

ORIGINAL ARTICLE

Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria

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ABSTRACT

BACKGROUND

Many patients with chronic idiopathic urticaria (also called chronic spontaneous urticaria) do not have a response to therapy with H₁-antihistamines, even at high doses. In phase 2 trials, omalizumab, an IgE monoclonal antibody that targets IgE and affects mast-cell and basophil function, has shown efficacy in such patients.

METHODS

In this phase 3, multicenter, randomized, double-blind study, we evaluated the efficacy and safety of omalizumab in patients with moderate-to-severe chronic idiopathic urticaria who remained symptomatic despite H₁-antihistamine therapy (licensed doses). We randomly assigned 323 patients to receive three subcutaneous injections, spaced 4 weeks apart, of omalizumab at doses of 75 mg, 150 mg, or 300 mg or placebo, followed by a 16-week observation period. The primary efficacy outcome was the change from baseline in a weekly itch-severity score (ranging from 0 to 21, with higher scores indicating more severe itching).

RESULTS

The baseline weekly itch-severity score was approximately 14 in all four study groups. At week 12, the mean ($\pm$ SD) change from baseline in the weekly itch-severity score was -5.1 ± 5.6 in the placebo group, -5.9 ± 6.5 in the 75-mg group ($P=0.46$), -8.1 ± 6.4 in the 150-mg group ($P=0.001$), and -9.8 ± 6.0 in the 300-mg group ($P<0.001$). Most prespecified secondary outcomes at week 12 showed similar dose-dependent effects. The frequency of adverse events was similar across groups. The frequency of serious adverse events was low, although the rate was higher in the 300-mg group (6%) than in the placebo group (3%) or in either the 75-mg or 150-mg group (1% for each).

CONCLUSIONS

Omalizumab diminished clinical symptoms and signs of chronic idiopathic urticaria in patients who had remained symptomatic despite the use of approved doses of H₁-antihistamines. (Funded by Genentech and Novartis Pharma; ClinicalTrials.gov number, NCT01292473.)

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CHRONIC IDIOPATHIC URTICARIA (ALSO called chronic spontaneous urticaria) is defined as itchy hives that last for at least 6 weeks, with or without angioedema, and that have no apparent external trigger.¹ The condition generally has a prolonged duration of 1 to 5 years (persisting for >5 years in 11 to 14% of patients^{2,3}) and has a detrimental effect on patients' emotional and physical health-related quality of life.^{4,5} The impairment accompanying this disorder has been likened to that seen in patients with ischemic heart disease, with patients feeling a similar lack of energy, social isolation, and emotional upset as those with heart disease.⁶ Nonsedating H₁-antihistamines are the current mainstay for initial treatment and are the only agents licensed for use in patients with chronic idiopathic urticaria.^{4,7} However, a majority of patients do not have a response to H₁-antihistamines, even when the drugs are administered at three to four times their licensed dose.^{4,8-10}

Treatment options for patients who do not have a response to H₁-antihistamines include the use of H₂-antihistamines, leukotriene-receptor antagonists, systemic glucocorticoids, cyclosporine, hydroxychloroquine, dapsone, methotrexate, sulfasalazine, and intravenous immune globulin.¹¹ None of these agents have yet received regulatory approval for the treatment of chronic idiopathic urticaria. In addition, the data supporting the use of these drugs are limited, and long-term use of some of the agents can be associated with substantial side effects.¹¹

Histamine release from cutaneous mast cells has long been associated with the pathogenesis of urticaria, whereas in patients with chronic idiopathic urticaria, basophils and IgE may also play an important role.¹² Omalizumab, a recombinant humanized monoclonal antibody approved as add-on therapy for moderate-to-severe persistent allergic asthma,^{13,14} reduces the levels of free IgE and the high-affinity receptor for the Fc region of IgE (FcεRI), both of which are essential in mast-cell and basophil activation.^{15,16} Studies have shown that omalizumab may suppress allergen-mediated skin reactions through its reduction of FcεRI function in basophils and mast cells.^{15,17} Initial evidence from two proof-of-concept studies showed that omalizumab may be effective in patients with chronic idiopathic urticaria who remained symptomatic despite antihistamine treatment.^{18,19} Subsequent data from

two phase 2, randomized, placebo-controlled multicenter studies involving a total of 139 patients corroborated these early findings, demonstrating that omalizumab, which has a known safety profile, has beneficial effects on symptoms in patients with chronic idiopathic urticaria who remain symptomatic despite the use of approved doses of H₁-antihistamines.^{20,21}

Here we report the results of the first of three phase 3 clinical trials in patients with chronic idiopathic urticaria in which we evaluated the effects of three doses of omalizumab as compared with placebo.

METHODS

STUDY DESIGN

In this international, multicenter, randomized, double-blind, placebo-controlled study, we investigated the efficacy and safety of omalizumab over 28 weeks in adult and adolescent (≥12 years) patients with chronic idiopathic urticaria who had remained symptomatic despite the use of approved doses of H₁-antihistamines. After a 2-week screening period, patients were randomly assigned to four groups in a 1:1:1:1 ratio to receive three subcutaneous injections of omalizumab (at doses of 75 mg, 150 mg, or 300 mg) or placebo.

We selected the doses for this study on the basis of the results of a previous phase 2 dose-ranging study.²⁰ Doses were administered at 4-week intervals, and to ensure that the blinding was maintained, each dose was administered by a qualified designated clinician who was not involved in the evaluation of the patient's symptoms. This 12-week treatment period was followed by a 16-week follow-up period (for further details, see the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients used an electronic handheld device to self-record data with a validated Urticaria Patient Daily Diary (UPDD)^{22,23} (see the Supplementary Appendix). This electronic diary was stamped with the time and date to ensure that data were not included outside of each assessment period.

Patients continued to receive stable doses of their prerandomization H₁-antihistamine throughout the treatment period. During the follow-up period, patients were permitted to use a licensed dose of one additional H₁-antihistamine. For the duration of the study, all patients were provided

with diphenhydramine (25 mg) as rescue medication for itch relief (up to a maximum of three doses in 24 hours on the basis of local regulations).

The study protocol, which is available at NEJM.org, was approved by the institutional review board or ethics committee at each study center or by a central institutional review board. The study was conducted in accordance with Food and Drug Administration regulations, Good Clinical Practice guidelines, and any other applicable laws of other countries. An independent data and safety monitoring committee oversaw the study conduct and reviewed blinded and unblinded safety data every 6 months (see the Supplementary Appendix).

STUDY OVERSIGHT

The study was sponsored by Genentech and Novartis Pharma, whose representatives were involved in data collection (along with the investigators) and in the interpretation and analysis of the data and who vouch for the accuracy and completeness of the data presented and for the fidelity of this report to the study protocol. Representatives of both companies were involved in the design of the study, with scientific advice obtained from external experts on chronic idiopathic urticaria. The authors wrote all drafts of the manuscript and made the decision to submit the manuscript for publication. Editorial support and assistance with incorporation of revisions was provided by a medical writer who was employed by Genentech. All authors and contributors were under nondisclosure agreements with Genentech.

PATIENTS

Patients were included in the study if they were between the ages of 12 and 75 years (between 18 and 75 years in Germany) and met all the following criteria: a history of at least 6 months of chronic idiopathic urticaria, the presence of hives associated with itching for at least 8 consecutive weeks at any time before enrollment despite current use of H₁-antihistamines, an urticaria activity score (UAS) during a 7-day period (UAS7) of 16 or more (on a scale ranging from 0 to 42, with higher scores indicating greater activity and a minimally important difference [MID] of 9.5 to 10.5),²⁴ a weekly itch-severity score of 8 or more (on a scale ranging from 0 to 21, with higher scores indicating more severe itching and an MID of ≥5)

during the 7 days before randomization (week 0), a score of 4 or more on the UAS (ranging from 0 to 6, with higher scores indicating greater activity) as assessed by a clinician on at least one of the screening-visit days, and receipt of a licensed dose of a second-generation H₁-antihistamine (see the Supplementary Appendix) for chronic idiopathic urticaria for at least 3 consecutive days immediately preceding the screening visit 14 days before randomization, and no missing electronic-diary entries for the 7 days before randomization.

Exclusion criteria included a clearly defined underlying cause for chronic urticaria (e.g., physical urticaria), routine administration (i.e., daily or every other day for ≥5 consecutive days) of systemic glucocorticoids, hydroxychloroquine, methotrexate, cyclosporine, cyclophosphamide, or intravenous immune globulin within the previous 30 days for any indication, the use of any H₂-antihistamine or leukotriene-receptor antagonist within 7 days preceding the screening visit 14 days before randomization, the use of H₁-antihistamines at greater-than-licensed doses within 3 days preceding the screening visit 14 days before randomization, a history of cancer, a weight of less than 20 kg, a known hypersensitivity to omalizumab, treatment with omalizumab within the previous year, or pregnancy.

Before inclusion in the study, all patients or a parent or legal guardian (for those under the age of 18 years) provided written informed consent.

ASSESSMENTS

Patients recorded their outcomes in the electronic diary,^{22,23} reporting every morning and evening the itch-severity score (with 0 indicating none, 1 indicating mild, 2 indicating moderate, and 3 indicating severe), the number of hives (with 0 indicating none, 1 indicating 1 to 6, 2 indicating 7 to 12, and 3 indicating >12, with an MID of 5.0 to 5.5 for the weekly average), and scores for the size of the largest hive (with 0 indicating none, 1 indicating <1.25 cm, 2 indicating 1.25 to 2.5 cm, and 3 indicating >2.5 cm, with an MID of 4.5 to 5 for the weekly average). The patients reported once daily on interference with sleep and daily activities (on a scale of 0 to 3, with higher scores indicating more interference on each measure), use of rescue medication as provided in 25-mg diphenhydramine tablets (0 to 9 tablets), the presence of angioedema (yes or no), angioedema man-

agement, and any contact with a health care provider (see the Supplementary Appendix for further details). Compliance with reporting in the electronic diary was evaluated throughout the study.

Average daily scores (morning and evening assessments) for itch severity and the number of hives were totaled each week to derive the UAS7.²⁴ Patients completed the Dermatology Life Quality Index (ranging from 0 to 30, with higher scores indicating a worse quality of life and an MID of 2.24 to 3.10)^{25,26} at baseline and at weeks 4, 12, and 28, and the Chronic Urticaria Quality-of-Life Questionnaire (ranging from 0 to 100, with higher scores indicating a worse quality of life) at baseline and at weeks 12 and 28.

STUDY END POINTS

The primary end point was the change from baseline to week 12 in the weekly itch-severity scores. The 12-week score was calculated as the sum of the averaged daily itch-severity score for the previous 7 days, and the baseline score was the sum of the daily itch-severity scores during the 7 days before randomization.

Secondary end points, which were all evaluated at week 12, were changes from baseline in the UAS7 and in the score for the weekly number of hives,²⁴ the time until a reduction from baseline of at least 5 points²³ in the weekly itch-severity score (the MID), the proportions of patients with a UAS7 of 6 or less (considered to represent improvement in disease), the number of patients with a weekly MID response in the itch-severity score, the change from baseline in the score for the size of the largest hive,²⁴ the change from baseline in the overall score on the Dermatology Life Quality Index, and the proportion of angioedema-free days from week 4 to week 12 (see the Supplementary Appendix for further details).

We conducted post hoc analyses of the proportion of patients who were free of hives or free of both hives and itching at week 12 (with the latter indicated by a UAS7 of 0) and 13 additional prespecified subgroup analyses for the primary end point. We assessed as exploratory end points changes from baseline in the use of rescue medication (diphenhydramine) and in the score on the Chronic Urticaria Quality-of-Life Questionnaire.

Safety was evaluated by recording and monitoring the frequency and severity of treatment-emergent adverse events and serious adverse events. Verbatim descriptions of adverse events

were coded with the use of the *Medical Dictionary for Regulatory Activities* (version 15.0) and analyzed with the use of appropriate thesaurus terms.

STATISTICAL ANALYSIS

In estimating the power for determining efficacy, we assumed a mean change from baseline to week 12 in the weekly itch-severity score of 9 points in the omalizumab group and a mean change of 3.5 points in the placebo group, with a common standard deviation of 6 points. Assuming an early discontinuation rate of 15% by week 12, we determined that the enrollment of 300 patients (75 patients in each treatment group) would yield a power of approximately 98% to detect a difference in treatment effect in the primary end point at the 0.05 level for any omalizumab group.

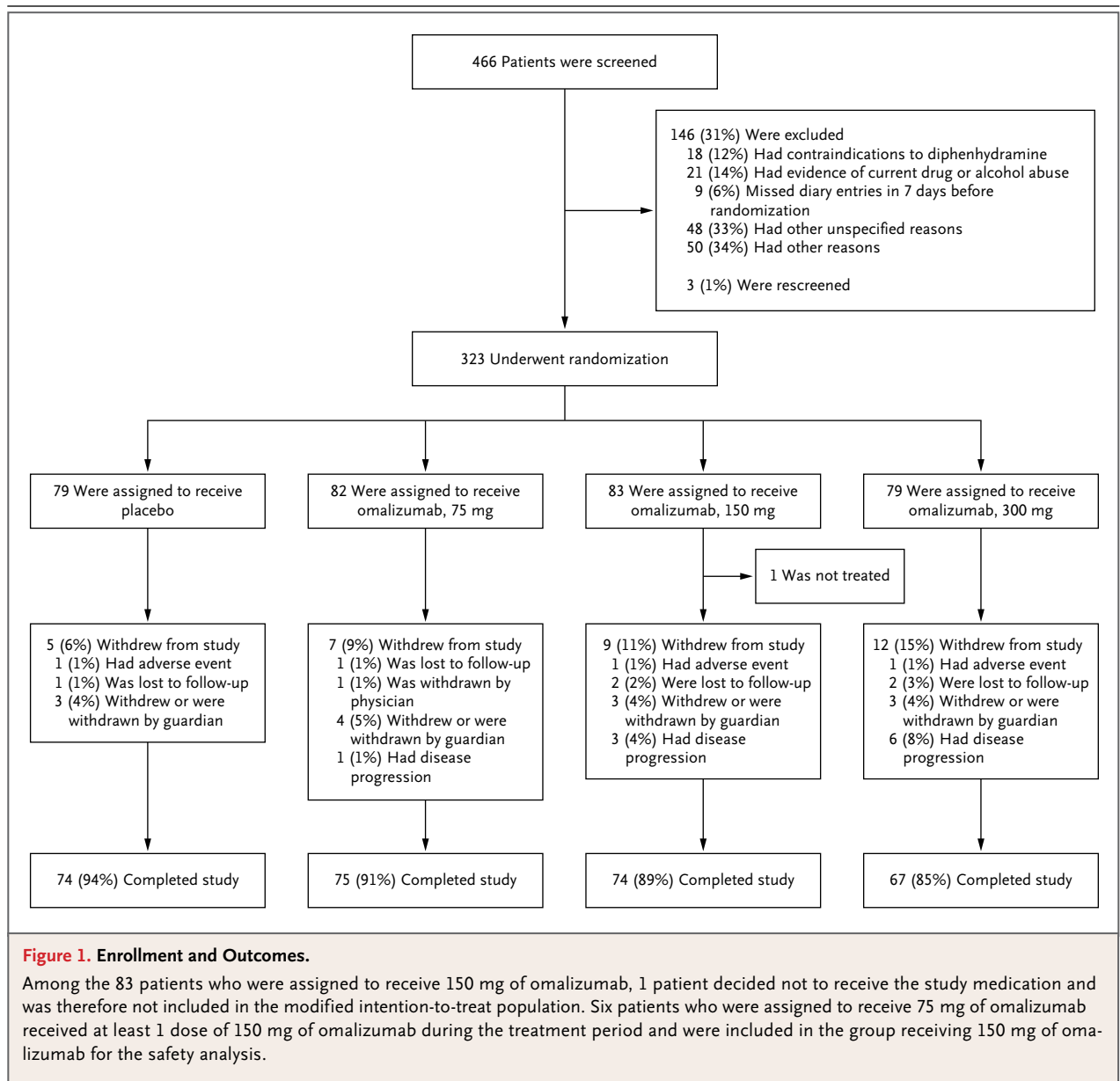
The efficacy analyses were conducted on the basis of data from the modified intention-to-treat population, which included all patients who had undergone randomization and who had received at least one dose of a study drug. The treatment group was defined according to the treatment the patient was assigned to receive, whereas the safety population was defined according to treatment actually received.

For the primary end point, we analyzed differences between each of the omalizumab treatment groups and the placebo group using an analysis-of-covariance model stratified according to the estimated baseline weekly itch-severity score (<13 vs. ≥13) and baseline weight (<80 kg vs. ≥80 kg). The strata were predefined on the basis of the medians reported in a phase 2 clinical study.²⁰ Missing data at week 12 were imputed with the baseline score (baseline observation carried forward). (Additional details on the statistical methods, including analyses of the secondary end points, are provided in the Supplementary Appendix.)

RESULTS

STUDY POPULATION

Of 466 patients who underwent screening, 146 were excluded and 3 were rescreened. The most frequent reasons for exclusion were evidence of current drug or alcohol abuse (14%), contraindications to the use of diphenhydramine (12%), and other reasons that were not specified (33%). Thus, 323 patients underwent randomization and received at least one dose of a study drug in



addition to stable doses of their prerandomization H_1 -antihistamine (Fig. 1). The overall treatment discontinuation rate was 6%, and the overall study discontinuation rate was 10%, with no major differences in these measures among the study groups (see the Supplementary Appendix for further details).

Baseline demographic and clinical characteristics were similar across the study groups (Table 1). For the overall population, the mean ($\pm$ SD) age was 42.5 ± 13.7 , women comprised 76% of patients, 85% were white, the mean body weight

was 82.4 ± 21.9 kg, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 29.8 ± 7.3 . The mean IgE level for patients at baseline was elevated: 168.2 ± 231.9 IU per milliliter (normal range, 13 to 127), with a median of 78 IU per milliliter. The mean time since the diagnosis of chronic idiopathic urticaria was 6.5 ± 8.6 years, the mean number of previous medications for chronic idiopathic urticaria was 4.3 ± 2.7 (Table S1 in the Supplementary Appendix), the mean in-clinic UAS was 5.3 ± 0.7 , the mean UAS7 was 30.7 ± 6.8 ,

the weekly itch-severity score was 14.0 ± 3.7 , the weekly score for the number of hives was 16.7 ± 4.3 , and the use of rescue medication was 7.3 ± 7.8 tablets per week. Angioedema was present during the week before randomization in 41% of patients.

The mean rates of diary compliance were high (>97%) and did not differ significantly across all study groups during the treatment period (Table S2 in the Supplementary Appendix).

EFFICACY

Baseline weekly itch-severity scores were approximately 14 in all treatment groups (Table 1). The mean changes from baseline in weekly itch-severity scores at week 12 (primary end point) were significantly improved in the group receiving 150 mg of omalizumab (-8.1 ± 6.4 , $P=0.001$) and 300 mg of omalizumab (-9.8 ± 6.0 , $P<0.001$) but not in the group receiving 75 mg of omalizumab (-5.9 ± 6.5 , $P=0.46$), as compared with placebo (-5.1 ± 5.6) (Table 2). The reductions from baseline in mean

weekly itch-severity scores were dose-responsive with all three omalizumab doses and were better than the placebo responses at the time points before week 12 (Fig. 2A). After week 12 (follow-up period), the mean weekly itch-severity scores for all omalizumab groups increased to reach values similar to those in the placebo group and did not return to baseline values for the duration of follow-up. Sensitivity analyses for the primary end point that used different methods for handling missing data showed similar results to those of the primary analysis (Tables S3, S4, and S5 in the Supplementary Appendix).

There was a significant difference between the group receiving either 150 mg or 300 mg of omalizumab and the placebo group with respect to all prespecified secondary end points (changes from baseline in UAS7 and the weekly score for the number of hives, the time to the MID in weekly itch-severity scores, the proportion of patients with a UAS7 of ≤ 6 , the proportion of patients with the MID response in weekly itch-severity

Table 1. Baseline Characteristics of the Patients (Modified Intention-to-Treat Population).*

Characteristic	Placebo (N = 79)		Omalizumab	
		75 mg (N = 82)	150 mg (N = 82)	300 mg (N = 79)
Demographic				
Age — yr	43.1±12.5	39.7±15.0	43.0±13.2	44.3±13.7
Age group — no. (%)				
12–17 yr	2 (3)	4 (5)	2 (2)	2 (3)
18–40 yr	30 (38)	42 (51)	32 (39)	31 (39)
41–64 yr	44 (56)	31 (38)	45 (55)	39 (49)
≥65 yr	3 (4)	5 (6)	3 (4)	7 (9)
Female sex — no. (%)	55 (70)	61 (74)	65 (79)	63 (80)
Race — no. (%)†				
White	70 (89)	64 (78)	70 (85)	68 (86)
Nonwhite	6 (8)	16 (20)	6 (7)	9 (11)
Not available	3 (4)	2 (2)	6 (7)	2 (3)
Weight				
Mean — kg	84.3±25.7	82.8±21.2	82.4±20.7	80.3±19.9
<80 kg — no. (%)	41 (52)	43 (52)	41 (50)	41 (52)
Body-mass index‡	30.0±7.7	30.2±7.7	30.0±7.3	29.0±6.3
Clinical				
Time since diagnosis of chronic idiopathic urticaria — yr§				
Mean	7.2±10.7	5.3±7.1	7.2±8.9	6.1±7.3
Median	3.3	2.5	3.9	3.5

Table 1. (Continued.)

