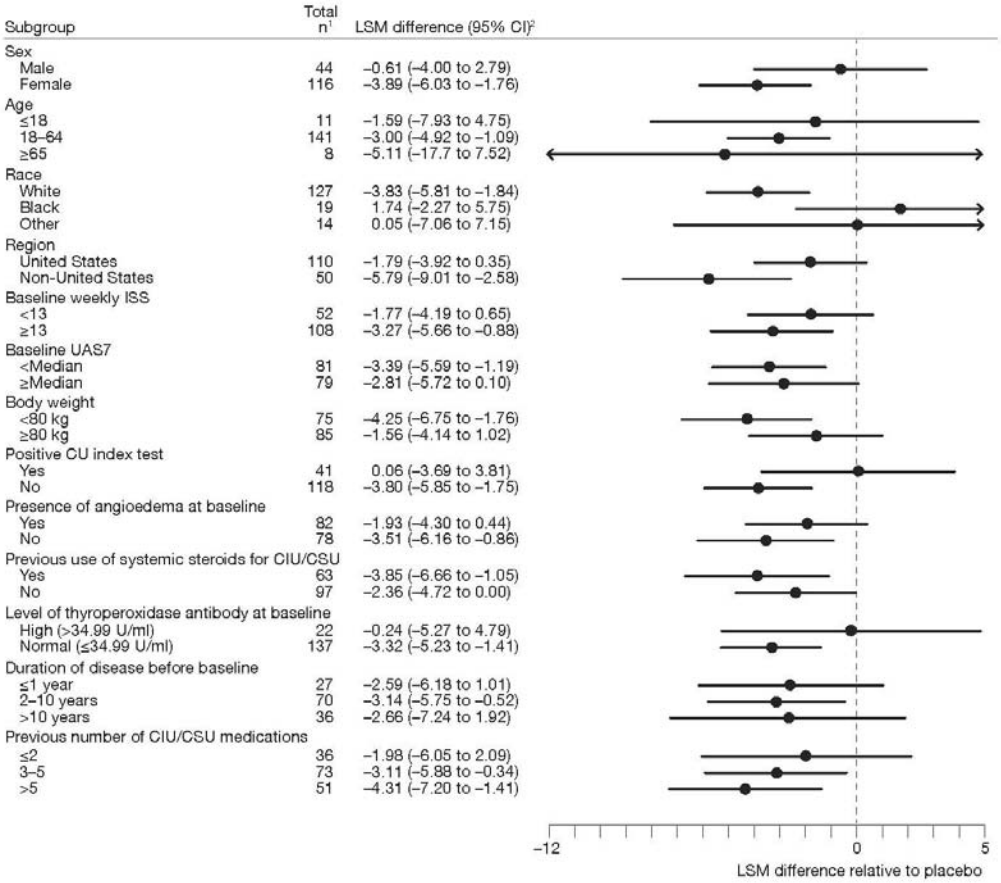


Figure S2. Mean change from baseline in weekly number of hives score by study week.[1] Errors bars represent standard error of the mean. Arrows indicate study drug injection day. [1]Analyses are based on the modified intention-to-treat population with missing weekly scores imputed using baseline weekly scores.


a
Subgroup
Total n[1]
LSM difference (95% CI)[2]
Sex
Male 50 −2.41 (−5.76 to 0.93)
Female 107 −3.42 (−5.54 to −1.31)
Age
≤18 9 1.88 (−5.77 to 9.53)
18–64 139 −3.25 (−5.13 to −1.36)
≥65 9 −2.22 (−9.51 to 5.07)
Race
White 126 −3.48 (−5.49 to −1.48)
Black 19 −3.43 (−7.78 to 0.92)
Other 12 4.56 (−4.61 to 13.73)
Region
United States 109 −1.39 (−3.40 to 0.61)
Non-United States 48 −7.04 (−10.4 to −3.65)
Baseline weekly ISS
<13 54 −1.78 (−4.26 to 0.69)
≥13 103 −3.49 (−5.88 to −1.11)
Baseline UAS7
<Median 74 −2.43 (−4.64 to −0.23)
≥Median 83 −3.46 (−6.19 to −0.74)
Body weight
<80 kg 73 −2.97 (−5.56 to −0.39)
≥80 kg 84 −2.91 (−5.42 to −0.40)
Positive CU index test
Yes 43 −4.19 (−7.96 to −0.42)
No 114 −2.46 (−4.51 to −0.41)
Presence of angioedema at baseline
Yes 79 −3.41 (−5.91 to −0.91)
No 78 −2.49 (−5.13 to 0.16)
Previous use of systemic steroids for CIU/CSU
Yes 72 −3.08 (−5.82 to −0.34)
No 85 −2.66 (−5.18 to −0.15)
Level of thyroperoxidase antibody at baseline
High (>34.99 U/ml) 28 −2.24 (−6.37 to 1.89)
Normal (≤34.99 U/ml) 125 −3.15 (−5.14 to −1.15)
Duration of disease before baseline
≤1 year 34 −3.71 (−6.84 to −0.59)
2–10 years 67 −3.23 (−6.19 to −0.28)
>10 years 32 −1.83 (−5.68 to 2.02)
Previous number of CIU/CSU medications
≤2 35 −3.84 (−7.40 to −0.28)
3–5 67 −2.69 (−5.31 to −0.07)
>5 55 −3.40 (−6.75 to −0.05)
−12
0
5
LSM difference relative to placebo