Characteristic	Placebo (N=79)	Omalizumab		
		75 mg (N=82)	150 mg (N=82)	300 mg (N=79)
Previous medications for chronic idiopathic urticaria — no.	4.4±2.9	4.1±2.1	4.5±3.2	4.3±2.5
In-clinic UAS¶	5.3±0.7	5.4±0.8	5.3±0.7	5.3±0.7
UAS7 **	31.0±6.6	30.7±6.9	31.4±7.0	29.5±6.9
Weekly itch-severity score**††	14.0±3.4	14.0±3.7	14.2±4.1	13.7±3.5
Weekly score for no. of hives**‡‡	17.0±4.2	16.8±4.2	17.1±4.1	15.8±4.6
Overall score on Dermatology Life Quality Index§§	12.6±5.9¶¶	12.6±6.5	13.0±6.1	12.7±6.4
Presence of angioedema — no. (%)**	30 (38)	31 (38)	38 (46)	32 (41)
Weekly no. of diphenhydramine tablets (25 mg) as rescue medication**	7.1±7.7	7.8±9.0	7.5±7.7	6.7±6.8

* Plus-minus values are means ±SD. The modified intention-to-treat population included all patients who had undergone randomization and received at least one dose of a study drug. There were no significant differences among the groups at baseline. Percentages may not total 100 because of rounding.

† Race was self-reported.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Data are for 77 patients in the placebo group, 80 in the group assigned to receive 75 mg of omalizumab, 81 in the group assigned to receive 150 mg of omalizumab, and 76 in the group assigned to receive 300 mg of omalizumab.

¶ The urticaria activity score (UAS) ranges from 0 to 6, with higher scores indicating greater activity. This value was defined as the largest value among those obtained on screening visits on days 14 and 7 before randomization and on the day 1 visit.

|| The UAS during a 7-day period (UAS7) ranges from 0 to 42, with higher scores indicating greater activity and a minimally important difference (MID) of 9.5 to 10.5.

** These values are based on data that were collected in a patient daily diary in the week before randomization.

†† Daily scores for itch severity were 0 indicating none, 1 indicating mild, 2 indicating moderate, and 3 indicating severe, with weekly totals ranging from 0 to 21 and an MID of 5 or more points.

‡‡ Daily scores for the number of hives were 0 indicating none, 1 indicating 1 to 6, 2 indicating 7 to 12, and 3 indicating ≥12, and an MID of 5.0 to 5.5 for the weekly average.

§§ The Dermatology Life Quality Index ranges from 0 to 30, with higher scores indicating a worse quality of life and an MID of 2.24 to 3.10.

¶¶ This value was measured in 78 patients in the placebo group.

scores, the change from baseline in the score for the size of the largest hive, the change from baseline in the overall Dermatology Life Quality Index, and the proportion of angioedema-free days from weeks 4 to 12) (Table 2, and Table S6 and Fig. S1 through S6 in the Supplementary Appendix), except for the difference in the number of angioedema-free days from week 4 to week 12, which reached significance only in the 300-mg group. Similar to weekly itch-severity scores, the weekly score for the number of hives decreased with all three doses of omalizumab to a greater extent than with placebo throughout the 12-week treatment period, with the largest difference observed in the 300-mg group (Fig. 2B). After week 12 (i.e., during the follow-up period), the mean weekly score for the number of hives for all omalizumab groups increased to reach values similar to those in the placebo

group and did not return to baseline values for the duration of follow-up.

The exploratory analysis of scores on the Chronic Urticaria Quality-of-Life Questionnaire showed similar results to those from the other end points that were assessed in this study (Fig. S7 in the Supplementary Appendix).

In the post hoc analyses at week 12, the proportions of patients who were completely free of hives were 10% in the placebo group, 18% in the group receiving 75 mg of omalizumab, 23% in the group receiving 150 mg of omalizumab, and 53% in the group receiving 300 mg of omalizumab; among patients who were free of both hives and itching (i.e., a UAS7 score of 0), the proportions were 5%, 16%, 22%, and 44%, respectively (Fig. S8 and S9 in the Supplementary Appendix).

At baseline, the mean number of diphenhydramine tablets (25 mg) that patients were taking as

Table 2. Primary and Secondary Efficacy End Points (Modified Intention-to-Treat Population).*

End Point	Placebo (N = 79)	Omalizumab		
		75 mg (N = 82)	150 mg (N = 82)	300 mg (N = 79)
Primary end point				
Itch-severity score				
Change from baseline to wk 12				
Mean	−5.1±5.6	−5.9±6.5	−8.1±6.4	−9.8±6.0
Median (range)	−4.0 (−20.5 to 6.0)	−6.5 (−21.0 to 10.0)	−8.5 (−21.0 to 5.1)	−10.5 (−21.0 to 4.5)
Least-squares mean difference for treatment vs. placebo (95% CI)†	NA	−0.7 (−2.5 to 1.2)	−3.0 (−4.9 to −1.2)‡	−4.8 (−6.5 to −3.1)§
Secondary end points				
Weekly no. of hives				
Change from baseline to week 12				
Mean	−5.2±6.6	−7.2±7.0	−9.8±7.3	−12.0±7.6
Median (range)	−2.4 (−19.5 to 5.5)	−6.5 (−21.0 to 8.5)	−10.0 (−21.0 to 3.0)	−13.0 (−21.0 to 10.5)
Least-squares mean difference for treatment vs. placebo (95% CI)¶	NA	−2.0 (−4.1 to −0.1)	−4.5 (−6.7 to −2.4)§	−7.1 (−9.3 to −4.9)§
Patients with UAS7 ≤6 at wk 12 — no. (%)	15 (19)	22 (27)	35 (43)‡	52 (66)§
Overall score on Dermatology Life Quality Index				
Change from baseline to week 12				
Mean	−6.1±7.5	−7.5±7.2	−8.3±6.3	−10.2±6.8
Median (range)	−5.0 (−25.0 to 13.0)	−7.0 (−26.0 to 11.0)	−8.0 (−27.0 to 6.0)	−10.0 (−27.0 to 8.0)
Least-squares mean difference for treatment vs. placebo (95% CI)**	NA	−1.7 (−3.8 to 0.5)	−2.5 (−4.6 to −0.4)††	−3.8 (−5.9 to −1.7)§
Angioedema-free days from wk 4 through wk 12 — %‡‡				
Mean	89.7±18.7	93.5±14.8	91.7±17.3	96.3±12.5
Median (range)	100.0 (15.4 to 100.0)	100.0 (30.4 to 100)	100.0 (14.3 to 100.0)	100 (17.9 to 100.0)§

* Plus-minus values are means ±SD. Missing scores for week 12 were imputed from baseline weekly scores. NA denotes not applicable.

† Least-squares means were estimated with the use of an analysis of covariance (ANCOVA) model stratified according to the baseline weekly itch-severity score (<13 vs. ≥13) and baseline weight (<80 kg vs. ≥80 kg).

‡ P<0.01 for the comparison with placebo.

§ P<0.001 for the comparison with placebo.

¶ The ANCOVA model was stratified according to the baseline weekly number of hives (<median vs. ≥median) and baseline weight (<80 kg vs. ≥80 kg).

|| The baseline score on the Dermatology Life Quality Index was obtained before administration of a study drug on day 1, and there was no imputation for missing scores for week 12.

** The ANCOVA model was stratified according to the baseline overall score on the Dermatology Life Quality Index (<median vs. ≥median) and baseline weight (<80 kg vs. ≥80 kg).

†† P=0.02 for the comparison with placebo.

‡‡ Angioedema-free days were 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 nonmissing diary entry starting at the week 4 visit and ending the day before the week 12 visit. Patients who withdrew before the week 4 visit or who had missing responses for more than 40% of the daily diary entries between the week 4 and week 12 study visits were not included in this analysis.

rescue medication was 7.3±7.8. The mean changes from baseline in the weekly number of tablets were -2.3±6.1 in the group receiving 75 mg of omalizumab (P=0.91), -3.7±6.0 in the group receiving 150 mg of omalizumab (P=0.07), and -4.1±5.4 in the group receiving 300 mg of omalizumab (P=0.01), as compared with -2.2±5.0 in the placebo group (Fig. S10 in the Supplementary Appendix).

In prespecified subgroup analyses for the pri-

mary end point, no meaningful interpretation of results or definitive conclusions could be made because of the reduced sample sizes for these analyses (data not shown).

SAFETY

The percentages of patients with at least one adverse event were similar across the treatment groups: 61% in the placebo group, 59% in those receiving 75 mg of omalizumab, 67% in those receiving 150 mg of omalizumab, and 65% in those receiving 300 mg of omalizumab (Table 3, and Table S7 in the Supplementary Appendix). During the 28-week study period, there were reports of nine serious adverse events, with five reported in the group receiving 300 mg of omalizumab (6%), two in the placebo group (3%), and one each in the groups receiving 75 mg and 150 mg of omalizumab (1% for each). Most of the adverse events were reported in the 150-mg and 300-mg groups during the follow-up period, when no drug was being administered (Table 3, and Table S8 in the Supplementary Appendix). No deaths or episodes of anaphylactic shock were reported during the study. There were no major imbalances in any of the system organ classes affected by adverse events, with the exception of headache, with more cases being reported in the group receiving 150 mg of omalizumab than in the placebo group. (Additional details on safety information are provided in the Supplementary Appendix.)

DISCUSSION

In this study, we found that omalizumab administered as three doses of 150 mg or 300 mg at 4-week intervals significantly reduced symptoms, as compared with placebo, in patients with chronic idiopathic urticaria who remained symptomatic despite the use of approved doses of H₁-antihistamines. Significant and clinically meaningful effects were seen for patients receiving either 150 mg or 300 mg of omalizumab in the change from baseline in the weekly itch-severity score (primary end point) and all secondary end points at week 12, with the exception of the proportion of angioedema-free days during week 4 through week 12 in the group receiving 150 mg of the drug. Furthermore, the safety profile for omalizumab was similar to that previously reported in omalizumab-treated patients with allergic asthma.^{13,14,27,28} However, the majority of serious adverse events

occurred in the group receiving the highest dose (300 mg) of omalizumab.

Omalizumab had an onset of effect within a week after initiation in this patient population (Fig. 2, and Fig. S1 in the Supplementary Appendix). The median time to MID response in the weekly itch-severity score was significantly shorter in the group receiving 300 mg of omalizumab (1 week) and in the group receiving 150 mg (2 weeks) than in the placebo group (4 weeks) (Table 2). The phase 2 studies also showed reductions in the UAS and UAS7 during the first week of omalizumab treatment.^{20,21}

The duration of suppression in the weekly itch-severity score after week 12 was greater in patients receiving the higher doses (150 mg and 300 mg) of omalizumab. There did not appear to be a rebound increase in symptoms back to baseline during the course of the study once omalizumab had been discontinued. However, it is possible that some patients' symptoms during follow-up may have remained under better control because they were allowed to take an additional H₁-antihistamine during this period. In the placebo group, after an initial small reduction in the mean weekly itch-severity score during the first couple of weeks, scores remained unchanged for the remainder of the study period. The observation that symptoms gradually recur after discontinuation (as shown by the increase in mean itch-severity scores and scores for the number of hives after week 12) suggests that omalizumab administered as three doses at 4-week intervals did not substantially modify the basic underlying disease process in this population during this time period (Fig. 2).

The mechanism by which omalizumab works to improve urticaria has not been fully elucidated. It has been reported that patients with active chronic idiopathic urticaria have abnormal basophil function, including suppression of the high-affinity IgE receptor (FcεRI) pathway (related to altered expression of Src homology 2-containing inositol phosphatase), blood basopenia, and recruitment of basophils to skin-lesion sites.¹² In patients with chronic idiopathic urticaria in remission, blood basopenia and suppressed FcεRI function revert toward normal.¹² In previous studies, the binding of circulating IgE by omalizumab has been shown to lead to a reduction in free IgE within hours after administration and down-regulation of FcεRI on blood basophils

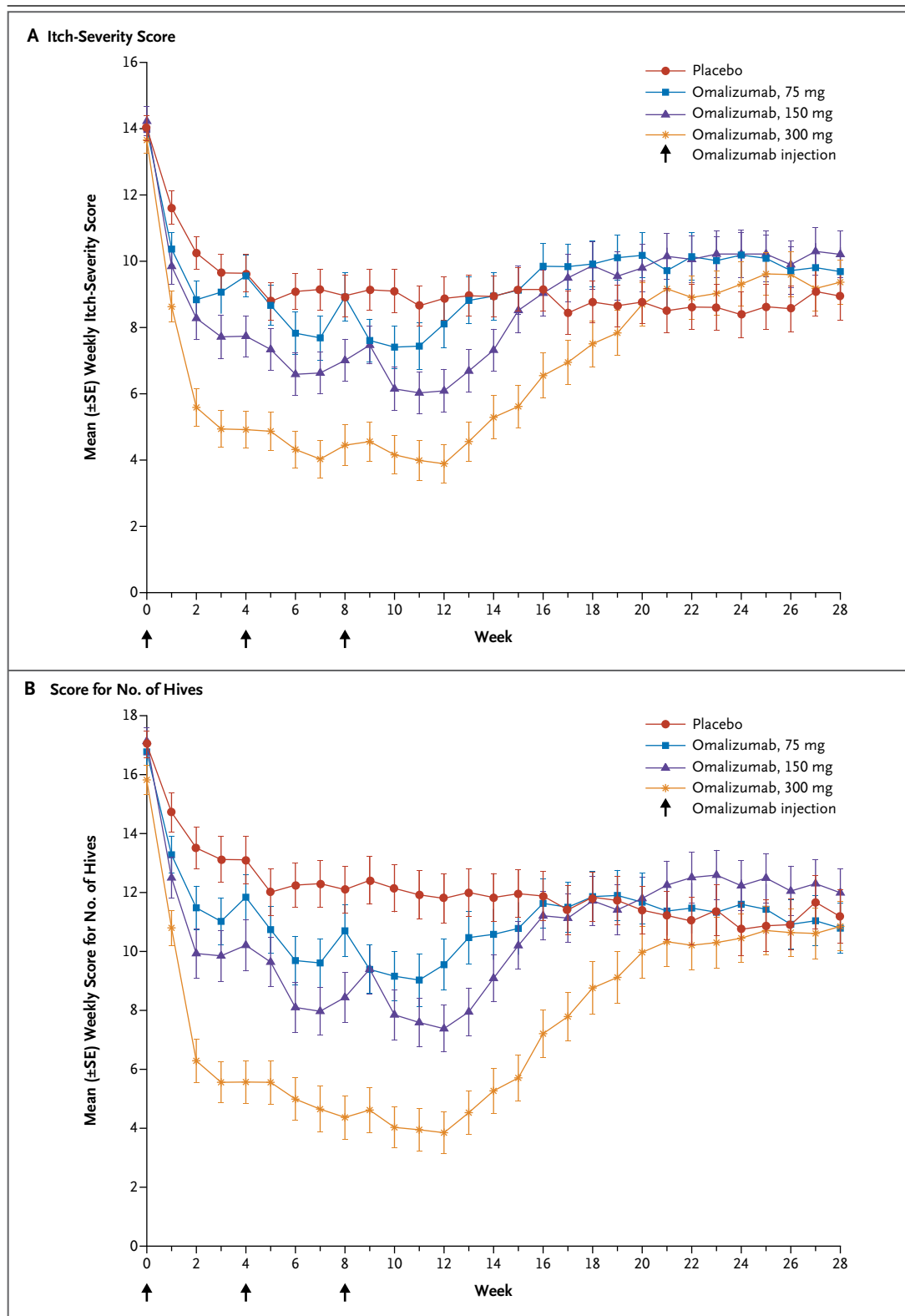


Table 3. Adverse Events (Safety Population).*

Event	Placebo (N = 79)	Omalizumab		
		75 mg (N = 76)	150 mg (N = 88)	300 mg (N = 79)
		<i>no. of patients (%)</i>		
At least one adverse event	48 (61)	45 (59)	59 (67)	51 (65)
Any adverse event leading to discontinuation of study drug	0	3 (4)	2 (2)	0
Early withdrawal from study due to an adverse event	1 (1)	0	1 (1)	0
Any serious adverse event†	2 (3)	1 (1)	1 (1)	5 (6)
Death	0	0	0	0
Any adverse event suspected to be caused by study drug	3 (4)	7 (9)	8 (9)	7 (9)
Any severe adverse event‡	7 (9)	4 (5)	5 (6)	6 (8)

* The safety population was defined according to the treatment actually received. A complete list of adverse events is provided in Table S7 in the Supplementary Appendix.

† The nine reported serious adverse events were pneumonia and hemorrhoids in one patient each in the placebo group; angioedema in one patient in the 75-mg group; angioedema and idiopathic urticaria in one patient in the 150-mg group; and melanoma in situ, nephrolithiasis, idiopathic urticaria, tonsillectomy, and melena in one patient each in the 300-mg group. After a review of the hospital discharge summary after the database lock, it was determined that the patient with melena had no anemia; the cause of hospital admission was elective endoscopy for nonanemic melena. The patient underwent upper gastrointestinal endoscopy and colonoscopy, which revealed only diverticulosis with no other potential source of bleeding. Thus, it was determined that this patient had a nonserious event of nonanemic melena rather than a serious adverse event, as initially reported. Additional details about the serious adverse events are provided in Table S8 in the Supplementary Appendix.

‡ A severe adverse event was defined as the occurrence of symptoms causing an inability to perform usual social and functional activities. A complete description of the severe adverse events is provided in the Safety section in the Supplementary Appendix.

within 2 weeks; in mast cells, reduction in FcεRI expression and degranulation typically occurs after 8 weeks.^{15,29,30} This study was not designed to further elucidate the mechanism of action of omalizumab in patients with chronic idiopathic urticaria.

In conclusion, during the initial 12 weeks of our study, omalizumab at doses of 150 mg and 300 mg significantly improved outcomes as re-

ported by patients with chronic idiopathic urticaria who remained symptomatic despite the use of approved doses of H₁-antihistamines. The number of patients who were treated was too small to draw any definitive safety conclusions, but serious adverse events were more common in the group treated with the highest dose of omalizumab. Further work is needed before the exact role of omalizumab in the treatment of chronic idiopathic or spontaneous urticaria can be defined.

Figure 2 (facing page). Mean Weekly Symptom Scores.

Mean weekly symptom scores are shown for itch severity, with totals ranging from 0 to 21 and with higher scores indicating greater severity (Panel A), and the number of hives, with daily totals of 0 indicating none, 1 indicating 1 to 6 hives, 2 indicating 7 to 12 hives, and 3 indicating more than 12 hives (for weekly totals of 0 to 21) (Panel B). Data are for patients in the modified intention-to-treat population (i.e., all patients who underwent randomization and received at least one dose of a study drug).

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Dr. Maurer reports receiving consulting fees from Uriach Pharma and UCB, advisory board fees from Uriach Pharma, lecture fees from Sanofi, Merck, FAES, Uriach Pharma, and Almirall, and grant support through his institution from Uriach Pharma; Dr. Rosén, being an employee of Genentech and having an equity interest in Roche; Drs. Hsieh and Doyle, being employees of and having an equity interest in Genentech; Dr. Saini, receiving consulting fees from Array, Kendle, MedImmune, Paracetylics, and Regeneron; Dr. Giménez-Arnau, receiving payment for serving on advisory boards from Uriach Pharma, Almirall, Basilea, and Unilever, payment for expert testimony on Sara Lee

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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SUPPLEMENTARY APPENDIX

Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria

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METHODS

STUDY DESIGN

Treatment administration

Each patient received two injections of study medication at every treatment visit, administered subcutaneously to patients in the deltoid region of the right or left arm. Alternatively the injections could be administered in the thigh if medically significant reasons preclude administration in the deltoid region. To minimize the risk of potential bias arising from access to laboratory results that could potentially unblind treatment assignments (e.g., free IgE levels and serum omalizumab concentrations), access to these results was restricted to the site and the Sponsor until study completion.

Randomization and Allocation to Treatment Groups

Eligible patients were randomly assigned (in a 1:1:1:1 ratio using an Interactive Voice and Web Response System) to receive omalizumab (75, 150, or 300 mg) or placebo by subcutaneous injection every 4 weeks during the 12-week double-blind treatment period. Randomization to treatment groups was stratified by baseline weekly itch severity score (ISS) (<13 vs. ≥13), baseline weight (<80 kg vs. ≥80 kg), and study site. A hierarchical dynamic randomization scheme was used to achieve overall balance between treatment groups and within strata. The hierarchy levels were overall study treatment balance, treatment balance within the baseline weekly ISS strata, treatment balance within the body weight strata, and balance within each study center. A biased-coin assignment is used when the imbalance at a given level exceeded the specified threshold.

DATA MONITORING COMMITTEE MEMBERS

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Anthony Gaspari M.D

Abdelmonem Afifi Ph.D

PATIENTS

The long-acting H₁-antihistamines and doses allowed during the study were cetirizine (5 or 10 mg once per day [QD]); levocetirizine dihydrochloride (2.5 or 5 mg QD); fexofenadine (60 mg twice per day or 180 mg QD); loratadine (10 mg QD); and desloratadine (5 mg QD).

STUDY ENDPOINTS

EVALUATION OF PATIENT-REPORTED DIARY OUTCOMES

The European Academy of Allergy and Clinical Immunology has proposed using the urticaria activity score (UAS), a combined score of itch severity and number of hives, as the official disease activity measure.¹ The Urticaria Patient Daily Diary, developed according to the United States 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 chronic idiopathic urticaria/chronic spontaneous urticaria patients.^{2,3} Patients were instructed to ask for help in counting and measuring hives located on the back or in a place that was hard to reach.

For occurrence of angioedema (yes/no), if the response was yes, patients were to record how the angioedema was treated (0=no treatment, 1=took medication, 2=called doctor/nurse, 3=visited doctor/nurse, 4=visited the emergency room, and 5=hospitalization).

STATISTICAL ANALYSIS

A sample of 75 patients per treatment group was calculated to provide approximately 98% power to detect a difference in treatment effect in the primary endpoint at the 0.05 level for any omalizumab group. This estimation of power assumes the mean change from baseline to Week 12 in weekly ISS to be 9 points with omalizumab and 3.5 points with placebo, with an SD of 6 points, and an early discontinuation rate of 15% (based on data from the Phase II studies^{4,5}). All statistical tests were two-sided with an overall significance level of 0.05 and

adjustment for multiple comparisons was performed according to the type-I error control plan.

Kaplan-Meier estimates of the distribution of time to first minimum important difference (MID) response in weekly ISS (i.e. time to a reduction from baseline in ≥ 5 points) were used to estimate the median time to MID. The treatment comparisons (between each of the omalizumab groups and the placebo group) were performed using the Cox proportional hazards model stratified by baseline weekly ISS (<13 vs. ≥ 13) and baseline weight (<80 kg vs. ≥ 80 kg).

For the proportions of patients with UAS7 ≤ 6 or MID response for weekly ISS at Week 12, treatment comparisons were performed using the Cochran-Mantel-Haenszel test stratified by baseline scores for the respective endpoint ($<\text{median}$ vs. $\geq\text{median}$) and baseline weight (<80 kg vs. ≥ 80 kg). The treatment comparison for the proportion of angioedema-free days from Weeks 4 to 12 was conducted using a stratified Wilcoxon rank-sum test, stratified by presence of angioedema at baseline (yes vs. no) and baseline weight (80 kg vs. ≥ 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 levels, the testing of the primary endpoint was conducted in the following hierarchical order:

Stage 1: omalizumab 300-mg group vs. placebo; 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 vs. placebo; 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 vs. placebo; the statistical test was conducted at a significance level of 0.05.

For secondary efficacy endpoints, a hierarchical analysis was performed for each omalizumab dose found to be significant at the primary endpoint, with all tests conducted at a significance level of 0.05. A P-value <0.05 could only be claimed 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, i.e. 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:

- Stage1: 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 itch severity score MID response at Week 12
- Stage 4: proportion of patients with UAS7 ≤ 6 at Week 12
- Stage 5: proportion of weekly itch severity score 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 (DLQI) at Week 12
- Stage 8: proportion of angioedema-free days from Week 4 to Week 12 of therapy.

RESULTS

STUDY POPULATION

Details of most frequent previous CIU/CSU medications prior to patients' enrollment in the study are shown in Table S1.

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

EFFICACY

Sensitivity analyses

Sensitivity analyses for the primary endpoint are presented in Tables S3–S5.

Secondary endpoints

Data for Time to MID in Weekly Itch Score, Proportions of Responders at Week 12 (Itch MID), Change from Baseline at Week 12 in UAS7 and Change from Baseline at Week 12 in Size of Largest Hive Score are presented in Table S6.

Time to MID in Weekly Itch Score

See Supplementary Appendix Fig. S1.

Proportions of Responders at Week 12 (UAS ≤ 6)

See Supplementary Appendix Fig. S2.

Proportions of Responders at Week 12 (Itch MID)

See Supplementary Appendix Fig. S3.

Change from Baseline at Week 12 in UAS7

See Supplementary Appendix Fig. S4.

Change from Baseline at Week 12 in Size of Largest Hive Score

See Supplementary Appendix Fig. S5.

Change from Baseline at Week 12 in DLQI

See Supplementary Appendix Fig. S6.

Mean Change from Baseline in Chronic Urticaria Quality-of-Life Questionnaire at Week 12

See Supplementary Appendix Fig. S7

Patients Who Were Completely Hive-Free at Week 12

See Supplementary Appendix Fig. S8.

Proportion of Patients Who Were Itch- and Hive-Free (UAS7=0) at Week 12

See Supplementary Appendix Fig. S9

Mean Change from Baseline in Number of Tablets/Week of Diphenhydramine

See Supplementary Appendix Fig. S10

SAFETY

Adverse events (AEs), severe AEs and serious AEs were low across the treatment groups.

There was a slightly higher incidence of serious AEs seen in the omalizumab 300 mg treatment group versus other treatment groups.

Severe AEs were reported in 7 (8.9%), 4 (5.3%), 5 (5.7%) and 6 (7.6%) patients in the placebo, 75-mg, 150-mg and 300-mg groups, respectively. These severe AEs occurred in each treatment groups as follows:

Placebo group: hemorrhoids and gastrointestinal varices (N=1); neck edema (N=1); upper respiratory tract infection (N=1); lower respiratory tract infection (N=1); neck injury (N=1); joint-related signs/symptoms (N=2); pruritis (N=1); urticarias (N=1).

75-mg group: influenza viral infection (N=1); headache (N=1); angioedemas (N=1); urticarias (N=4).

150-mg group: neck pain and discomfort (N=1); upper respiratory tract infection (N=1); angioedemas (N=2); urticarias (N=3).

300-mg group: asthenic conditions (N=1); musculoskeletal and connective tissue pain and discomfort (N=1); tendon disorders (N=1); mononeuropathies (N=1); urticarias (N=2).

The reported melanoma in situ in one patient in the omalizumab 300-mg group was a pre-malignant condition and not considered treatment related (see Supplementary Appendix Tables S7–8).

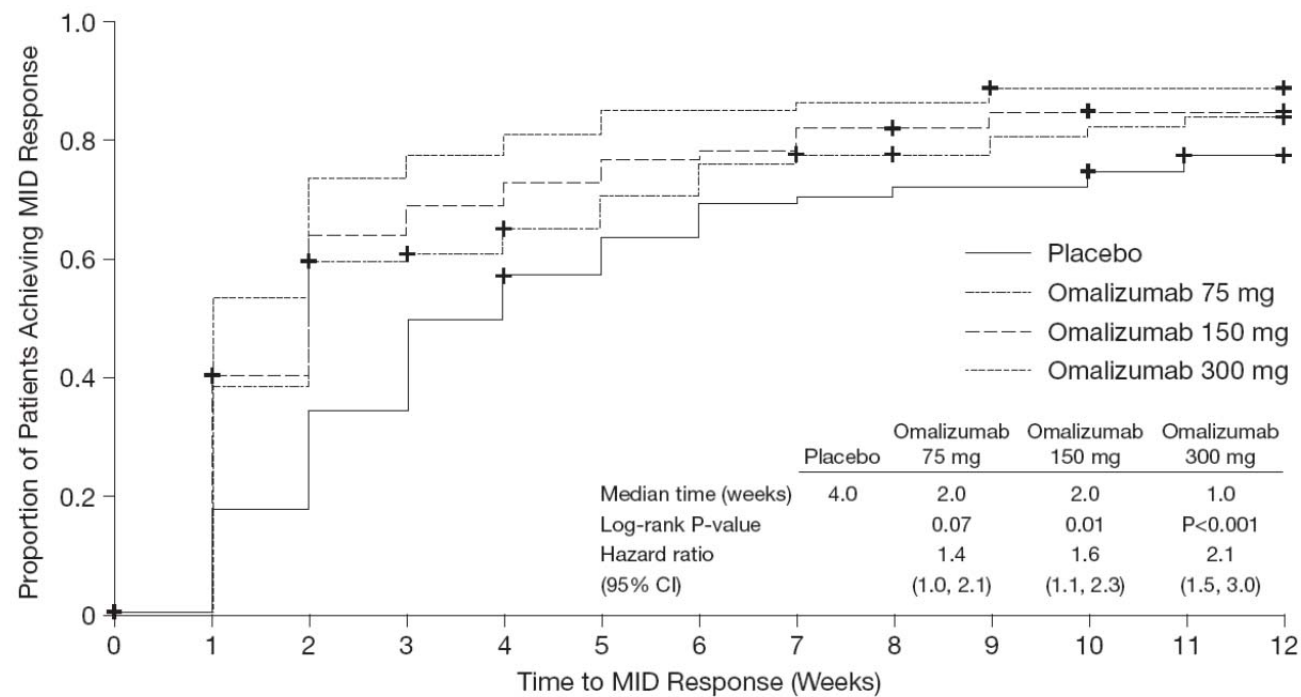
There were no cases of anaphylactic shock reported in the study. Based on the broad standardized medical dictionary for regulatory activities query search of symptoms forming possible components of anaphylaxis there were two cases reported fulfilling Sampson criteria:⁶

- A 49-year-old female who received omalizumab 75 mg, experienced moderate edema of the left eye and mouth on Day 31, which resolved on Day 35. The patient received no treatment for these events and there was no change in study drug as a result of these events. The investigator assessed the events as non serious and not related to study drug. The patient had a medical history of angioedema.
- A 27-year-old male who received omalizumab 75 mg, experienced severe angioedema (eyes and lips), severe urticaria, and mild dyspnea on Day 1, which resolved between Days 3 and 5. The patient received treatment (prednisone) for angioedema and urticaria in the emergency room. There was no change in study drug due to these events. The severe angioedema event history for this patient dates back to >2 years, and in the interval over the 2 years prior to study enrollment, the patient had multiple angioedema events every 2–

3 months which were characterized as severe events with mild dyspnea. The investigator assessed the angioedema event as serious and not related to the study drug.

SUPPLEMENTARY FIGURES

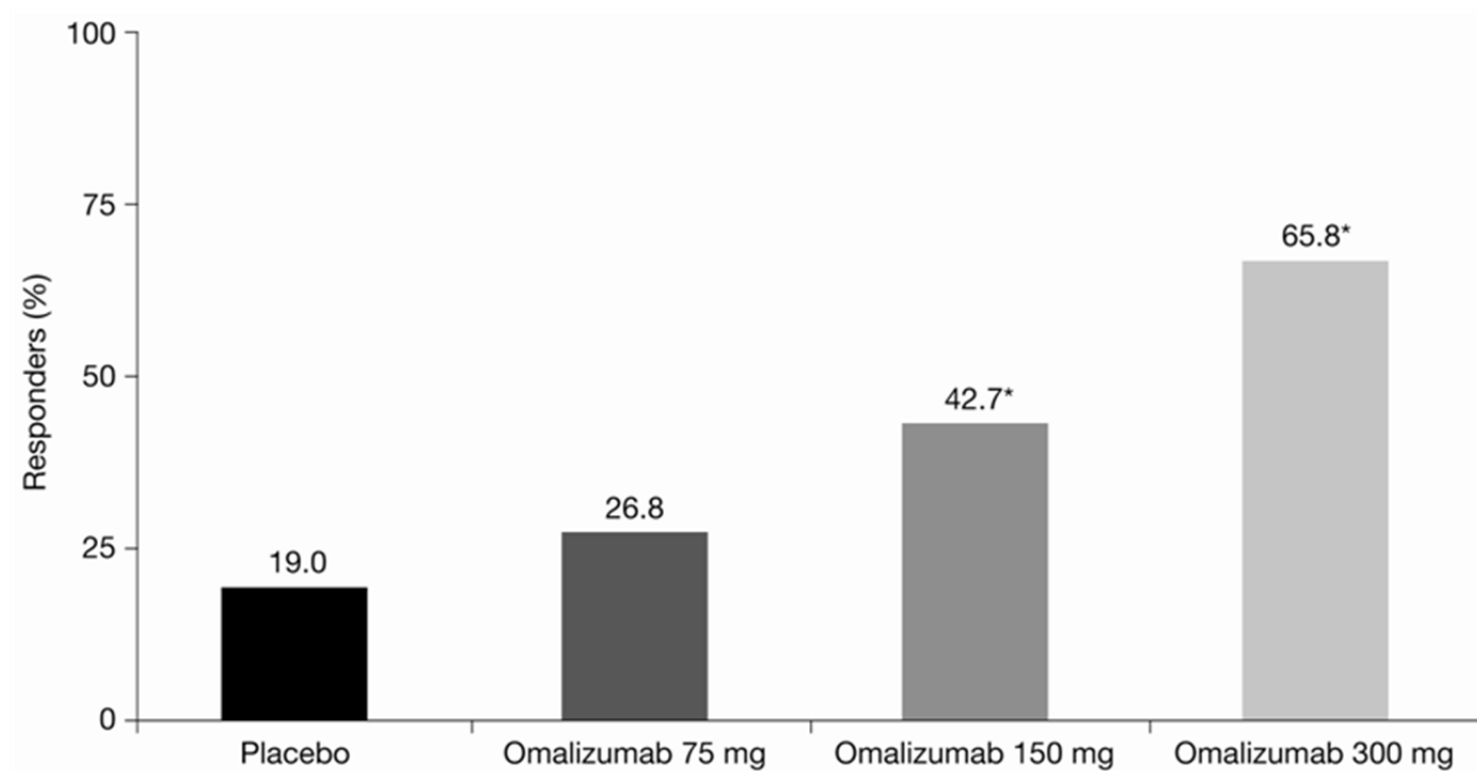
Figure S1. Time to MID* in Weekly Itch Score (mITT Population).



MID denotes minimum important difference, and mITT modified intention-to-treat population.

*Kaplan-Meier estimate.

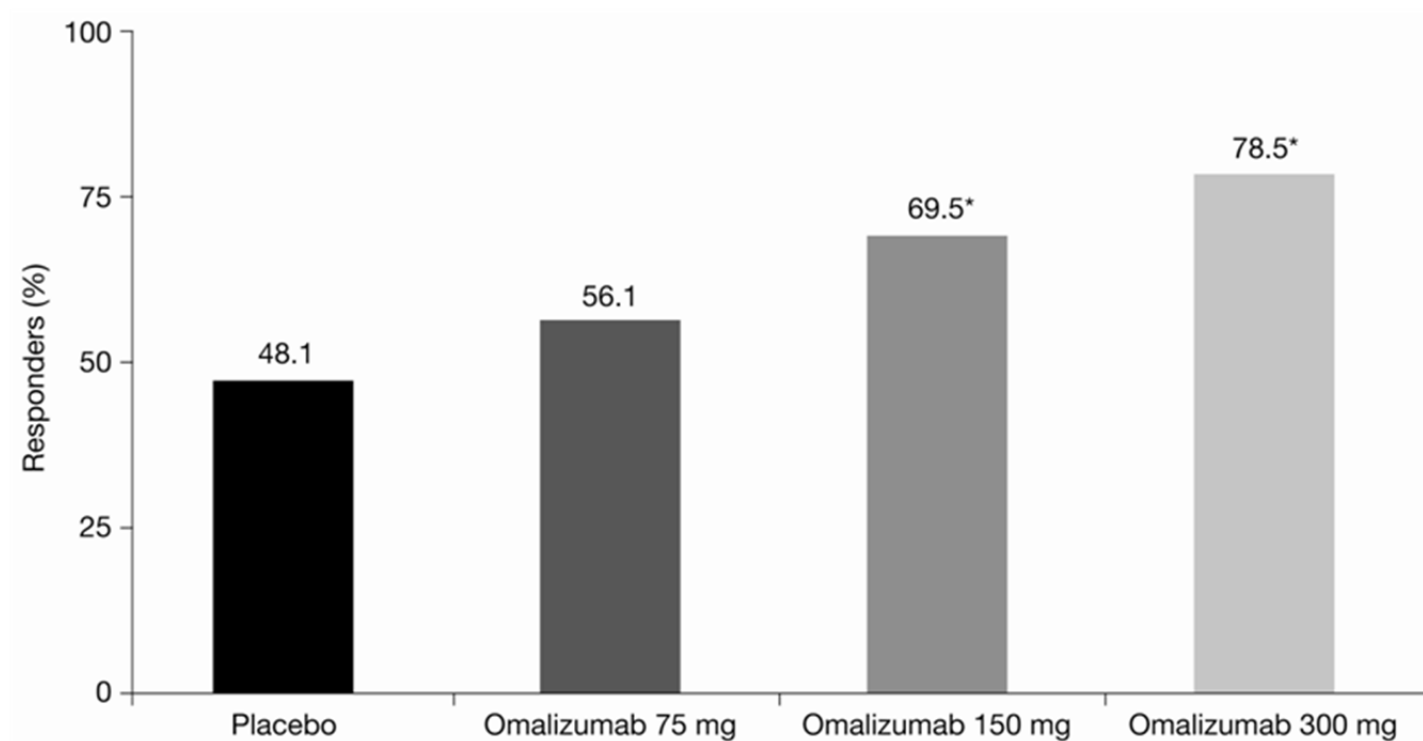
Figure S2. Proportions of Responders at Week12 (UAS≤6; mITT Population).



mITT denotes modified intention-to-treat population, and UAS urticaria activity score.

*statistically significant ($P < 0.05$) vs. placebo, according to statistical analysis plan.

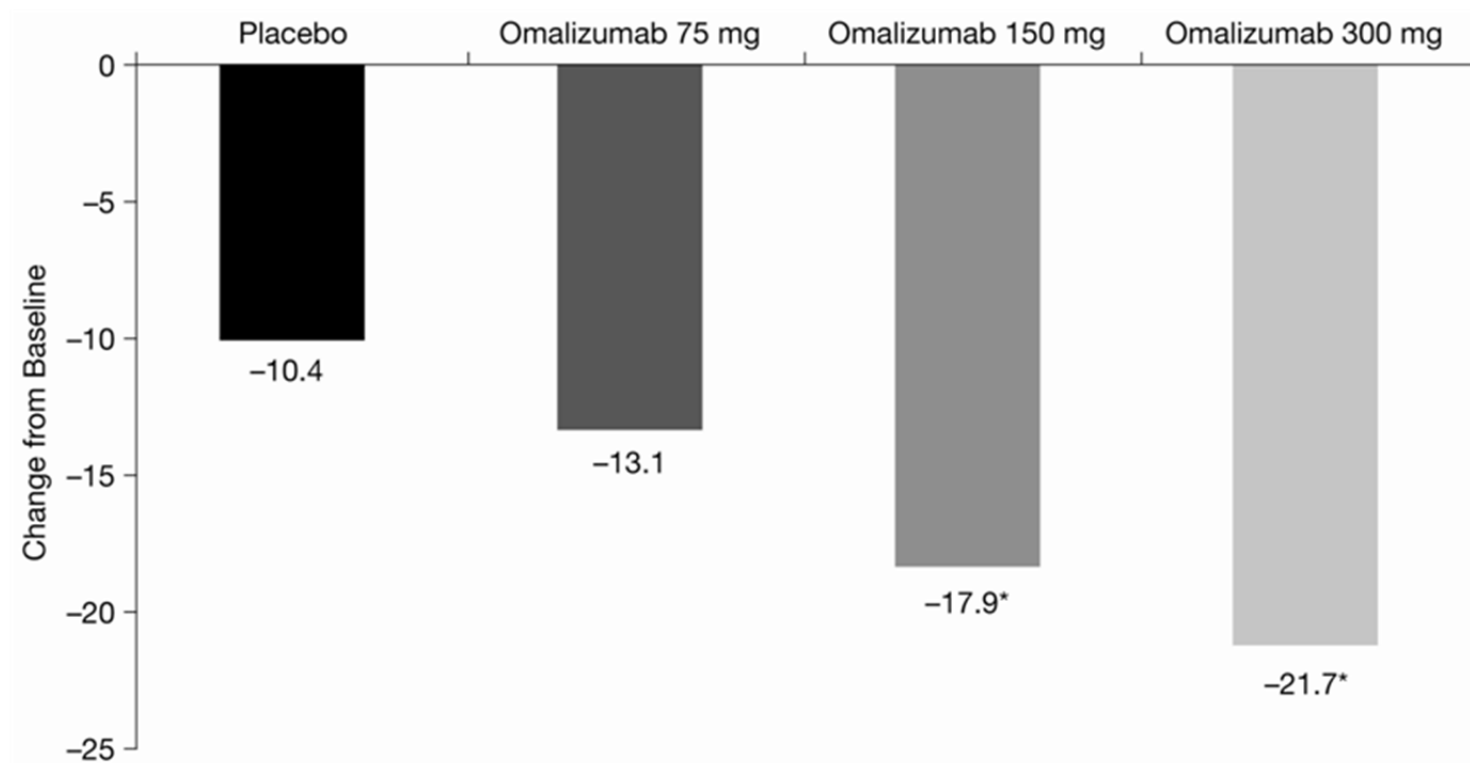
Figure S3. Proportions of Responders at Week12 (Itch MID; mITT Population).



MID denotes minimum important difference, and mITT modified intention-to-treat population.

*statistically significant ($P<0.05$) vs. placebo, according to statistical analysis plan.