b


Subgroup
Total n[1]
LSM difference (95% CI)[2]
Sex
Male 44 −0.61 (−4.00 to 2.79)
Female 116 −3.89 (−6.03 to −1.76)
Age
≤18 11 −1.59 (−7.93 to 4.75)
18–64 141 −3.00 (−4.92 to −1.09)
≥65 8 −5.11 (−17.7 to 7.52)
Race
White 127 −3.83 (−5.81 to −1.84)
Black 19 1.74 (−2.27 to 5.75)
Other 14 0.05 (−7.06 to 7.15)
Region
United States 110 −1.79 (−3.92 to 0.35)
Non-United States 50 −5.79 (−9.01 to −2.58)
Baseline weekly ISS
<13 52 −1.77 (−4.19 to 0.65)
≥13 108 −3.27 (−5.66 to −0.88)
Baseline UAS7
<Median 81 −3.39 (−5.59 to −1.19)
≥Median 79 −2.81 (−5.72 to 0.10)
Body weight
<80 kg 75 −4.25 (−6.75 to −1.76)
≥80 kg 85 −1.56 (−4.14 to 1.02)
Positive CU index test
Yes 41 0.06 (−3.69 to 3.81)
No 118 −3.80 (−5.85 to −1.75)
Presence of angioedema at baseline
Yes 82 −1.93 (−4.30 to 0.44)
No 78 −3.51 (−6.16 to −0.86)
Previous use of systemic steroids for CIU/CSU
Yes 63 −3.85 (−6.66 to −1.05)
No 97 −2.36 (−4.72 to 0.00)
Level of thyroperoxidase antibody at baseline
High (>34.99 U/ml) 22 −0.24 (−5.27 to 4.79)
Normal (≤34.99 U/ml) 137 −3.32 (−5.23 to −1.41)
Duration of disease before baseline
≤1 year 27 −2.59 (−6.18 to 1.01)
2–10 years 70 −3.14 (−5.75 to −0.52)
>10 years 36 −2.66 (−7.24 to 1.92)
Previous number of CIU/CSU medications
≤2 36 −1.98 (−6.05 to 2.09)
3–5 73 −3.11 (−5.88 to −0.34)
>5 51 −4.31 (−7.20 to −1.41)
−12
0
5
LSM difference relative to placebo

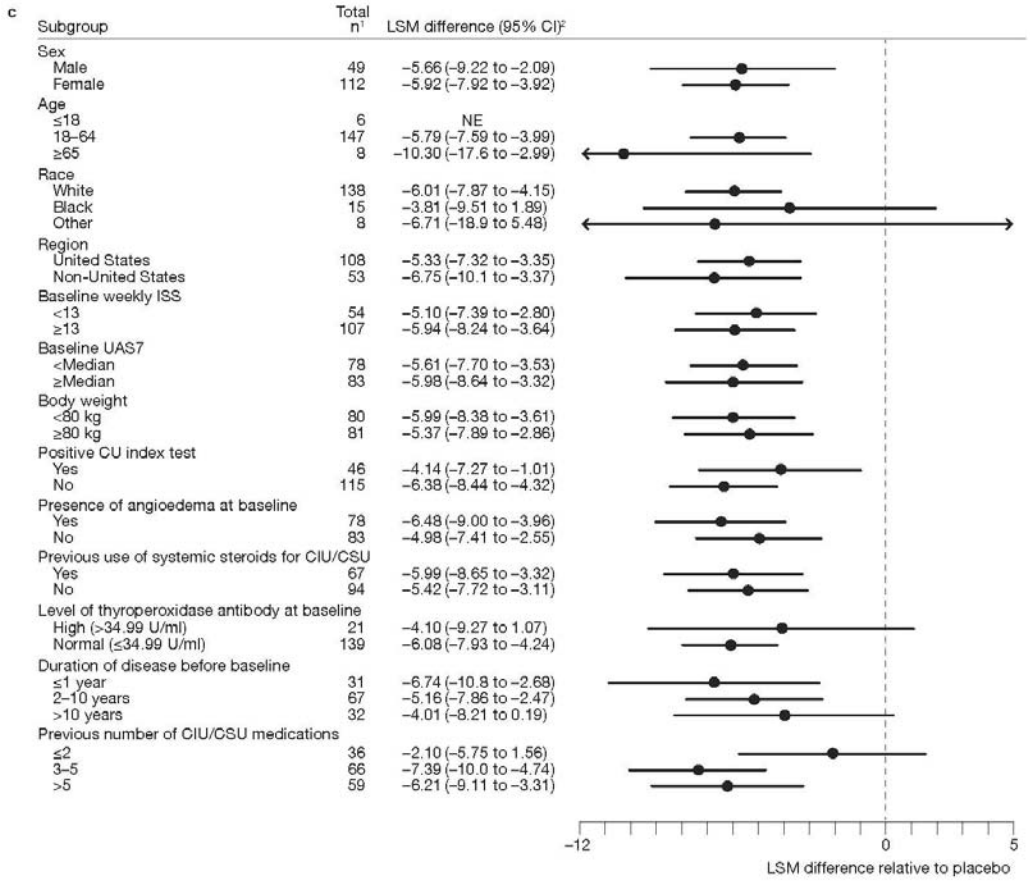


Figure S3. Prespecified subgroup analysis of change from baseline in weekly ISS at week 12 for (a) omalizumab 75 mg, (b) omalizumab 150 mg, and (c) omalizumab 300 mg compared with placebo.[1] [1]Total *n* represents the sum of the patients in the placebo and specified omalizumab groups combined. [2]Analyses are based on the modified intention-to-treat population. CIU/CSU, chronic idiopathic urticaria/chronic spontaneous urticaria; ISS, itch severity score; LSM, least-squares mean; LSM difference, treatment difference in LSMs (relative to placebo) for change from baseline in weekly ISS at week 12 (baseline observation carried forward); MID, minimally important difference; NE, not evaluable; UAS7, urticaria activity score over 7 days.