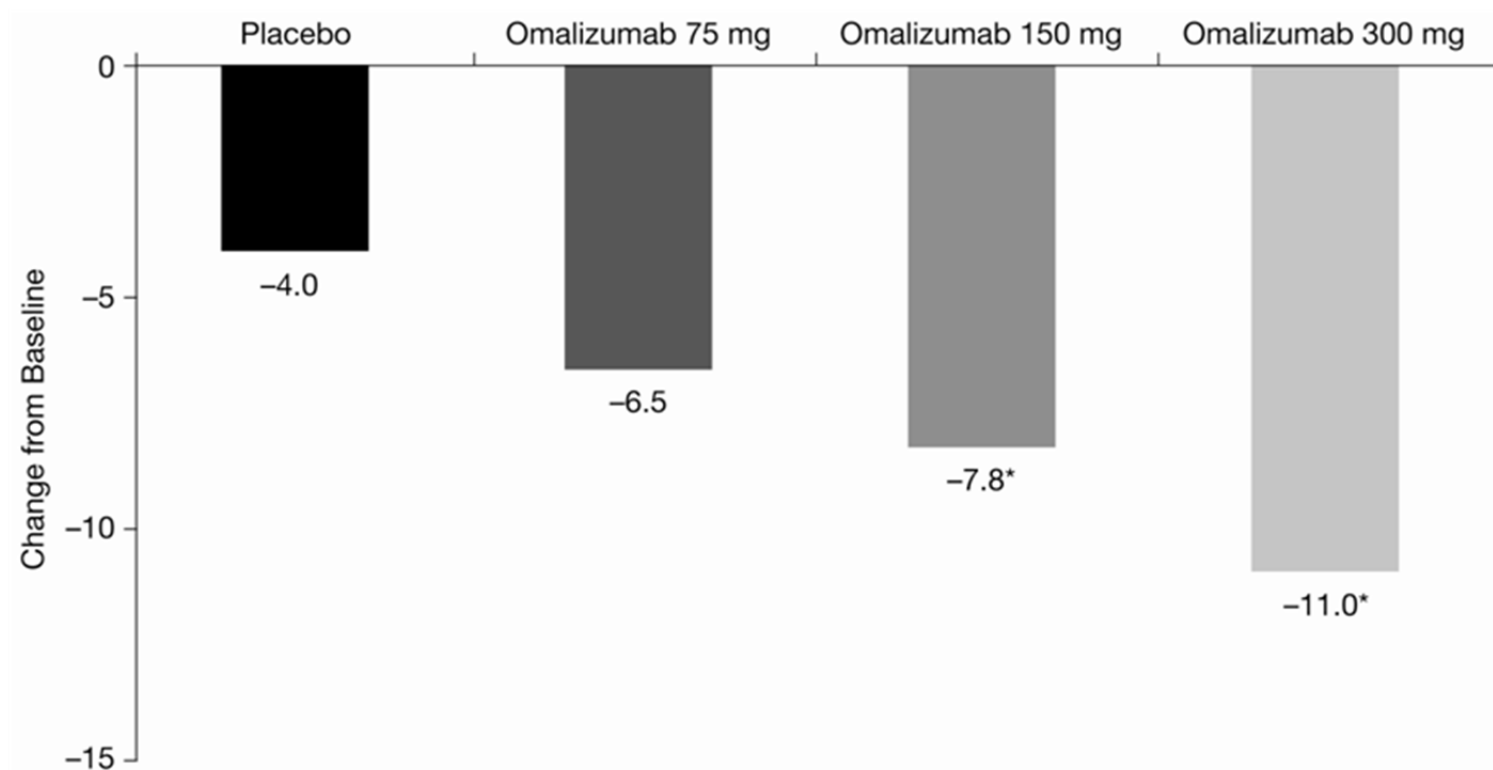
Figure S4. Change from Baseline at Week12 UAS7 (mITT Population).



mITT denotes modified intention-to-treat population, and UAS7 urticaria activity score over 7 days.

*statistically significant ($P<0.05$) vs. placebo, according to statistical analysis plan.

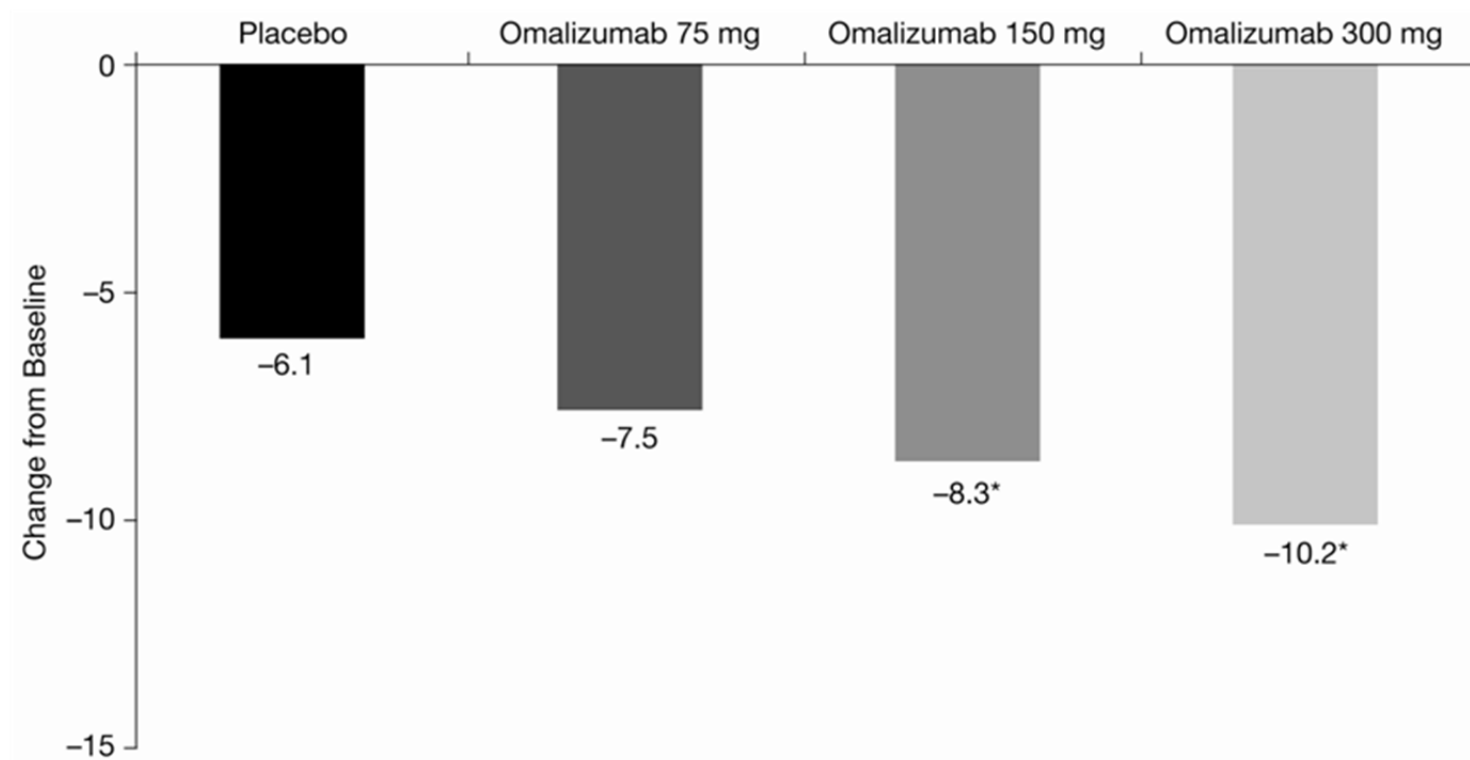
Figure S5. Change from Baseline at Week 12 in Size of Largest Hive Score (mITT Population).



mITT denotes modified intention-to-treat population.

*statistically significant ($P<0.05$) vs. placebo, according to statistical analysis plan.

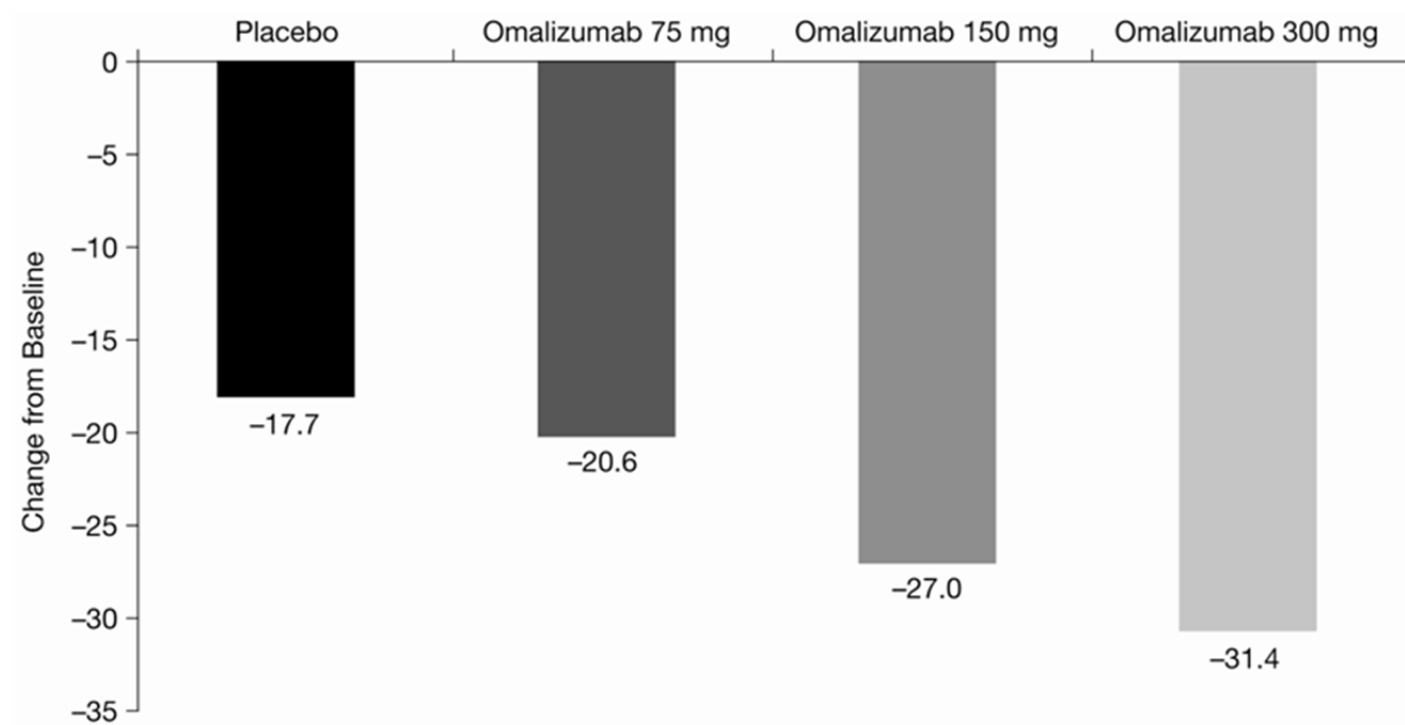
Figure S6. Change from Baseline at Week12 in DLQI (mITT Population).



DLQI denotes Dermatology Life Quality Index, and mITT modified intention-to-treat population.

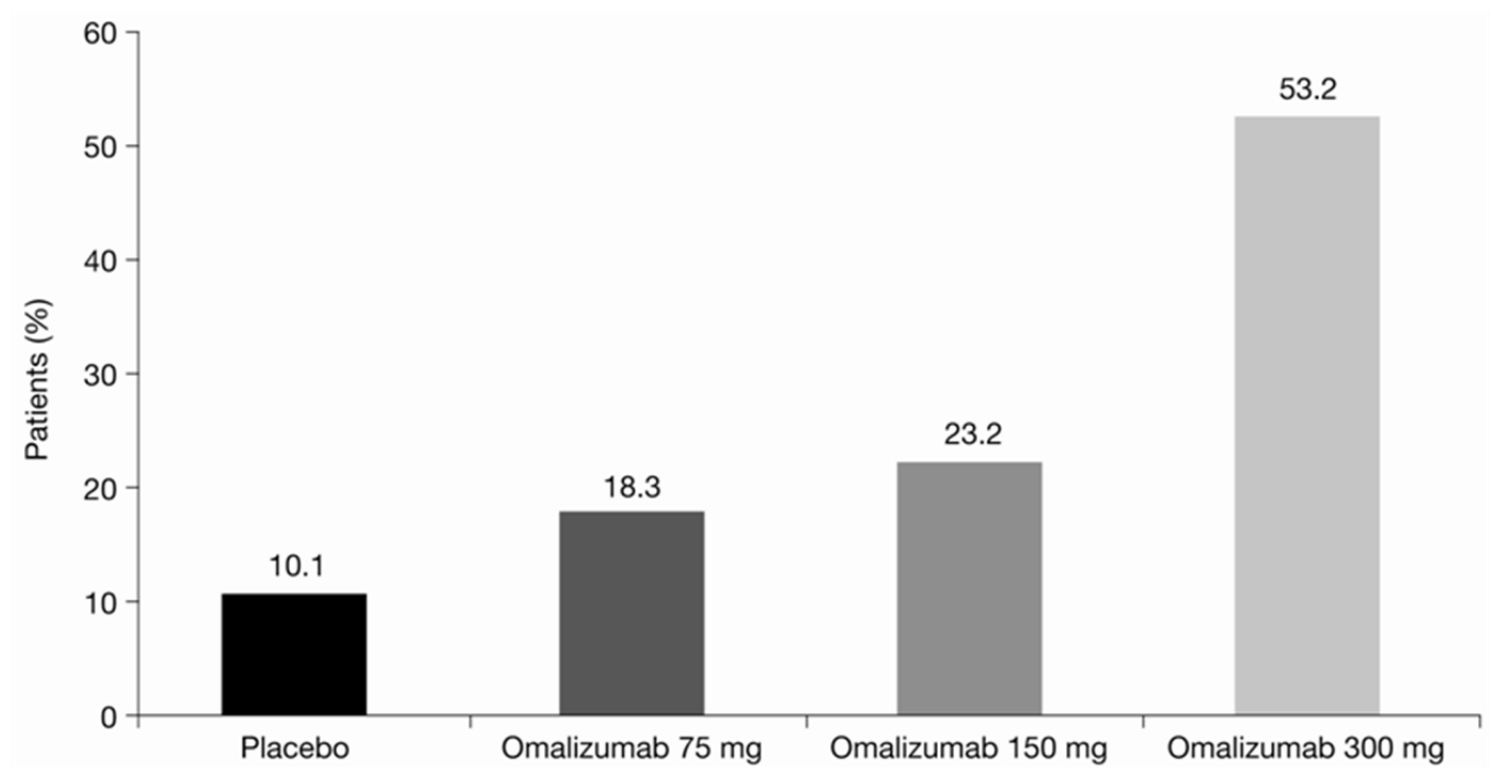
*statistically significant ($p < 0.05$) vs. placebo, according to statistical analysis plan.

Figure S7. Mean Change from Baseline in Chronic Urticaria Quality-of-Life Questionnaire at Week 12 (mITT Population).



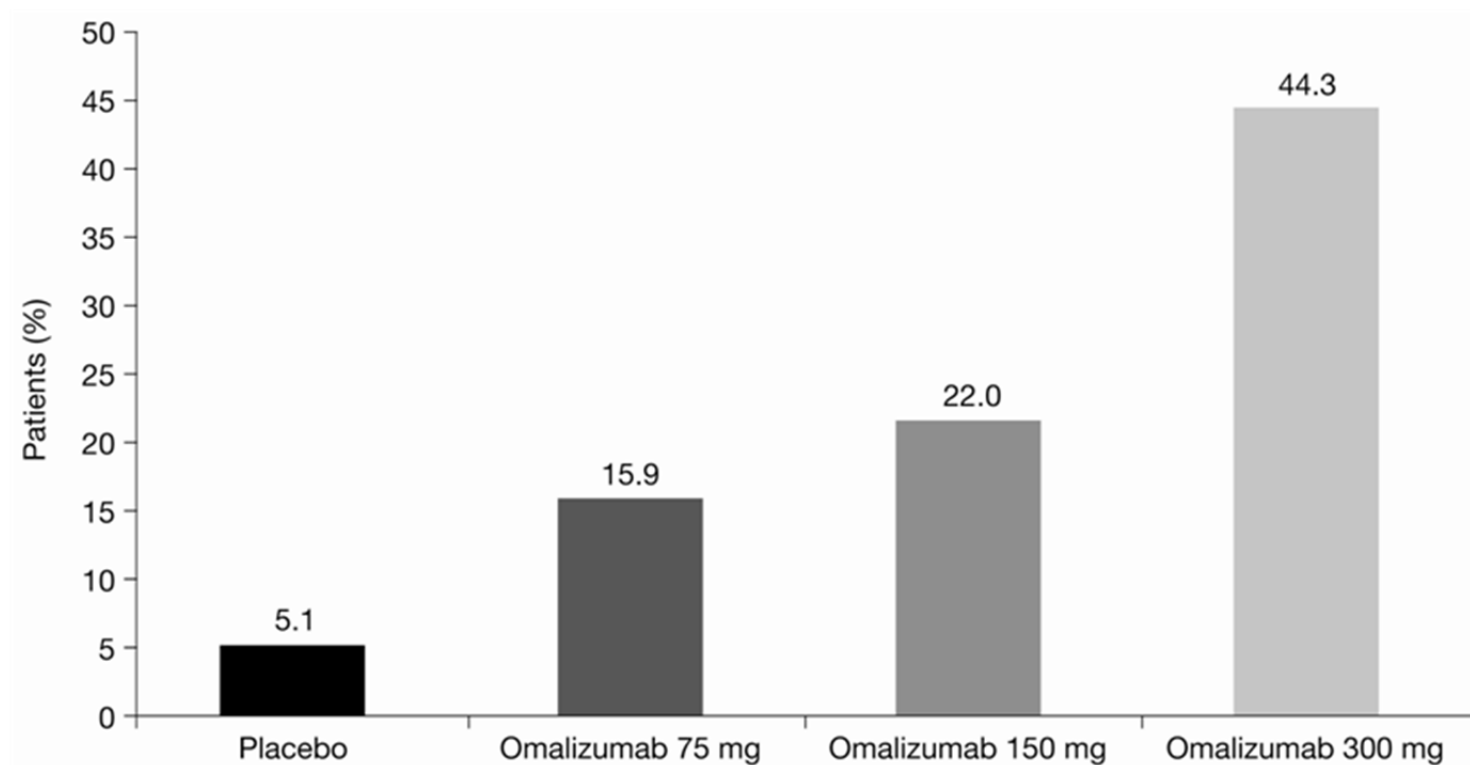
mITT denotes modified intention-to-treat population.

Figure S8. Patients Who Were Completely Hive-Free at Week 12 (mITT Population).



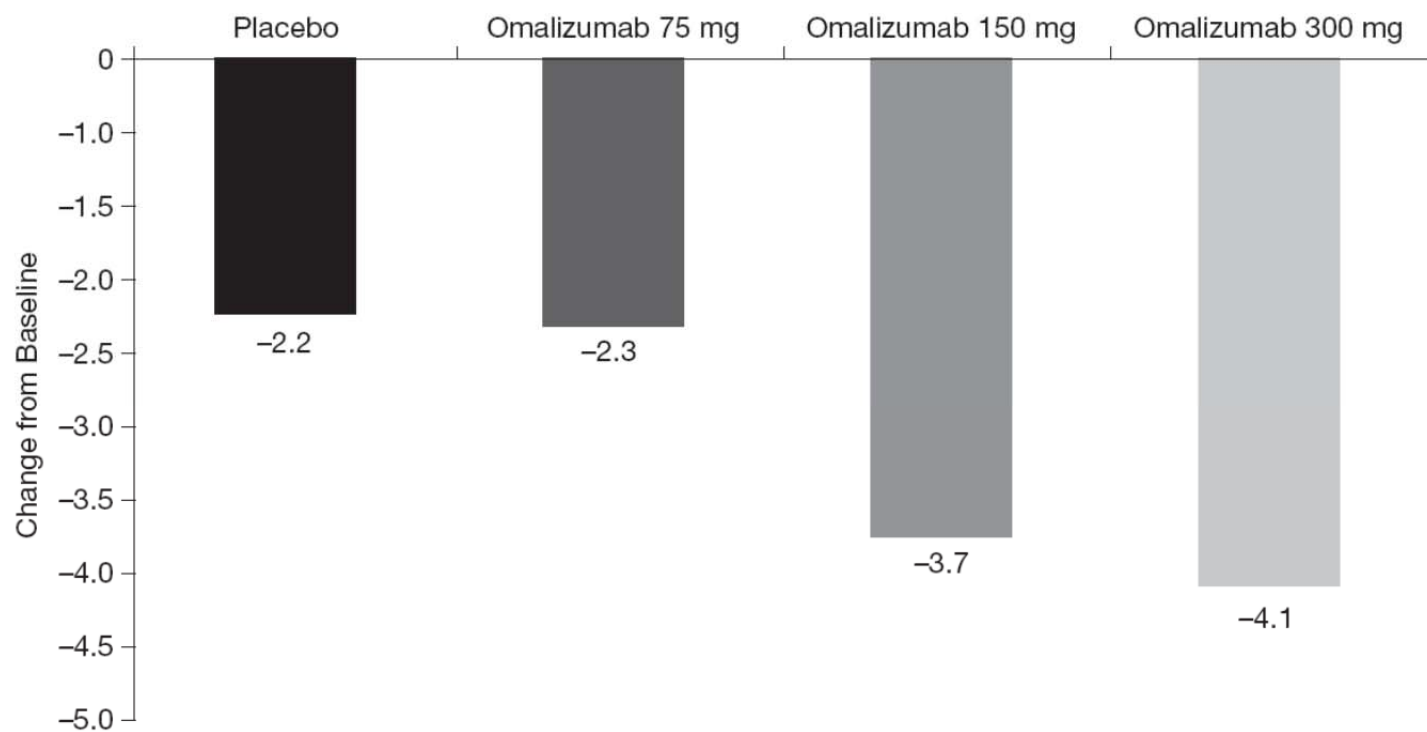
mITT denotes modified intention-to-treat population.

Figure S9. Proportion of Patients Who Were Itch- and Hive-Free (UAS7=0) at Week 12 (mITT Population; Ad-Hoc Analysis).



mITT denotes modified intention-to-treat population, and UAS7 urticaria activity score over 7 days.

Figure S10. Mean Change from Baseline in Number of Tablets/Week of Diphenhydramine (mITT Population).



mITT denotes modified intention-to-treat population.

SUPPLEMENTARY TABLES

Table S1. Most frequent prior steroid, immunosuppressant, LTRA and H2-antihistamine use for CIU/CSU before enrollment in the study (mITT)

Medication Class, N (%)	Placebo (N=79)	Omalizumab 75 mg (N=82)	Omalizumab 150 mg (N=82)	Omalizumab 300 mg (N=79)
Steroids, overall	41 (51.9)	46 (56.1)	38 (46.3)	36 (45.6)
Prednisone	21 (26.6)	29 (35.4)	21 (25.6)	18 (22.8)
Prednisolone	6 (7.6)	5 (6.1)	8 (9.8)	5 (6.3)
Immunosuppressants, overall	9 (11.4)	3 (3.7)	9 (11.0)	5 (6.3)
Cyclosporine	8 (10.1)	3 (3.7)	8 (9.8)	5 (6.3)
LTRAs, overall	21 (26.6)	17 (20.7)	30 (36.6)	15 (19.0)
Montelukast sodium	20 (25.3)	17 (20.7)	30 (36.6)	12 (15.2)
H2-antihistamines, overall	25 (31.6)	24 (29.3)	38 (46.3)	26 (32.9)
Ranitidine hydrochloride	16 (20.3)	15 (18.3)	16 (19.5)	17 (21.5)

mITT denotes modified intention-to-treat population.

LTRA, leukotriene receptor antagonist

Table S2. Diary Compliance Rate (mITT Population).*

	Placebo (N=79)	Omalizumab 75 mg (N=76)	Omalizumab 150 mg (N=88)	Omalizumab 300 mg (N=79)
Treatment period (up to Week 12)				
N	79	82	82	79
Mean (±SD) – %	97.2±8.4	97.8±6.3	98.9±6.0	98.6±4.3
Range – %	57.6–100.0	53.6–100.0	46.7–100.0	66.4–100.0
>85% – n (%)	73 (92.4)	79 (96.3)	81 (98.8)	78 (98.7)
Follow-up period (after Week 12)				
N	76	78	80	77
Mean (±SD) – %	94.9±13.7	95.5±12.6	96.3±11.4	97.6±5.6
Range – %	21.6–100.0	16.4–100.0	8.3–100.0	69.8–100.0
>85% – n (%)	69 (87.3)	74 (90.2)	75 (91.5)	73 (92.4)

mITT denotes modified intention-to-treat population.

*Compliance defined as filling out the diary at least once per day. The eDiary was time/date stamped to ensure data were not included outside of each assessment period.

Table S3. Sensitivity analysis for the Primary Efficacy Endpoint using the worst-case scenario for missing data (mITT Population)^a

Itch Severity Score at Week 12 (Imputation using the worst-case scenario for missing data)	Placebo (N=79)	Omalizumab 75 mg (N=82)	Omalizumab 150 mg (N=82)	Omalizumab 300 mg (N=79)
Change from baseline				
Mean (±SD)	-5.8±5.4	-5.8±6.5	-7.9±6.8	-9.8±6.0
Median (range)	-5.0 (-20.5, 6.0)	-6.5 (-21.0, 10.0)	-8.5 (-21.0, 9.4)	-10.5 (-21.0, 4.5)
LSM treatment difference vs. placebo (95% CI) [†]		-0.1 (-1.8, 1.9)	-2.2* (-4.0, -0.3)	-4.8*** (-5.8, -2.5)

CI denotes confidence interval, LSM least squares mean, and mITT modified intention-to-treat population

^aData imputed using worst-case scenario for missing data

[†]LSMs were estimated using an analysis of covariance (ANCOVA) model stratified by baseline weekly itch severity score (<13 vs. ≥13) and baseline weight (<80 kg vs. ≥80 kg).

*P<0.05; ***P<0.001 (derived from ANCOVA t-test).

Table S4. Sensitivity analysis for the Primary Efficacy Endpoint using LOCF method (mITT Population)^a

Itch Severity Score at Week 12 (Imputation using the LOCF method)	Placebo (N=79)	Omalizumab 75 mg (N=82)	Omalizumab 150 mg (N=82)	Omalizumab 300 mg (N=79)
Change from baseline				
Mean (±SD)	−5.5±5.7	6.6±6.4	−8.2 ±6.4	10.1±5.6
Median (range)	−5.0 (−20.5, 7.0)	−7.5 (−21.0, 10.0)	−8.8 (−21.0, 5.1)	−11.0 (−21.0, 4.5)
LSM treatment difference vs. placebo (95% CI) [†]		−1.1 (−2.88, 0.76)	−2.8* (−4.6, −1.01)	−4.9*** (−6.5, −3.3)

CI denotes confidence interval, LOCF last observation carried forward, LSM least squares mean, and mITT modified intention-to-treat population.

^aData imputed using LOCF

[†]LSMs were estimated using an analysis of covariance (ANCOVA) model stratified by baseline weekly itch severity score (<13 vs. ≥13) and baseline weight (<80 kg vs. ≥80 kg).

*P<0.05, ***P<0.001 (derived from ANCOVA t-test).

Table S5. Sensitivity analysis for the Primary Efficacy Endpoint using the mixed effects model (mITT Population)^a

Itch Severity Score at Week 12 (Longitudinal mixed effects model)	Placebo (N=79)	Omalizumab 75 mg (N=82)	Omalizumab 150 mg (N=82)	Omalizumab 300 mg (N=79)
N	69	70	73	76
LSM treatment difference vs. placebo (95% CI) [†]		-1.2 (-3.1, 0.7)	-2.8** (-4.6, -1.0)	-4.8*** (-6.5, -3.2)

CI denotes confidence interval, LSM least squares mean, and mITT modified intention-to-treat population

^aData imputed using mixed effects model

[†]LSM and p-values were derived from a mixed effects model with the following covariates: baseline weekly itch severity score (original scale), and baseline weight (<80 kg vs. ≥80 kg).

P<0.01, *P<0.001

Table S6. Secondary endpoints (mITT population)^a

Secondary Endpoints	Placebo (N=79)	Omalizumab 75 mg (N=82)	Omalizumab 150 mg (N=82)	Omalizumab 300 mg (N=79)
UAS7				
Change from baseline to Week 12				
Mean (±SD)	−10.4±11.6	−13.1±12.7	−17.9±13.2	−21.7±12.8
Median (range)	−6.1 (−34.0, 11.0)	−13.2 (−42.0, 11.5)	−19.8 (−42.0, 6.4)	−25.0 (−42.0, 13.5)
LSM treatment difference vs. placebo (95% CI) [†]	–	−2.7 (−6.5, 1.1)	−7.7*** (−11.5, −3.9)	−12.4*** (−16.1, −8.7)
Time to MID Response for Weekly Itch Severity Score – Weeks				
Median (95% CI) [¶]	4.0 (3.0, 5.0)	2.0 (2.0, 3.0)	2.0 (1.0, 2.0)	1.0 (1.0, 2.0)
Minimum, maximum	1.0, 12.0+	0, 12.0+	1.0, 12.0+	1.0, 12.0+
Hazard ratio vs. placebo (95% CI)	–	1.43 (1.0, 2.1)	1.6* (1.1, 2.3)	2.1** (1.5, 3.0)
Patients with MID Response in Weekly Itch^{aa} Severity Score at Week 12 – No. (%)	38 (48.1)	46 (56.1)	57** (69.5)	62*** (78.5)

Secondary Endpoints	Placebo (N=79)	Omalizumab 75 mg (N=82)	Omalizumab 150 mg (N=82)	Omalizumab 300 mg (N=79)
Weekly Size of Largest Hive Score				
Change from baseline to Week 12				
Mean ($\pm$ SD)	-4.0 $\pm$ 5.6	-6.5 $\pm$ 6.3	-7.8 $\pm$ 6.8	-11.0 $\pm$ 7.2
Range	-18.5, 7.5	-21.0, 7.5	-21.0, 1.5	-21.0, 7.5
LSM treatment difference vs. placebo (95% CI) ^{§§}	–	-2.5** (-4.3, -0.7)	-3.8*** (-5.6, -1.9)	-7.2*** (-9.0, -5.3)

^aMissing Week 12 scores were imputed from baseline weekly score.

[†]ANCOVA model stratified by baseline UAS7 (<median vs. $\geq$ median) and baseline weight (<80 kg vs. $\geq$ 80 kg).

[¶]Based on Kaplan–Meier estimates.

^{||}Estimated using Cox proportional hazards models stratified by baseline weekly itch severity score (<13 vs. $\geq$ 13) and baseline weight (<80 kg vs. $\geq$ 80 kg).

^{aa}If a patient discontinued treatment before Week 12, the patient was counted as a non-responder (i.e. UAS7 >6 or did not achieve the MID response in weekly itch severity score) at Week 12.

^{§§}ANCOVA model stratified by baseline weekly size of largest hive score (<median vs. $\geq$ median) and baseline weight (<80 kg vs. $\geq$ 80 kg).

Table S7. Summary of Treatment-Emergent Adverse Events According to Study Group (≥3% in Any Group; Safety Population).

	No. of patients (%)			
MedDRA System Organ Class	Placebo	Omalizumab 75mg	Omalizumab 150mg	Omalizumab 300mg
Preferred Term	(N=79)	(N=76)	(N=88)	(N=79)
Any adverse event	48 (60.8)	45 (59.2)	59 (67.0)	51 (64.6)
Gastrointestinal disorders				
Overall	12 (15.2)	6 (7.9)	12 (13.6)	9 (11.4)
Diarrhea	4 (5.1)	2 (2.6)	4 (4.5)	3 (3.8)
General disorders and administration site conditions				
Overall	6 (7.6)	10 (13.2)	7 (8.0)	6 (7.6)
Edema, peripheral	1 (1.3)	3 (3.9)	1 (1.1)	1 (1.3)
Infections and infestations				
Overall	30 (38.0)	26 (34.2)	34 (38.6)	28 (35.4)
Nasopharyngitis	13 (16.5)	13 (17.1)	12 (3.6)	10 (12.7)
Influenza	4 (5.1)	5 (6.6)	3 (3.4)	2 (2.5)
Upper respiratory tract infection	7 (8.9)	0	2 (2.3)	5 (6.3)
Sinusitis	2 (2.5)	3 (3.9)	1 (1.1)	6 (7.6)
Bronchitis	2 (2.5)	4 (5.3)	0	2 (2.5)

	No. of patients (%)			
MedDRA System Organ Class	Placebo	Omalizumab 75mg	Omalizumab 150mg	Omalizumab 300mg
Preferred Term	(N=79)	(N=76)	(N=88)	(N=79)
Urinary tract infection	1 (1.3)	4 (5.3)	3 (3.4)	0
Viral upper respiratory tract infection	1 (1.3)	1 (1.3)	4 (4.5)	1 (1.3)
Musculoskeletal and connective tissue disorders				
Overall	9 (11.4)	4 (5.3)	9 (10.2)	9 (11.4)
Arthralgia	4 (5.1)	1 (1.3)	1 (1.1)	4 (5.1)
Nervous system disorders				
Overall	8 (10.1)	9 (11.8)	19 (21.6)	8 (10.1)
Headache	5 (6.3)	4 (5.3)	16 (18.2)	8 (10.1)
Respiratory, thoracic and mediastinal disorders				
Overall	8 (10.1)	8 (10.5)	4 (4.5)	7 (8.9)
Cough	3 (3.8)	4 (5.3)	2 (2.3)	2 (2.5)
Epistaxis	3 (3.8)	0	0	0
Skin and subcutaneous tissue disorders				
Overall	7 (8.9)	14 (18.4)	14 (15.9)	14 (17.7)
Idiopathic urticaria	2 (2.5)	8 (10.5)	6 (6.8)	4 (5.1)

	No. of patients (%)			
MedDRA System Organ Class	Placebo	Omalizumab 75mg	Omalizumab 150mg	Omalizumab 300mg
Preferred Term	(N=79)	(N=76)	(N=88)	(N=79)
Urticaria	2 (2.5)	2 (2.6)	4 (4.5)	1 (1.3)
Angioedema	1 (1.3)	3 (3.9)	2 (2.3)	1 (1.3)
Vascular disorders				
Overall	2 (2.5)	0	3 (3.4)	3 (3.8)
Hypertension	2 (2.5)	0	2 (2.3)	3 (3.8)

Note: Both urticaria and idiopathic urticaria were terms that could be selected by the investigator

MedDRA denotes Medical Dictionary for Regulatory Activities.

Table S8. Summary of Treatment-Emergent Serious Adverse Events According to Treatment Group, Reported During the Treatment period and During the 16-Week Follow-up Period (Safety Population).

Treatment Group	No. of Patients Who Experienced any serious AEs, N (%)	Serious AE (Preferred Term)	Days from First Treatment	Days from Last Treatment
Serious AEs During the 12-Week Treatment Period				
Placebo	2 (2.5)	Pneumonia	44	9
		Hemorrhoids	4	4
Omalizumab 75mg	1 (1.3)	Angioedema [†]	1	1
Omalizumab 150 mg	–			
Omalizumab 300 mg	2 (2.5)	Tonsillectomy	79	23
		Melena [§]	39	18
Serious AEs During the 16-Week Follow-up Period (no study drug administered)				
Placebo	–			
Omalizumab 75mg	–			
Omalizumab 150 mg	1 (1.1)*	Urticaria	109	50
		Angioedema [†]	109	50
		Idiopathic urticaria	144	85

Omalizumab 300 mg	3 (3.8)	Melanoma in situ	121	63
		Nephrolithiasis	104	48
		Idiopathic urticaria	147	90

AE denotes adverse event.

Note: Both urticaria and idiopathic urticaria were terms that could be selected by the investigator

*three serious AEs occurred in the same patient; [†]angioedema located in lips and eyes; [‡]angioedema location not reported; [§]after reviewing the hospital discharge summary post-database lock, it was determined that the patient experienced no anemia with the reported melena. Cause of hospital admission was elective endoscopy for non-anemic melena. Patient underwent upper gastrointestinal endoscopy and colonoscopy which revealed only diverticulosis with no other potential source of bleeding. Thus, it was determined that melena as a serious AE was not the correct report; rather this patient experienced a non-serious event of non-anemic melena.

Treatment-emergent serious AE includes adverse events in follow-up with onset dates on or after the first treatment date.

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Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Maurer M, Rosén K, Hsieh H-J, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med 2013;368:924-35. DOI: 10.1056/NEJMoa1215372

This supplement contains the following items:

- 1) The original, and final protocol with the summary of changes included
- 2) The original (final) statistical analysis plan

PROTOCOL AMENDMENT SUMMARY

TITLE: A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, DOSE-RANGING, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, RESPONSE DURATION AND SAFETY OF XOLAIR® (OMALIZUMAB) IN PATIENTS WITH CHRONIC IDIOPATHIC URTICARIA (CIU) WHO REMAIN SYMPTOMATIC DESPITE ANTIHISTAMINE TREATMENT (H1)

PROTOCOL NUMBER: Q4882g

EUDRACT NUMBER: 2010-022785-27

STUDY DRUG: XOLAIR® (Omalizumab)

IND: 101,612

MEDICAL MONITOR: Edward R. Conner, M.D.

SPONSOR: Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990 U.S.A.

DATE FINAL: 24 September 2010

DATE AMENDED: 11 January 2011

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**PROTOCOL AMENDMENT SUMMARY:
11 JANUARY 2011 AMENDMENT**

RATIONALE

Study Q4882g has been amended to modify the study design according to recommendations by the U.S. Food and Drug Administration, internal Genentech staff, and external experts. The changes to the protocol are as follows:

- The secondary objectives have been clarified to indicate that a goal of this study is to provide information regarding the recurrence of disease/symptoms after withdrawal of omalizumab in patients with refractory CIU. Secondary and exploratory endpoints have been modified as a result.
- The second treatment period (STP), including the re-randomization portion, has been removed. The study duration is 12 weeks shorter as a result. Secondary endpoints have been either removed or modified to reflect this change.
- The planned number of patients within each treatment group has been changed to 75 per group. The total number of patients in the study remains unchanged at approximately 300.
- The number of weeks that a patient must have had CIU symptoms despite being on H1 antihistamines has been increased from 6 to 8 weeks
- Procedures regarding the use of excluded therapy have been modified in an effort to continue to follow patients for safety evaluation after they have discontinued study drug
- The washout period required after regular doxepin use prior to enrollment has been reduced from 6 weeks to 14 days.
- The criterion for women of childbearing potential and pregnancy has been clarified. Additionally, nursing women are excluded from study participation.
- Contraindications to diphenhydramine have been added.
- The in-clinic urticaria activity score terminology has been corrected.
- The start of the screening period has been modified from 14–18 to 12–18 days prior to Day 1.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in *italics*. This amendment represents cumulative changes to the original protocol.

**SUMMARY OF CHANGES:
11 JANUARY 2011 AMENDMENT**

PROTOCOL AMENDMENT ACCEPTANCE FORM

A Protocol Amendment Acceptance Form has been added.

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

SECTION 1.3: RATIONALE FOR DOING THIS STUDY

The main purpose of this study is to demonstrate the efficacy and safety of omalizumab, compared with placebo, as an add-on therapy in patients aged 12–75 who remain symptomatic despite H1 antihistamine (anti-H1) therapy. In addition, the study is designed to evaluate the appropriate dose of omalizumab, ~~the appropriate duration of therapy,~~ and the time to onset of clinical effect in patients with CIU, *as well as to provide information regarding disease recurrence after study treatment is withdrawn.*

SECTION 2: OBJECTIVES

- To evaluate the dose, ~~duration and disease recurrence~~ of omalizumab therapy in patients with refractory CIU
- *To evaluate duration of response after withdrawal of omalizumab in patients with refractory CIU*

SECTION 3.1: DESCRIPTION OF THE STUDY

The study will consist of ~~four~~*three* distinct study periods over a time period of ~~42~~*30* weeks, as outlined below (see also Figure 1):

- Screening period: Day –14 to Day –1
- ~~First~~ Treatment Period (FTP): Day 1 to Day 85 Pre-dose (Week 0 to Week 12)
- ~~Second Treatment Period (STP): Day 85 to Day 169 (Week 12 to Week 24)~~
- Follow-Up Period (~~FUP~~): Day ~~169~~*85* to Day ~~284~~*197* (Week ~~24~~*12* to Week ~~40~~*28*)

. . . Circumstances that may permit re-screening include, but are not limited to, an in-clinic UAS7 score or laboratory test results that do not meet eligibility requirements. . . .

On Day 1, eligible patients will be randomly assigned (in a 4:4:4:31:1:1:1 ratio using Interactive Voice and Web Response System [IxRS]) to receive omalizumab (75, 150, or 300 mg) or placebo by subcutaneous (SC) injection every 4 weeks during the first 12-week double-blind treatment period (FTP). There will be approximately 8075 patients in *each of* the 75, 150, and 300 mg omalizumab treatment arms and approximately 60 patients in the placebo arm. Randomization to treatment groups will be stratified by baseline weekly itch score, baseline weight, and study site. A hierarchical dynamic randomization scheme will be used to achieve overall balance between treatment groups and within strata. Efficacy, and safety, pharmacokinetic (PK), and pharmacodynamic (PD) data will be collected. In addition, trough (predose) serum levels of omalizumab, free and total IgE will be evaluated. For the duration of the FTP treatment period, patients must maintain stable doses of their pre-randomization CIU H1 antihistamine treatment. The last dose of study drug during the FTP treatment period will be given at the Day 57 (Week 8) study visit. Patients who withdraw from study treatment prior to the end of the FTP will not be eligible to receive treatment during the STP but will be followed until the final study visit (Week 40) or early termination visit. The primary endpoint will be measured at Week 12. In the follow-up period, patients may add up to one additional H1 antihistamine therapy (refer to Section 4.3.2). Increasing the dose of antihistamine above the approved dose is not permitted. The goal of allowing additional H1 antihistamine therapy after the primary endpoint has been assessed is to reduce patient dropout for improved safety evaluation.

On Day 85 (Week 12 visit), patients will be classified into two categories based on their degree of symptom improvement:

- Week 12 responders (W12-R) if the absolute UAS7 score is ≤ 6 at Week 12
- Week 12 non-responders (W12-NR) if the absolute UAS7 score is > 6 at Week 12

These categories will be used when patients are reassigned to study treatment for the STP.

Patients who were assigned to the 75, 150, or 300 mg omalizumab group during the FTP will be re-randomized (in a 1:1 ratio) to receive the same dose of omalizumab

received during the FTP (75, 150, or 300 mg) or placebo by SC injection every 4 weeks during the STP.

~~Patients who were assigned to the placebo group during the FTP will be reassigned based on their Week 12 response status. Week 12 NRs will be assigned to receive omalizumab 300 mg by SC injection every 4 weeks and W12-Rs will continue to receive placebo by SC injection every 4 weeks during the STP.~~

~~Efficacy and safety data will be collected during the STP. In addition, trough (predose) serum levels of omalizumab, free and total IgE will be evaluated. The last treatment will be given at the Week 20 visit. For the duration of the STP, patients must maintain stable doses of their pre-randomization CIU H1 antihistamine treatment.~~

After completion of the 12-week STP *treatment period*, all patients will enter a 16-week follow-up period to allow for further characterization of the pharmacokinetics (PK) and pharmacodynamics (PD) of omalizumab, collection of additional efficacy and safety data, and evaluation of the presence of anti-therapeutic antibodies (ATAs).

...

The blind will be maintained for the full 4028 weeks of the study (post-randomization).

...

FIGURE 1: Study Schema

The Study Schema has been revised to reflect the changes to the study design.

SECTION 3.2: RATIONALE FOR STUDY DESIGN

... This study will evaluate the comparative efficacy between omalizumab and placebo, *and* the time to onset of clinical effect, ~~and the duration of omalizumab therapy~~ for H1 antihistamine refractory patients with CIU. ...

... Time to onset of the clinical effect of treatment with omalizumab will be evaluated during ~~this first~~ *the* treatment period ~~as well~~. ...

~~The length of therapy will be evaluated in the STP. The objective is to determine if omalizumab is needed to maintain the response once the symptoms have been resolved to a minimal level. The STP will evaluate if patients on omalizumab who~~

~~have a robust clinical response in the first 12 weeks of therapy maintain their response better through Week 24 if they continue on omalizumab.~~

Disease recurrence after study drug is withdrawn will be measured during this study. For all patients, symptom scores will be measured during both the treatment and follow-up periods. Patients treated with omalizumab who have an excellent clinical response ($UAS7 \leq 6$) will be evaluated to determine when they have symptom relapse. This important information will be used along with data from other studies to provide guidance for the duration of therapy.

SECTION 3.3.2: Secondary Efficacy Outcome Measures

- Proportion of patients with $UAS7 \leq 6$ (~~W12-R~~) at Week 12
- *Proportion of patients with $UAS7 \leq 6$ at Week 28*
- ~~• Proportion of W12-R patients treated with omalizumab for 12 weeks who maintain their response ($UAS7 \leq 6$) to the Week 24 visit~~

SECTION 3.3.5: Exploratory Efficacy Outcome Measures

The following exploratory *efficacy* outcome measures will be assessed:

- ~~• Change from Week 12 in weekly itch score at Week 24~~
- ~~• Change from Week 12 in $UAS7$ at Week 24~~
- ~~• Change from Week 12 in weekly hives score at Week 24~~
- ~~• Change from Week 12 in weekly largest hive score at Week 24~~
- Proportion of patients with $UAS7 \leq 6$ at Week 24²⁸
- *Proportion of Week 12 responders who maintain their response ($UAS7 \leq 6$) to the Week 28 visit*
 - Week 12 responders are defined as patients who achieve an absolute $UAS7 \leq 6$ at Week 12.*
- *Time to relapse in Week 12 responders*
 - Time to relapse is defined as the date of the Week 12 visit to the date where $UAS7 > 6$.*
- Change from baseline in health-related quality-of-life as measured by the Chronic Urticaria Quality-of-Life Questionnaire (CU-Q2oL) at Week 12 and Week 28
- Change from baseline in health-related quality-of-life as measured by the DLQI at Week 28

- Change from baseline in the number of itch-free days and/or hive-free days at Week 12 ~~and Week 24~~
- Change from baseline in weekly sleep interference score at Week 12 ~~and Week 24~~
- Change from baseline in weekly interference with daily activities score at Week 12 ~~and Week 24~~
- Change from baseline in health utility as measured by the EQ-5D at Week 12 *and Week 28*
- Change from baseline in MOS sleep score at Week 12 ~~and Week 24~~
- ~~Time to recurrence of symptoms during Week 12 to Week 24 for W12-R defined as a UAS7 score ≥ 6~~

SECTION 3.5: STUDY PATIENTS AND ANALYSIS GROUPS

Patients enrolled in this study will have a CIU diagnosis for ≥ 6 months and will be refractory to approved-dose antihistamines as demonstrated by the presence of itch and hives for ~~≥ 6~~ ≥ 8 consecutive weeks at any time prior to enrollment and a UAS7 score of ≥ 16 and itch component of UAS7 (range 0–21) ≥ 8 during the 7 days prior to randomization despite current use of approved-dose H1 antihistamine treatment. In addition, medical history will be obtained to evaluate what prior therapies the patients have used. Specifically, type of therapy, ~~dose~~ and duration of treatment will be recorded from patient history. . . .

The sites selected for this study will be specialty dermatology and immunology clinics with experience in treating CIU. The analysis group for the ~~FTP~~*treatment period* will include all patients who are randomized and received at least one dose of study drug (mITT: modified intention to treat). The number of patients randomized but not receiving study drug is expected to be very small, if not zero. ~~The analysis group for the STP will include all patients who receive at least one dose of study drug in the STP. The analyses of the secondary endpoints measured in the STP will include all patients randomized to the omalizumab group (75, 150, or 300 mg) in the FTP, were Week 12 Responders (W12-R), who were re-randomized and received at least one dose of study drug in the STP.~~

SECTION 3.7: MINIMIZATION OF BIAS

Randomization and blinding will be employed to minimize bias in treatment assignment and to provide the basis for valid statistical inference. To minimize the

risk of potential bias arising from confounding factors, a hierarchical dynamic randomization will be employed to ~~assign treatment for the FTP~~. The factors for balancing between the treatment groups will be in the following hierarchical order: overall balance, baseline weekly itch score (< 13 vs. ≥13), body weight (< 80 kg vs. ≥ 80 kg) and study site. Due to the large number of study sites in the study (approximately 70), the study site is planned to be last in the hierarchy. ~~To minimize potential bias in the analyses of the secondary endpoint from the STP, a permuted block design will be used to re-randomize patients who receive omalizumab during the FTP using the degree of symptom improvement (W12-Rs or Week 12-NRs) as the stratification factor.~~ Please refer to Section 4.2 for a description of the method of treatment assignment and blinding.

SECTION 4.1.2: Inclusion Criteria

- Diagnosis of CIU refractory to H1 antihistamines at the time of randomization, as defined by all of the following:

The presence of itch and hives for ~~>6~~≥8 consecutive weeks at any time prior to enrollment despite current use of H1 antihistamine treatment during this time period

...

- ~~• For women of childbearing potential, agreement to use an acceptable form of contraception (as determined by the site investigator) and to continue its use for the duration of the study~~

SECTION 4.1.3: Exclusion Criteria

- Regular (daily/every other day) doxepin (oral) use within ~~6 weeks~~14 days prior to Day -14

...

- *Nursing women or women of childbearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they meet the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels >40 mIU/mL or 6 weeks post-surgical bilateral oophorectomy (with or without hysterectomy) or hysterectomy OR are using one or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation, vasectomy), hormonal contraception (implantable, patch, oral), and double-barrier methods (any double combination of: IUD, male or female condom with spermicidal gel, diaphragm, sponge, or cervical cap)*

- *Contraindications to diphenhydramine: Overreactivity against the agent diphenhydramine, other antihistaminic agents, or other components of this agent; acute bronchial asthma; acute angle-closure glaucoma; pheochromocytoma; hyperplasia of the prostate gland with formation of residual urine; epilepsy; hypokalemia; hypomagnesemia; bradycardia; a congenital long QT syndrome or other clinically significant cardiac disorders (especially coronary heart disease, disturbances in conduction, arrhythmias); the simultaneous application of drugs which prolong the QT interval (e.g., antiarrhythmic drugs class IA or III, antibiotics, cisapride, malaria drugs, antihistaminic drugs, neuroleptic drugs) or lead to hypokalemia (e.g., certain diuretic drugs); the simultaneous application of MAO inhibitors; the simultaneous uptake of alcohol*

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT AND BLINDING

At the Day 1 visit, patients will be randomized to one of 3 doses of omalizumab (75, 150, or 300 mg) or placebo at an approximately 4:4:4:31:1:1:1 ratio using an IxRS.

...

~~At the Week 12 visit, each patient's Week 12 responder status will be evaluated using the eDiary device. An encrypted code of responder status for each patient will be transmitted to the IxRS by a site representative who is blinded to the patient's Week 12 responder status. The patients, all study personnel, and the designated evaluating physician(s) will not be able to view the patient's W12-responder status.~~

~~At the Week 12 visit (Day 85), patients who were assigned to the 75, 150, or 300 mg omalizumab group during the FTP will be re-randomized (in a 1:1 ratio) to receive the same dose of omalizumab received during the FTP (75, 150, or 300 mg) or placebo by SC injection every 4 weeks during the STP. To ensure treatment balance in the analysis population, the randomization will be stratified by the Week 12 responder status (W12-R or W12-NR). For patients who were treated with placebo in the FTP, the W12-R will be treated with placebo while the W12-NR will be treated with omalizumab 300 mg.~~

SECTION 4.4.1: Concomitant Therapy

... Therapies used for the treatment of CIU prior to enrollment will be collected as part of the patient's medical history.

SECTION 4.4.2: Excluded Therapy

Prior to the screening visit (–14 days) and during the study, the following medications and treatments will be restricted: ~~Patients who receive these medications as therapy for CIU will be discontinued from the study.~~

. . .

- Routine (daily or every other day during 5 or more consecutive days) doses of doxepin within ~~6 weeks~~^{14 days} prior to Day –14

. . .

Patients who receive any excluded therapy during screening should be considered a screening failure. Patients who receive any excluded therapy after randomization will be discontinued from study treatment; if a patient has received at least one dose of omalizumab following enrollment, the patient should be followed for safety for the remainder of the study.

SECTION 4.5.1: Definitions of Study Assessments

a. Medical History and Concomitant Medications

. . . The Day –14 medical history will include a comprehensive review of the patient's CIU medical history. This will include onset of symptoms, date of diagnosis, and therapies received ~~including the type of therapy, dose and treatment received for CIU.~~

d. Laboratory Assessments

- Total blood cell histamine assay – test to evaluate histamine as a marker for overall intravascular basophil volume (~~U.S.~~^{North American} sites only)

SECTION 4.10: STATISTICAL METHODS

~~. . . Analysis populations for efficacy outcomes from the STP will vary depending on the outcome measure and will be specified in the sections describing the analyses.~~

. . . .

SECTION 4.10.1: Analysis of the Conduct of the Study

. . . Patient discontinuation and the reason for discontinuation will be summarized by treatment group for each ~~treatment~~^{study} period. . . .

SECTION 4.10.3: Efficacy Analyses

b. Secondary Endpoints

- Proportion of patients with $UAS7 \leq 6$ at Week 12 (W12-R)
- ~~Proportion of W12-R patients treated with omalizumab during FTP who maintain their response ($UAS7 \leq 6$) to the Week 24 visit~~

~~The analyses of this endpoint will only include a subgroup of patients from the FTP. These patients must be Week 12 responders (W12-R), randomized to one of the omalizumab groups (75, 150, or 300 mg) in the FTP, who were re-randomized and received at least one dose of study drug in the STP. The Fisher's exact test will be performed to compare each of the omalizumab groups to the placebo group with respect to the proportions W12-Rs who maintain UAS7 response ($UAS7 \leq 6$) from Week 12 to Week 24.~~

- Proportion of patients with $UAS7 \leq 6$ at Week 28

The Cochran-Mantel-Haenszel test stratified by baseline UAS7 and baseline weight (<80 kg vs. ≥ 80 kg) will be performed to compare the proportions of patients with $UAS7 \leq 6$ at Week 28 in each of the omalizumab groups versus placebo.

d. Type-I Error Control Plan for the Primary and Secondary Endpoints

- Proportion of patients with $UAS7 \leq 6$ at Week 12 (W12-R)
- ~~Proportion of W12-Rs treated with omalizumab during the FTP who maintain their response ($UAS7 \leq 6$) to the Week 24 visit~~

e. Exploratory Endpoints

The details of the methods for the analysis of exploratory endpoints listed in Section 3.3.5 will be specified in the Statistical Analysis Plan. For the endpoints used to characterize disease/symptom recurrence, which include but are not limited to the following two outcome measures, descriptive summary statistics for each treatment group will be provided but no statistical tests will be conducted to compare between treatment groups given that there is no proper comparison group:

- *Proportion of Week 12 responders who maintain their response ($UAS7 \leq 6$) to the Week 28 visit, with Week 12 responders defined as patients who achieve an absolute $UAS7 \leq 6$ at Week 12*
- *Time to relapse in Week 12 responders, with relapse defined as the first time $UAS7 > 6$ after the Week 12 visit*

SECTION 4.10.4: Safety Analysis

Safety will be assessed through the summary of adverse events, laboratory test results, vital signs, and antibodies to omalizumab. These summaries will be produced for the whole study and separately for the ~~FTP, STP,~~ *treatment period* and ~~FUP~~ *the follow-up period*. . . .

SECTION 4.10.6: Handling of Missing Data

b. Imputation of Missing Values for Primary Endpoint and Other Weekly Scores **Weekly Itch Score**

~~For the score changes from Week 12 to Week 24, patients whose Week 24 score is missing will be imputed by their Week 12 scores.~~

Response Status

. . . The same principle will be applied to responder endpoints evaluated at Week ~~24~~28.

SECTION 4.10.7: Determination of Sample Size

. . . Assuming an early discontinuation rate of 15% (based on data from the MYSTIQUE and XCUISITE studies) by Week 12, a total of 300 patients (~~4:4:4:31:1:1:1~~ randomization ratio for omalizumab 75 mg [N=80], omalizumab 150 mg [N=80], omalizumab 300 mg [N=80] and placebo [N=60], ~~respectively~~ *with 75 patients in each treatment group*) will yield approximately 98% power to detect a difference in treatment effect in the primary endpoint at the 0.05 level for any omalizumab group. . . .

APPENDIX A-1: Study Flowchart

APPENDIX A-2: Study Flowchart: Pharmacokinetics/Pharmacodynamics

The Study Flowcharts have been revised to reflect the changes to the protocol.

APPENDIX G: Study Drug Preparation and Administration

Instructions regarding labelling study drug syringes have been clarified. Details regarding kit number are to be included on each label.

PROTOCOL

TITLE: A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, DOSE-RANGING, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, RESPONSE DURATION AND SAFETY OF XOLAIR® (OMALIZUMAB) IN PATIENTS WITH CHRONIC IDIOPATHIC URTICARIA (CIU) WHO REMAIN SYMPTOMATIC DESPITE ANTIHISTAMINE TREATMENT (H1)

PROTOCOL NUMBER: Q4882g

EUDRACT NUMBER: 2010-022785-27

STUDY DRUG: XOLAIR® (Omalizumab)

IND: 101,612

MEDICAL MONITOR: Edward R. Conner, M.D.

SPONSOR: Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990 U.S.A.

DATE FINAL: 24 September 2010

DATE AMENDED: 11 January 2011

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PROTOCOL AMENDMENT FINALIZATION SIGNATURE PAGE

TITLE: A PHASE III, MULTICENTER, RANDOMIZED,
DOUBLE-BLIND, DOSE-RANGING,
PLACEBO-CONTROLLED STUDY TO EVALUATE
THE EFFICACY, RESPONSE DURATION AND
SAFETY OF XOLAIR® (OMALIZUMAB)
IN PATIENTS WITH CHRONIC IDIOPATHIC
URTICARIA (CIU) WHO REMAIN SYMPTOMATIC
DESPITE ANTIHISTAMINE TREATMENT (H1)

PROTOCOL NUMBER: Q4882g

EUDRACT NUMBER: 2010-022785-27

STUDY DRUG: XOLAIR® (Omalizumab)

IND: 101,612

MEDICAL MONITOR: Edward R. Conner, M.D.

SPONSOR: Genentech, Inc.
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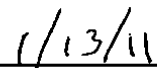
DATE FINAL: 24 September 2010

DATE AMENDED: 11 January 2011

This protocol was amended on the date shown above.



Edward R. Conner, M.D.



Date

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE: A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, DOSE-RANGING, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, RESPONSE DURATION AND SAFETY OF XOLAIR® (OMALIZUMAB) IN PATIENTS WITH CHRONIC IDIOPATHIC URTICARIA (CIU) WHO REMAIN SYMPTOMATIC DESPITE ANTIHISTAMINE TREATMENT (H1)

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STUDY DRUG: XOLAIR® (Omalizumab)

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SPONSOR: Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990 U.S.A.

DATE FINAL: 24 September 2010

DATE AMENDED: 11 January 2011

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please return a copy of the signed form to the Sponsor or designee. Please retain the original signature page for your study files.

PROTOCOL SYNOPSIS

TITLE: A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, DOSE-RANGING, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, RESPONSE DURATION AND SAFETY OF XOLAIR® (OMALIZUMAB) IN PATIENTS WITH CHRONIC IDIOPATHIC URTICARIA (CIU) WHO REMAIN SYMPTOMATIC DESPITE ANTIHISTAMINE TREATMENT (H1)

PROTOCOL NUMBER: Q4882g

EUDRACT NUMBER: 2010-022785-27

STUDY DRUG: XOLAIR® (Omalizumab)

PHASE: III

INDICATION: Chronic idiopathic urticaria

IND: 101,612

SPONSOR: Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990 U.S.A.

DATE FINAL: 24 September 2010

DATE AMENDED: 11 January 2011

OBJECTIVES

Primary Objective

- To evaluate the efficacy of omalizumab compared with placebo in patients with refractory chronic idiopathic urticaria (CIU) receiving concomitant H1 antihistamine therapy

Secondary Objectives

- To evaluate the safety of omalizumab therapy in patients with refractory CIU
- To evaluate onset of clinical effect of omalizumab therapy in CIU
- To evaluate the dose of omalizumab therapy in patients with refractory CIU
- *To evaluate duration of response after withdrawal of omalizumab in patients with refractory CIU*
- To evaluate the quality-of-life benefit of omalizumab therapy in patients with refractory CIU

STUDY DESIGN

The study is a global Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of omalizumab administered subcutaneously as an add-on therapy for the treatment of adolescent and adult patients aged 12–75 who have been diagnosed with refractory CIU and who remain symptomatic despite standard-dosed H1 antihistamine treatment. The study will enroll approximately 300 patients at approximately 70 study sites globally.

The study will consist of *three* distinct study periods over a time period of 30 weeks, as outlined below (see also Figure 1):

- Screening period: Day –14 to Day –1
- Treatment Period: Day 1 to Day 85 Pre-dose (Week 0 to Week 12)
- Follow-Up Period: Day 85 to Day 197 (Week 12 to Week 28)

The screening period will consist of visits at Day –14 and Day –7. Patients must meet all of the following criteria to enter the screening period:

- Non-electronic diary based UAS of ≥ 4 established in the clinic based on the patient's condition over 12 hours prior to either Day –14, Day –7, or Day 1 despite being on H1 antihistamine therapy
- Use of an approved dose of an H1 antihistamine for CIU at Day –14 and for at least the 3 consecutive days immediately prior to Day –14 (see Section 4.3.2 for list of H1 antihistamines available for use in this study)
- Willing and able to complete a symptom electronic diary (eDiary) twice daily throughout the screening period to establish the patient's UAS7 score

Patients will have the 2-week screening period to establish their eligibility for the study and baseline symptom scores. For the duration of the screening period, patients must maintain stable doses of their pre-screening H1 antihistamine treatment. To be eligible for the study, patients must have no missing eDiary entries, a UAS7 symptom score of ≥ 16 (equivalent to moderate to severe CIU symptoms for at least 4 out of the 7 days in a week), and a weekly itch score (a component of the UAS7) of ≥ 8 for the 7 days prior to randomization.

Only in exceptional circumstances, when information concerning eligibility is outstanding (e.g., pending laboratory data) will a longer screening period be permitted. Upon approval from the Medical Monitor, patients may be re-screened. Circumstances that may permit re-screening include, but are not limited to, an in-clinic UAS score or laboratory test results that do not meet eligibility requirements.

On Day 1, eligible patients will be randomly assigned (in a 1:1:1:1 ratio using Interactive Voice and Web Response System [IxRS]) to receive omalizumab (75, 150, or 300 mg) or placebo by subcutaneous (SC) injection every 4 weeks during the 12-week double-blind treatment period. There will be approximately 75 patients in *each* of the 75, 150, and 300 mg omalizumab treatment arms and in the placebo arm. Randomization to treatment groups will be stratified by baseline weekly itch score, baseline weight, and study site. A hierarchical dynamic randomization scheme will be used to achieve overall balance between treatment groups and within strata. Efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) data will be collected. For the duration of the *treatment period*, patients must maintain stable doses of their pre-randomization CIU H1 antihistamine treatment. The last dose of study drug during the *treatment period* will be given at the Day 57 (Week 8) study visit. *The primary endpoint will be measured at Week 12. In the follow-up period, patients may add up to one additional H1 antihistamine therapy (refer to Section 4.3.2). Increasing the dose of antihistamine above the approved dose is not permitted. The goal of allowing additional H1 antihistamine therapy after the primary endpoint has been assessed is to reduce patient dropout for improved safety evaluation.*

After completion of the 12-week *treatment period*, all patients will enter a 16-week follow-up period to allow for further characterization of the pharmacokinetics (PK) and pharmacodynamics (PD) of omalizumab, collection of additional efficacy and safety data, and evaluation of the presence of anti-therapeutic antibodies (ATAs). Patients will continue to visit the study center at 4-week intervals. No study treatment will be given; patients must maintain stable doses of their pre-randomization CIU H1 antihistamine treatment.

The blind will be maintained for the full 28 weeks of the study (post-randomization). For the duration of the study, all patients will be provided with diphenhydramine (25 mg) for itch relief on an as-needed basis (up to a maximum of three doses in 24 hours or less based on local regulations).

OUTCOME MEASURES

Primary Efficacy Outcome Measure

The primary efficacy outcome measure is the change from baseline in weekly itch score (a component of the UAS7) at Week 12 (see Table 1). The itch score will be recorded twice daily (morning and evening) in the patient eDiary, on a scale of 0 (none) to 3 (severe). The daily itch score is the average of the morning and evening scores. The baseline weekly itch score is the sum of the daily itch scores over the 7 days prior to randomization (Day 1 visit), and the weekly itch score at Week 12 is the sum of daily itch scores over the 7 days prior to the Week 12 visit (Day 85). The same principles of calculating baseline and Week 12 weekly scores will be applied to the following weekly outcomes unless otherwise stated.

Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures are as follows:

- Change from baseline in UAS7 at Week 12

The UAS is a composite eDiary-recorded score with numeric severity intensity ratings on a scale of 0–3 (0 = none to 3 = intense/severe) for 1) the number of wheals (hives); and 2) the intensity of the itch (see Table 1), measured twice daily (morning and evening). The daily UAS is the average of the morning and evening scores and the UAS7 is the sum of the daily UAS scores over 7 days.

Table 1 Twice Daily Assessment of Disease Activity in Patients with CIU (UAS Scale)		
Score	Wheals (Hives)	Pruritus (Itch)
0	None	None
1	Mild (1–6 hives/12 hour)	Mild
2	Moderate (7–12 hives/12 hour)	Moderate
3	Intense (> 12 hives/12 hour)	Severe

CIU = chronic idiopathic urticaria.

- Change from baseline in weekly hives score at Week 12
The number of hives is measured twice daily (morning and evening), on a scale of 0 (none) to 3 (> 12). The daily hives score is the average of the morning and evening scores, and the weekly hives score is the sum of the daily hives scores over 7 days.
- Time to weekly itch score minimally important difference (MID) response by Week 12
Weekly itch score MID response is defined as a reduction from baseline in weekly itch score of ≥ 5 points. Time to weekly itch score MID response is the time (in weeks) from the date of the first dose to the date where weekly itch score MID response is first achieved.
- Proportion of patients with UAS7 ≤ 6 at Week 12
UAS7 ≤ 6 identifies patients with an excellent clinical response who may be considering discontinuing therapy as they have minimal or no symptoms.
- Change from baseline in weekly largest hive score at Week 12
The largest hive score is measured twice daily, on a scale of 0 (none) to 3 (> 2.5 cm). The daily largest hive score is the average of the morning and evening scores, and the weekly largest hive score is the sum of the daily scores over 7 days.
- Proportion of weekly itch score MID Responders at Week 12
Weekly itch score MID responders are defined as patients who achieve a weekly itch score MID response at the Week 12 visit.
- *Proportion of patients with UAS7 ≤ 6 at Week 28*
- Change from baseline in health-related quality-of-life as measured by the Dermatology Life Quality Index (DLQI) at Week 12
- Proportion of angioedema-free days from Week 4 to Week 12 of therapy

Safety Outcome Measures

The safety of omalizumab will be assessed using the following safety outcome measures:

- Incidence and severity of adverse events and serious adverse events
- Changes in vital signs
- Clinical laboratory evaluations
- ATA evaluation at the end of the follow-up period

Pharmacokinetic/Pharmacodynamic Outcome Measures

The following PK and PD outcome measures will be reported:

- Summary trough serum levels of omalizumab, total and free IgE

Exploratory Outcome Measures

The following exploratory *efficacy* outcome measures will be assessed:

- Proportion of patients with UAS7 ≤ 6 at Week 28
- Time to UAS7 minimally important difference (MID) response by Week 12
UAS7 MID response is defined as a reduction from baseline in UAS7 score of ≥ 11 points.
Time to UAS7 MID response is the time (in weeks) from the date of the first dose to the date where UAS7 MID response is first achieved.
- *Proportion of Week 12 responders who maintain their response (UAS7 ≤ 6) to the Week 28 visit*
Week 12 responders are defined as patients who achieve an absolute UAS7 ≤ 6 at Week 12.
- *Time to relapse in Week 12 responders*
Time to relapse is defined as the date of the Week 12 visit to the date where UAS7 > 6 .
- Change from baseline in health-related quality-of-life as measured by the Chronic Urticaria Quality-of-Life Questionnaire (CU-Q2oL) at Week 12 and Week 28
- *Change from baseline in health-related quality-of-life as measured by the DLQI at Week 28*
- Change from baseline in the number of itch-free days and/or hive-free days at Week 12
- Change in number of tablets/week of sedating H1 antihistamine (diphenhydramine) for itch relief from baseline to Week 12
- Change from baseline in weekly sleep interference score at Week 12
The sleep interference score is measured daily, on a scale of 0 (No interference) to 3 (substantial, woke up often, severe impact on sleep). The weekly sleep interference score is the sum of the daily scores over 7 days.
- Change from baseline in weekly interference with daily activities score at Week 12
The daily activities interference score is measured daily on a 0 (No interference) to 3 (Substantial, severe interference with daily activities) scale. The weekly interference with daily activities score is the sum of the daily scores over 7 days.
- Change from baseline in health utility as measured by the EQ-5D at Week 12 and Week 28
- Change from baseline in MOS sleep score at Week 12

A number of laboratory investigations will be conducted to gain an insight into the mechanism of action of omalizumab in the patient population under study.

SAFETY PLAN

Omalizumab is currently approved for marketing in approximately 52 countries for patients 6 years and above (including, but not limited, to the European Union, New Zealand and Russia). In some regions the indicated age is limited to 12 years and above (including, but not limited to the U.S., Canada, and Australia). Each individual country basic prescribing information may vary, but in general, it is for the prevention of asthma exacerbations and control of asthma symptoms when given as add-on therapy for adult and adolescent patients with moderate to severe persistent allergic asthma who remain inadequately controlled. Consult the local prescribing information for more information.

Patient injections will be administered by a qualified healthcare professional, and patients will be monitored for an appropriate period of time after each dosing event. Patients will be instructed to recognize the signs and symptoms of any severe hypersensitivity reaction, and to contact a healthcare provider in case of any such symptoms.

Patients with CIU can have angioedema as part of their symptoms. When that angioedema poses a risk to the airway, the emergent use of systemic corticosteroids is indicated. Patients who need to be treated with systemic corticosteroids will be discontinued from study treatment and followed for safety for the remainder of the study. Patients will be provided emergency contact information and advised to contact a physician during the entire study, in case of angioedema.

During the conduct of the study, a treatment assignment should be unblinded only in the event of a life-threatening medical emergency that requires immediate unblinding/unmasking, or in the event of an unexpected serious adverse event judged by the investigator as related to study drug, for FDA safety reporting. In such cases, unblinding will be implemented following standard procedures, and only following agreement by both the investigator and Medical Monitor that unblinding is necessary.

Safety data including serious and non-serious adverse events and laboratory test results will be reviewed internally on a periodic basis during the conduct of the study. See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

An independent Data Monitoring Committee (iDMC) will review blinded and unblinded safety data provided to them by an independent Data Coordinating Center (iDCC) every 6 months for the duration of the study.

Please refer to the Omalizumab Investigator Brochure for additional information on safety risks.

STUDY TREATMENT

Patients will receive omalizumab (75 ,150, or 300 mg) or placebo administered subcutaneously every 4 weeks at the study center.

Study medication will be supplied as a lyophilized, sterile powder in a single-use, 5-mL vial that is designed to deliver 150 mg of omalizumab or placebo for SC administration upon reconstitution with 1.4 mL Sterile Water for Injection.

Each patient will receive two injections of study medication. For details regarding each individual's injection, please refer to Appendix H.

CONCOMITANT THERAPY AND CLINICAL PRACTICE

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF). Patients will be encouraged to use the minimal dose required to control their symptoms.

All patients will be allowed to take study-defined H1 antihistamine medications at approved doses during the screening, treatment, and follow-up periods. Patients should remain on a stable H1 antihistamine treatment regimen throughout the study period. Diphenhydramine (25 mg) will be provided and used on an as-needed basis (maximum 3 times/day) during screening, treatment and follow-up periods.

Therapies used for the treatment of CIU prior to enrollment will be collected as part of the patient's medical history.

Excluded Therapy

Prior to the screening visit (-14 days) and during the study, the following medications and treatments will be restricted:

- Routine (daily or every other day during 5 or more consecutive days) doses of the following medications within 30 days prior to Day -14: systemic or cutaneous (topical) corticosteroids (prescription or over the counter), hydroxychloroquine, methotrexate, cyclosporine, or cyclophosphamide
- Routine (daily or every other day during 5 or more consecutive days) doses of doxepin within 14 days prior to Day -14
- Omalizumab within 1 year prior to screening
- Any LTRAs (montelukast or zafirlukast) or H2 blockers within 7 days prior to Day -14
- Any H1 antihistamines at greater than approved doses within 3 days prior to Day -14
- Either intravenous immunoglobulin G (IVIG) or plasmapheresis within 30 days prior to Day -14

Patients who receive any excluded therapy during screening should be considered a screening failure.

Patients who receive any excluded therapy after randomization will be discontinued from study treatment; if a patient has received at least one dose of omalizumab following enrollment, the patient should be followed for safety for the remainder of the study.

Patients taking either LTRAs or H2 blockers for diseases other than CIU (e.g. asthma or GERD, respectively) will be permitted to continue their use during the study. These diseases must be recorded as part of the medical history collected during the screening period. Inhaled asthma controllers, including corticosteroids, are also permitted during the study.

STATISTICAL METHODS

Primary Efficacy Analysis

The primary efficacy endpoint is the change in weekly itch score from baseline to Week 12.

The analysis of the primary endpoint will consist of treatment comparisons made using analysis of covariance (ANCOVA) controlling for baseline weekly itch score, and baseline weight (<80 kg vs. ≥80 kg).

The ANCOVA model will be based on the mITT patients. Missing Week 12 itch scores will be imputed by carrying forward the patients' baseline scores (BOCF). The Week 12 itch scores for patients who received excluded therapy listed in Section 4.4.2 by Week 12 will also be imputed using their baseline scores.

Determination of Sample Size

The sample size for this study is primarily based on safety and regulatory considerations. The estimation of power for efficacy assumes a mean change from baseline in the weekly itch score at Week 12 to be 9 points and 3.5 points for the omalizumab and placebo group, respectively, with a common standard deviation of 6 points (based on data from the MYSTIQUE and XCUISITE studies). Assuming an early discontinuation rate of 15% (based on data from the MYSTIQUE and XCUISITE studies) by Week 12, a total of 300 patients (1:1:1:1 randomization ratio *with 75 patients in each treatment group*) will yield approximately 98% power to detect a difference in treatment effect in the primary endpoint at the 0.05 level for any omalizumab group. A multiplicity type-I error control plan will be employed to adjust for the comparisons of multiple omalizumab groups to the placebo group in order to maintain an overall type I error rate of 0.05 (two sided).

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
ATA	anti-therapeutic antibody
CIU	chronic idiopathic urticaria
CSU	chronic spontaneous urticaria
CU-Q2OL	Chronic Urticaria Quality of Life Questionnaire
DLQI	Dermatology Life Quality Index
EC	ethics committee
eDiary	electronic diary
ELISA	enzyme-linked immunosorbent assay
EQ5D	EuroQoL-5D Questionnaire
FcεRI	high-affinity IgE receptor
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IgE	immunoglobulin E
IVIG	intravenous immunoglobulin G
IxRS	interactive voice and web response systems
LTRA	leukotriene receptor antagonist
MID	minimally important difference
MMP9	matrix metalloproteinase 9
MOS	Medical Outcomes Study
PD	pharmacodynamic
PK	pharmacokinetic
PRO	patient reported outcome
SAE	serious adverse event
SC	subcutaneous
UAS	urticaria activity score

1. BACKGROUND

1.1 BACKGROUND ON DISEASE

Chronic idiopathic urticaria (CIU) is defined as the spontaneous occurrence of daily, or almost daily, hives and itching for at least 6 weeks without an obvious cause (Greaves 2003). Note that CIU can also be referred to as chronic spontaneous urticaria (CSU) as shown in recent guidelines adopted by European and global allergy and dermatology associations (Zuberbier 2009). In this document, the term CIU will be used to refer to the disease of interest and should be read as interchangeable with CSU. The majority of CIU patients achieve symptomatic control with conventional H1 antihistamine therapy. Less commonly, a triple regimen of H1 and H2 antihistamines combined with a leukotriene receptor antagonist (LTRA) is used, although H2 antihistamines and LTRAs are not approved for the treatment of CIU. In some patients, CIU can be a debilitating condition because of a lack of clinical response as well as the unpredictable course of the disease, both of which can have a profound negative influence on the patient's quality of life (Tilles 2005).

Some patients may remain symptomatic despite ongoing H1 antihistamine treatment, and for this group of patients, therapies such as immunosuppressants (including cyclosporine, corticosteroids, intravenous immunoglobulin G [IVIG], and methotrexate) and plasmapheresis have been used (Kozel 2004). These agents have variable success and may be associated with severe adverse effects.

The etiology of CIU is not clear. There are several proposed theories including one proposing an infectious origin and another related to an autoimmune origin. Some studies have found that approximately 30%–60% of patients with CIU have an autoimmune component (Fiebiger et al. 1995; Tong et al. 1997; Zweiman et al. 1998). In patients suspected of having an autoimmune etiology for their CIU, symptoms result from mediator release following the cross-linking of high-affinity IgE receptors on mast cells and basophils. Anti-IgE antibodies and functional antibodies against the alpha chain of the high-affinity IgE receptor found on mast cells, basophils, and antigen-presenting cells have been isolated from the serum of patients with CIU (Grattan 1991; Hide et al. 1993; Niimi et al. 1996). Given the association of high-affinity receptor activation, mediator release, and CIU, several studies have been conducted to determine if omalizumab could be a useful therapy for this disease.

1.2 BACKGROUND ON THE MOLECULE

1.2.1 Omalizumab Background

Xolair[®] (omalizumab) is a humanized anti-immunoglobulin E (IgE) recombinant monoclonal antibody approved to treat allergic asthma by inhibiting the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface-bound IgE on the FcεRI-expressing cells limits the degree of release of mediators in the allergic response.

Omalizumab has been studied for safety and efficacy in over 5,000 adult and adolescent (≥ 12 years of age) patients with moderate to severe asthma. More than 60,000 patients have been treated with omalizumab worldwide. Omalizumab treatment results in a decrease in free IgE levels of 89%–98%. The decrease in free IgE levels results in down regulation in the expression of FcεRI on basophils and mast cells, which makes these cells more resistant to other releasing factors.

1.2.2 Omalizumab in CIU Patients

There are two hypotheses for the mechanism of action of omalizumab in CIU patients. One hypothesis is that the density of IgE receptors at the surface of mast cells and basophils is proportional to the plasma IgE level. Lowering free IgE to near undetectable levels should therefore down regulate the IgE receptors so that the IgG autoantibody cannot cross-link the high-affinity receptor (FcεRI). Cell activation would be suppressed, and all the subsequent inflammatory processes (complement activation, cellular infiltration) would be suppressed as well. As a consequence, the frequency and severity of symptoms of chronic urticaria should be markedly diminished. It has also been hypothesized that the down regulation of FcεRI may be accompanied by an increase in the threshold above which degranulation of mast cells is triggered. This may be an independent mechanism of action, unrelated to prevention of cross-linkage of surface receptors, or the two mechanisms might be complementary. The exact mechanism for how omalizumab may work for CIU patients is, however, unknown.

A Phase II study, an industry-sponsored study and two investigator-sponsored clinical studies using omalizumab to treat CIU have demonstrated positive effects, as outlined below.

- Study Q4577g (MYSTIQUE)

Design: This Phase II, dose-ranging, randomized, double-blind, placebo-controlled study was conducted to assess the safety and efficacy of omalizumab as a treatment for CIU in patients ≥ 12 years of age who remained symptomatic despite treatment with H1 antihistamine treatment at approved doses ($n=90$). Patients were treated with a single dose of omalizumab at 75 mg, 300 mg, or 600 mg or placebo and assessed for a change from baseline in the urticaria activity score (UAS) over 1 week (UAS7) at Week 4. The UAS7 score is a composite measure of itch (0–3 point scale) and hives (0–3 point scale) recorded twice daily (morning and evening) that is averaged daily and summed over the course of 1 week (maximum score of 42).

Results: At Week 4, the 300-mg and 600-mg omalizumab groups had significantly greater improvement from baseline in UAS7 compared with the placebo group (mean change: -19.93 vs. -6.94 for 300 mg and -14.56 vs. -6.94 for 600 mg, with p -values of 0.0003 and 0.0473, respectively). Treatment effects were observed as early as Week 1, for which the mean change from baseline was -10.9 in the 300-mg omalizumab group compared with a -2.9 in the placebo group. In addition, a key secondary endpoint of change from baseline in weekly itch score (maximum score of 21) at Week 4 was significantly different in the 300 mg omalizumab group and showed a trend toward a difference in the 600 mg omalizumab group compared with placebo (mean change: -9.22 vs. -3.46 for 300 mg and -6.46 vs. -3.46 for 600 mg, with p -values of 0.0005 and 0.0558, respectively). Similarly, there was significantly greater improvement from baseline in weekly hive score at Week 4 for the 300-mg and 600-mg omalizumab groups compared with the placebo group. The 75-mg omalizumab group was not statistically significantly different from the placebo group for any of the outcomes measured.

- Study CIGE025ADE05 (XCUISITE)

Design: This 24-week randomized, double-blind, placebo-controlled multicenter study was conducted to evaluate the safety and efficacy of omalizumab in patients with moderate to severe chronic urticaria who exhibited IgE against thyroperoxidase. Patients were treated with either omalizumab or placebo. The omalizumab dose and regimen were based on body weight and IgE levels, in accordance with the European Union product label for allergic asthma. Patients with body weight or IgE level not in accordance with the product label for allergic asthma were excluded from the study.

Results: 49 patients were treated overall, 27 with omalizumab and 22 with placebo. The omalizumab group showed significantly greater improvement from baseline in UAS7 compared with the placebo group, with a mean change from baseline of 12 points in the UAS7 scale (–17.8 vs. –5.8; $p=0.0089$). In addition, 48% of omalizumab-treated patients versus 9% of placebo-treated patients achieved 100% resolution of symptoms (UAS7=0); 56% of omalizumab-treated patients versus 14% of placebo-treated patients achieved a 90% improvement from their baseline symptom score; 71% of omalizumab-treated patients versus 14% of placebo-treated patients achieved a 75% improvement from their baseline symptom score.

- Study Q3983s

Design: This 20-week crossover, single-blind, placebo-controlled study was conducted to assess the efficacy and safety of omalizumab as a treatment for adult CIU patients identified as having an autoimmune cause for their disease on the basis of having positive results for the autologous skin test and histamine release assay. These patients were symptomatic despite H1 antihistamine therapy ($n=12$). After 4 weeks of placebo treatment, patients were treated with omalizumab for 16 weeks. The omalizumab dose and regimen were based on body weight and IgE levels, in accordance with the U.S. product label for allergic asthma. Patients with a measurable serum IgE below the range covered by the dosing table in the product label (<30 IU/mL) received omalizumab 150 mg every 4 weeks during the omalizumab treatment phase.

Results: A significant reduction in the mean daily urticaria symptom score was observed at the end of the study compared with baseline ($p=0.0002$), and a statistically significant reduction was observed after the 4th week of omalizumab treatment. A significant improvement in quality of life was also noted (Dermatology Life Quality Index total score, $p<0.05$). Seven patients achieved complete symptom resolution. Three additional patients had marked improvement, one moderate improvement, and one failed to show improvement. There were no adverse effects (Kaplan and Joseph 2008).

- Study Q3245s

Design: This 24-week, randomized, double-blind, placebo-controlled study was conducted to assess the efficacy and safety of omalizumab in CIU patients with active disease despite H1 antihistamine therapy at up to twice the approved dose. Twenty adults were treated with omalizumab or placebo for 16 weeks, followed by 8 weeks of follow-up without treatment. The omalizumab dose and regimen were based on body weight and IgE levels, in accordance with the U.S. product label for allergic asthma. Patients randomized to the omalizumab group who had a measurable serum IgE below the range covered by the dosing table in the product label (<30 IU/mL) received omalizumab 150 mg every 4 weeks.

Results: Patients on omalizumab (n=10) demonstrated a significantly decreased urticaria symptom score beginning at 2 weeks (patient-assessed, p=0.002; physician-assessed, p=0.003) that continued throughout treatment (patient, p=0.007; physician, p=0.003 at 16 weeks), improved quality of life at 16 weeks (Skindex-29: symptoms, p=0.005, functioning, p=0.006, emotions, p=0.02), and significantly increased symptom-free days (p=0.02 by 2 weeks, p=0.0004 by 16 weeks) when compared with placebo controls (n=10) (Gober et al. 2008).

In summary, on the basis of positive data from four clinical studies, omalizumab may have a beneficial effect in the treatment of CIU.

1.3 RATIONALE FOR DOING THIS STUDY

Proof-of-concept data from completed studies suggest that omalizumab improves urticaria/pruritus in patients with CIU who have failed treatment with H1 antihistamines as well as those who have failed treatment with a combination of H1 and H2 antihistamines and a leukotriene receptor antagonist (Gober et al. 2008; Kaplan et al. 2008). In addition, data from the Phase II MYSTIQUE study (Q4577g), demonstrate that omalizumab at 300 mg and 600 mg significantly improves efficacy outcomes at Week 4 with no new safety signals. To further evaluate the safety of omalizumab in refractory CIU patients, this Phase III study is designed to evaluate the effect of omalizumab in patients with CIU refractory to treatment with H1 antihistamines.

The main purpose of this study is to demonstrate the efficacy and safety of omalizumab, compared with placebo, as an add-on therapy in patients aged 12–75 who remain symptomatic despite H1 antihistamine (anti-H1) therapy. In addition, the study is designed to evaluate the appropriate dose of omalizumab and the time to onset of clinical effect in patients with CIU, *as well as to provide information regarding disease recurrence after study treatment is withdrawn.*

2. OBJECTIVES

The primary objective for this study is as follows:

- To evaluate the efficacy of omalizumab compared with placebo in patients with refractory CIU receiving concomitant H1 antihistamine therapy

The secondary objectives for this study are as follows:

- To evaluate the safety of omalizumab therapy in patients with refractory CIU
- To evaluate onset of clinical effect of omalizumab therapy in CIU
- To evaluate the dose of omalizumab therapy in patients with refractory CIU
- *To evaluate duration of response after withdrawal of omalizumab in patients with refractory CIU*
- To evaluate the quality-of-life benefit of omalizumab therapy in patients with refractory CIU

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

The study is a global Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of omalizumab administered subcutaneously as an add-on therapy for the treatment of adolescent and adult patients aged 12–75 who have been diagnosed with refractory CIU and who remain symptomatic despite standard-dosed H1 antihistamine treatment. The study will enroll approximately 300 patients at approximately 70 study sites globally.

The study will consist of *three* distinct study periods over a time period of 30 weeks, as outlined below (see also Figure 1):

- Screening period: Day –14 to Day –1
- Treatment Period: Day 1 to Day 85 Pre-dose (Week 0 to Week 12)
- Follow-Up Period: Day 85 to Day 197 (Week 12 to Week 28)

The screening period will consist of visits at Day –14 and Day –7. Patients must meet all of the following criteria to enter the screening period:

- Non-electronic diary based UAS of ≥ 4 established in the clinic based on the patient's condition over 12 hours prior to either Day –14, Day –7, or Day 1 despite being on H1 antihistamine therapy
- Use of an approved dose of an H1 antihistamine for CIU at Day –14 and for at least the 3 consecutive days immediately prior to Day –14 (see Section 4.3.2 for list of H1 antihistamines available for use in this study)
- Willing and able to complete a symptom electronic diary (eDiary) twice daily throughout the screening period to establish the patient's UAS7 score

Patients will have the 2-week screening period to establish their eligibility for the study and baseline symptom scores. For the duration of the screening period, patients must maintain stable doses of their pre-screening H1 antihistamine treatment. To be eligible for the study, patients must have no missing eDiary entries, a UAS7 symptom score of ≥ 16 (equivalent to moderate to severe CIU symptoms for at least 4 out of the 7 days in a week), and a weekly itch score (a component of the UAS7) of ≥ 8 for the 7 days prior to randomization.

Only in exceptional circumstances, when information concerning eligibility is outstanding (e.g., pending laboratory data) will a longer screening period be permitted. Upon approval from the Medical Monitor, patients may be re-screened. Circumstances that may permit re-screening include, but are not limited to, an in-clinic UAS score or laboratory test results that do not meet eligibility requirements.

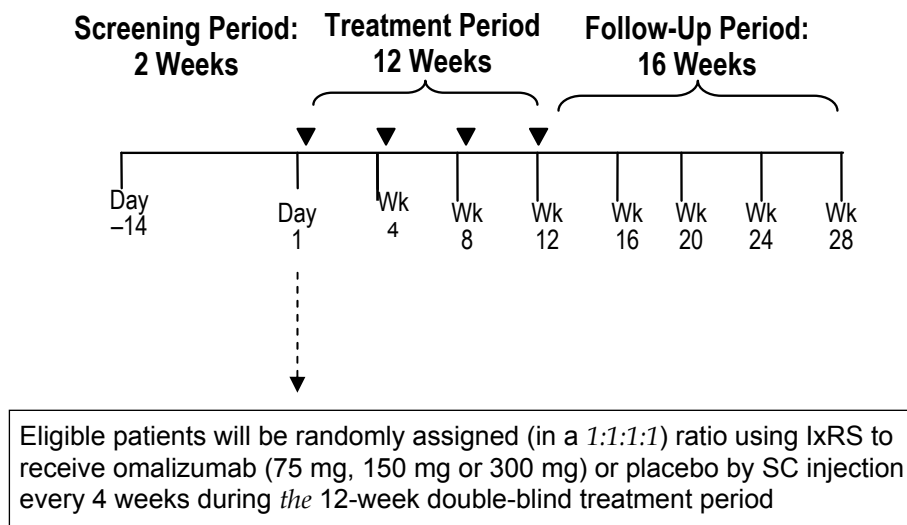
On Day 1, eligible patients will be randomly assigned (in a 1:1:1:1 ratio using Interactive Voice and Web Response System [IxRS]) to receive omalizumab (75, 150, or 300 mg) or placebo by subcutaneous (SC) injection every 4 weeks during the 12-week double-blind treatment period. There will be approximately 75 patients in *each of* the 75, 150, and 300 mg omalizumab treatment arms and in the placebo arm. Randomization to treatment groups will be stratified by baseline weekly itch score, baseline weight, and study site. A hierarchical dynamic randomization scheme will be used to achieve overall balance between treatment groups and within strata. Efficacy, safety, *pharmacokinetic (PK), and pharmacodynamic (PD)* data will be collected. For the duration of the *treatment period*, patients must maintain stable doses of their pre-randomization CIU H1 antihistamine treatment. The last dose of study drug during the *treatment period* will be given at the Day 57 (Week 8) study visit. *The primary endpoint will be measured at Week 12. In the follow-up period, patients may add up to one additional H1 antihistamine therapy (refer to Section 4.3.2). Increasing the dose of antihistamine above the approved dose is not permitted. The goal of allowing additional H1 antihistamine therapy after the primary endpoint has been assessed is to reduce patient dropout for improved safety evaluation.*

After completion of the 12-week *treatment period*, all patients will enter a 16-week follow-up period to allow for further characterization of the pharmacokinetics (PK) and pharmacodynamics (PD) of omalizumab, collection of additional efficacy and

safety data, and evaluation of the presence of anti-therapeutic antibodies (ATAs). Patients will continue to visit the study center at 4-week intervals. No study treatment will be given; patients must maintain stable doses of their pre-randomization CIU H1 antihistamine treatment.

The blind will be maintained for the full 28 weeks of the study (post-randomization). For the duration of the study, all patients will be provided with diphenhydramine (25 mg) for itch relief on an as-needed basis (up to a maximum of three doses in 24 hours or less based on local regulations).

Figure 1
Study Schema



An independent Data Monitoring Committee (iDMC) will be established to monitor safety and study conduct. Members of the iDMC will be external to the Sponsor, and will meet at regular intervals (at least once every 6 months).

The end of the study is defined as the last enrolled patient's last visit.

3.2 RATIONALE FOR STUDY DESIGN

The data from the MYSTIQUE study (Q4577g) demonstrated that omalizumab has significant efficacy in patients with CIU refractory to H1 antihistamine therapy. This effect was observed within the first week of a single administration

of the study drug. The objective of this Phase III study is to determine the efficacy and safety of omalizumab dosed every 4 weeks in patients with CIU refractory to non-sedating H1 antihistamines. This study will evaluate the comparative efficacy between omalizumab and placebo *and* the time to onset of clinical effect for H1 antihistamine refractory patients with CIU. The dose levels for this study are selected based on the efficacy results from the XCUISTE and MYSTIQUE studies.

Comparative efficacy between omalizumab and placebo will be evaluated during the *treatment period*. Efficacy will be determined using the primary endpoint of the change from baseline in the weekly itch score at Week 12. Assessment of itch is important as this is the most concerning symptom to patients as well as the most impactful on their quality of life. As CIU is both a disease of hives and intense itch, it is appropriate to evaluate clinical response using a composite endpoint, UAS, which incorporates both of these symptoms and this will be incorporated as a secondary endpoint.

Time to onset of the clinical effect of treatment with omalizumab will be evaluated during *the* treatment period. Time to onset of clinical effect is important to establish so that guidance can be given to patients with regards to both when a response should be expected as well as a period of time beyond which minimal, if any, response is expected to occur.

Disease recurrence after study drug is withdrawn will be measured during this study. For all patients, symptom scores will be measured during both the treatment and follow-up periods. Patients treated with omalizumab who have an excellent clinical response ($UAS7 \leq 6$) will be evaluated to determine when they have symptom relapse. This important information will be used along with data from other studies to provide guidance for the duration of therapy.

3.2.1 Rationale for Dose Selection

The doses for this study were selected based on the results of the Phase II MYSTIQUE study that tested a broad array of omalizumab doses (75, 300, and 600 mg) as a single SC injection in patients with CIU refractory to H1 antihistamines as well as the industry-sponsored XCUISTE study. In the MYSTIQUE study, the 300 mg and the 600 mg omalizumab dose groups

both demonstrated efficacy superior to the placebo group. However, there was no additional benefit observed for the 600 mg omalizumab group compared with the 300 mg omalizumab group. Finally, 75 mg of omalizumab showed only marginal differences in the UAS7 and weekly itch score endpoints compared with placebo and these differences were not statistically significant. Given that in the MYSTIQUE study patients received only a single-dose of study drug, it remains unclear whether multiple doses of 75 mg of omalizumab, administered over time, would show some benefit. It was also observed that for all dose levels, although drug exposure did vary by weight, no effect of weight on efficacy was observed in the MYSTIQUE study. Additionally, no effect of baseline IgE or reduction of post-treatment free IgE levels on efficacy was observed. The incidence of adverse events was similar for all treatment groups.

In the XCUISITE study, dosing was determined according to the omalizumab asthma dosing table which assigns patients to a dose level and frequency based on IgE level and weight. Patients were randomized to receive either omalizumab at the specified dose level or placebo. Treatment effects were analyzed by individual dose levels for the primary endpoint of change from baseline in UAS7 (using a different scale for the number of hives than in the MYSTIQUE study) after 24 weeks of therapy. The median treatment effect for the group receiving 300 mg omalizumab every 4 weeks was a reduction from baseline in UAS7 of 21 points and a reduction of 11 points for the group receiving 150 mg omalizumab every 4 weeks compared with a reduction of 3 points for patients receiving placebo. While this may suggest a difference in clinical effect between the 150 mg and 300 mg doses, it is difficult to draw conclusions about comparative efficacy between the dose levels, as the number of patients in each group was small ($n=6-7$) and the patients were assigned, not randomized, to the different dose levels.

To determine the appropriate dose of omalizumab for patients with CIU refractory to H1 antihistamines, three dose levels of omalizumab (75, 150, and 300 mg) given every 4 weeks will be evaluated during the *treatment period* in order to better define the dose-response relationship between omalizumab and a reduction of CIU symptoms. The highest dose level of 300 mg has been selected as the MYSTIQUE study results suggest an efficacy plateau might have been reached at this dose level when given as single dose. Additionally, the lowest dose level of 75 mg is included to evaluate whether efficacy is achieved at this level with multiple dosing given that

a single dose at 75 mg was not effective in MYSTIQUE. Finally, an intermediate dose level of 150 mg will be tested to better characterize the dose-response relationship suggested by the XCUISTE study. Flat dosing will be used in this study as the MYSTIQUE study results showed no clear relationship between efficacy and body weight or baseline IgE level, despite an effect of body weight on systemic exposure to omalizumab. The time at which peak efficacy was observed in MYSTIQUE defined the dosing interval of once every 4 weeks to minimize breakthrough CIU symptoms while avoiding over-dosing from giving omalizumab more frequently than necessary.

3.3 OUTCOME MEASURES

3.3.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure is the change from baseline in weekly itch score (a component of the UAS7) at Week 12 (see Table 1). The itch score will be recorded twice daily (morning and evening) in the patient eDiary, on a scale of 0 (none) to 3 (severe). The daily itch score is the average of the morning and evening scores. The baseline weekly itch score is the sum of the daily itch scores over the 7 days prior to randomization (Day 1 visit), and the weekly itch score at Week 12 is the sum of daily itch scores over the 7 days prior to the Week 12 visit (Day 85). The same principles of calculating baseline and Week 12 weekly scores will be applied to the following weekly outcomes unless otherwise stated.

3.3.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures are as follows:

- Change from baseline in UAS7 at Week 12

The UAS is a composite eDiary-recorded score with numeric severity intensity ratings on a scale of 0–3 (0=none to 3=intense/severe) for 1) the number of wheals (hives); and 2) the intensity of the itch (see Table 1), measured twice daily (morning and evening). The daily UAS is the average of the morning and evening scores and the UAS7 is the sum of the daily UAS scores over 7 days.

Table 1
Twice Daily Assessment of Disease Activity in Patients with CIU
(UAS Scale)

Score	Wheals (Hives)	Pruritus (Itch)
0	None	None
1	Mild (1–6 hives/12 hour)	Mild
2	Moderate (7–12 hives/12 hour)	Moderate
3	Intense (> 12 hives/12 hour)	Severe

CIU = chronic idiopathic urticaria.

- Change from baseline in weekly hives score at Week 12
The number of hives is measured twice daily (morning and evening), on a scale of 0 (none) to 3 (> 12). The daily hives score is the average of the morning and evening scores, and the weekly hives score is the sum of the daily hives scores over 7 days.
- Time to weekly itch score minimally important difference (MID) response by Week 12
Weekly itch score MID response is defined as a reduction from baseline in weekly itch score of ≥ 5 points. Time to weekly itch score MID response is the time (in weeks) from the date of the first dose to the date where weekly itch score MID response is first achieved.
- Proportion of patients with $UAS_7 \leq 6$ at Week 12
 $UAS_7 \leq 6$ identifies patients with an excellent clinical response who may be considering discontinuing therapy as they have minimal or no symptoms.
- Change from baseline in weekly largest hive score at Week 12
The largest hive score is measured twice daily, on a scale of 0 (none) to 3 (> 2.5 cm). The daily largest hive score is the average of the morning and evening scores, and the weekly largest hive score is the sum of the daily scores over 7 days.
- Proportion of weekly itch score MID Responders at Week 12
Weekly itch score MID responders are defined as patients who achieve a weekly itch score MID response at the Week 12 visit.
- *Proportion of patients with $UAS_7 \leq 6$ at Week 28*
- Change from baseline in health-related quality-of-life as measured by the Dermatology Life Quality Index (DLQI) at Week 12
- Proportion of angioedema-free days from Week 4 to Week 12 of therapy

3.3.3 **Safety Outcome Measures**

The safety of omalizumab will be assessed using the following safety outcome measures:

- Incidence and severity of adverse events and serious adverse events
- Changes in vital signs
- Clinical laboratory evaluations
- ATA evaluation at the end of the follow-up period

3.3.4 **Pharmacokinetic/Pharmacodynamic Outcome Measures**

The following PK and PD outcome measures will be reported:

- Summary trough serum levels of omalizumab, total and free IgE

3.3.5 **Exploratory Efficacy Outcome Measures**

The following exploratory *efficacy* outcome measures will be assessed:

- Proportion of patients with $UAS7 \leq 6$ at Week 28
- Time to UAS7 minimally important difference (MID) response by Week 12
UAS7 MID response is defined as a reduction from baseline in UAS7 score of ≥ 11 points. Time to UAS7 MID response is the time (in weeks) from the date of the first dose to the date where UAS7 MID response is first achieved.
- *Proportion of Week 12 responders who maintain their response ($UAS7 \leq 6$) to the Week 28 visit*
Week 12 responders are defined as patients who achieve an absolute $UAS7 \leq 6$ at Week 12.
- *Time to relapse in Week 12 responders*
Time to relapse is defined as the date of the Week 12 visit to the date where $UAS7 > 6$.
- Change from baseline in health-related quality-of-life as measured by the Chronic Urticaria Quality-of-Life Questionnaire (CU-Q2oL) at Week 12 and Week 28
- Change from baseline in health-related quality-of-life as measured by the DLQI at Week 28
- Change from baseline in the number of itch-free days and/or hive-free days at Week 12

- Change in number of tablets/week of sedating H1 antihistamine (diphenhydramine) for itch relief from baseline to Week 12
- Change from baseline in weekly sleep interference score at Week 12
 The sleep interference score is measured daily, on a scale of 0 (No interference) to 3 (substantial, woke up often, severe impact on sleep).
 The weekly sleep interference score is the sum of the daily scores over 7 days.
- Change from baseline in weekly interference with daily activities score at Week 12
 The daily activities interference score is measured daily on a 0 (No interference) to 3 (Substantial, severe interference with daily activities) scale. The weekly interference with daily activities score is the sum of the daily scores over 7 days.
- Change from baseline in health utility as measured by the EQ-5D at Week 12 and Week 28
- Change from baseline in MOS sleep score at Week 12

A number of laboratory investigations will be conducted to gain an insight into the mechanism of action of omalizumab in the patient population under study.

3.4 SAFETY PLAN

Omalizumab is currently approved for marketing in approximately 52 countries for patients 6 years and above (including, but not limited, to the European Union, New Zealand, and Russia). In some regions the indicated age is limited to 12 years and above (including, but not limited to the U.S., Canada, and Australia). Each individual country's basic prescribing information may vary, but in general, it is for the prevention of asthma exacerbations and control of asthma symptoms when given as add-on therapy for adult and adolescent patients with moderate to severe persistent allergic asthma who remain inadequately controlled. Consult the local prescribing information for more information.

Patient injections will be administered by a qualified healthcare professional, and patients will be monitored for an appropriate period of time after each dosing event. Patients will be instructed to recognize the signs and symptoms of any severe hypersensitivity reaction, and to contact a healthcare provider in case of any such symptoms.

Patients with CIU can have angioedema as part of their symptoms. When that angioedema poses a risk to the airway, the emergent use of systemic corticosteroids is indicated. Patients who need to be treated with systemic corticosteroids will be discontinued from study treatment and followed for safety for the remainder of the study. Patients will be provided emergency contact information and advised to contact a physician during the entire study, in case of angioedema.

During the conduct of the study, a treatment assignment should be unblinded only in the event of a life-threatening medical emergency that requires immediate unblinding/unmasking, or in the event of an unexpected serious adverse event judged by the investigator as related to study drug, for FDA safety reporting. In such cases, unblinding will be implemented following standard procedures, and only following agreement by both the investigator and Medical Monitor that unblinding is necessary.

Safety data including serious and non-serious adverse events and laboratory test results will be reviewed internally on a periodic basis during the conduct of the study. See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

An iDMC will review blinded and unblinded safety data provided to them by an independent Data Coordinating Center (iDCC) every 6 months for the duration of the study.

Please refer to the Omalizumab Investigator Brochure for additional information on safety risks.

3.5 STUDY PATIENTS AND ANALYSIS GROUPS

Patients enrolled in this study will have a CIU diagnosis for ≥ 6 months and will be refractory to approved-dose antihistamines as demonstrated by the presence of itch and hives for ≥ 8 consecutive weeks at any time prior to enrollment and a UAS7 score of ≥ 16 and itch component of UAS7 (range 0–21) ≥ 8 during the 7 days prior to randomization despite current use of approved-dose H1 antihistamine treatment. In addition, medical history will be obtained to evaluate what prior therapies the patients have used. Specifically, type of therapy and duration of treatment will be recorded from patient history.

This patient population was selected because while H1 antihistamines are the mainstay of therapy for CIU, some patients do not respond or respond only partially to these therapies and these tend to be the patients with more severe disease. Furthermore, therapeutic options are limited in these refractory patients.

The majority of CIU patients (approximately 55%) can be treated with H1 antihistamines, the majority of which have been approved for over-the-counter use (Kozel and Sabroe 2004). More recent analysis, however, suggests that an absence of CIU symptoms occurs in less than 50% of patients receiving regular-dosed H1 antihistamines (Maurer). For resistant cases of CIU, combinations of antihistamines (including highly sedating diphenhydramine and doxepin) and triple therapy (H1 antihistamine, H2 antihistamine, and LTRAs) have been reported to have some efficacy (Nettis 2001; Erbagci 2002; Di Lorenzo et al. 2004; Powell et al. 2007). While the majority of patients find relief with these medications, the most resistant patients have less attractive alternatives including immunosuppressive therapy with known side effects from chronic use.

The lifetime prevalence of CIU is widely published as 0.1% and when projected to the U.S. general population (i.e., 303,300,000); the total number of CIU patients is approximately 303,300 (Greaves 2000; U.S. Census Bureau 2008). Assuming that 50% of CIU is “truly” idiopathic, the estimated number of true CIU patients is 151,650, among which anywhere from 27%–55% (i.e., 40,946 to 87,957 CIU patients) may not respond to varying standard-of-care representing an unmet medical need (Grattan et al. 2000; Grattan et al. 2002; Gimenez-Arnau et al. 2007). More recent evidence suggests that CIU is more common than previously thought and may be increasing with current incidence estimates as high as 0.5%–1% of the population (Maurer).

Only a small group of CIU patients, approximately 40,000 to 89,000 patients in the United States, represent a population having a significant unmet medical need. These CIU patients remain symptomatic with symptoms including hives, angioedema, and pruritus, despite maximal doses of antihistamine medication for months to years (Grattan 2000; Powell et al. 2007). This study is designed to include moderate to severe CIU patients who are still symptomatic despite being treated with approved doses of H1 antihistamines.

The sites selected for this study will be specialty dermatology and immunology clinics with experience in treating CIU. The analysis group for the *treatment period* will include all patients who are randomized and received at least one dose of study drug (mITT: modified intention to treat). The number of patients randomized but not receiving study drug is expected to be very small, if not zero.

3.6 CONTROL GROUPS

Patients randomized to the placebo group will undergo the same assessments as the omalizumab group and receive their injections at the same time (every 4 weeks) as the omalizumab groups.

3.7 MINIMIZATION OF BIAS

Randomization and blinding will be employed to minimize bias in treatment assignment and to provide the basis for valid statistical inference. To minimize the risk of potential bias arising from confounding factors, a hierarchical dynamic randomization will be employed. The factors for balancing between the treatment groups will be in the following hierarchical order: overall balance, baseline weekly itch score (< 13 vs. ≥ 13), body weight (< 80 kg vs. ≥ 80 kg) and study site. Due to the large number of study sites in the study (approximately 70), the study site is planned to be last in the hierarchy. Please refer to Section 4.2 for a description of the method of treatment assignment and blinding.

3.8 ETHICAL CONSIDERATIONS

The potential adverse events associated with a placebo injection pose minimal risk to the patients in this population with an otherwise normal life expectancy and intact immune system. Adverse events for patients randomized to the active drug treatment are not expected to differ from other omalizumab clinical trials. All patients are receiving standard of care H1 antihistamine treatment at approved doses. In addition, all patients will be provided additional diphenhydramine treatment on an as-needed basis. Necessary precautions will be taken to ensure patient safety.

3.9 ADMINISTRATIVE STRUCTURE

Omalizumab in the treatment of CIU is a joint development project between Genentech, Inc., and Novartis Pharmaceuticals. This study is sponsored by Genentech, Inc., and will be managed by Genentech and a contract research

organization. Genentech, Inc., is the holder of the U.S. IND under which this study is being conducted. Novartis Pharmaceuticals and the contract research organization will file clinical trial applications and ethics committee submissions for this study outside of the U.S., as appropriate.

Approximately 70 sites globally will participate in the study. Approximately 300 patients will be randomized into this study. Randomization will occur through an IxRS (see Section 4.2).

An iDMC will be convened to evaluate safety data at 6-month intervals. This committee will consist of one biostatistician and two clinicians experienced in treating patients with CIU.

3.10 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with the U.S. Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), and applicable local, state, and federal laws, as well as other applicable country laws.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Patient Selection

A total of approximately 300 patients aged 12 to 75 years old who have been diagnosed with refractory CIU and who remain symptomatic despite conventional H1 antihistamine treatment will be randomized into this study.

4.1.2 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Aged 12–75 years (age limits may vary dependent upon regional restrictions)
- Diagnosis of CIU refractory to H1 antihistamines at the time of randomization, as defined by all of the following:

The presence of itch and hives for ≥ 8 consecutive weeks at any time prior to enrollment despite current use of H1 antihistamine treatment during this time period

UAS7 score (range 0–42) ≥ 16 and itch component of UAS7 (range 0–21) ≥ 8 during 7 days prior to randomization (Week 0)

In-clinic UAS ≥ 4 on at least one of the screening visit days (Day –14, Day –7, or Day 1)

Patients must have been on an approved dose of an H1 antihistamine for CIU for at least the 3 consecutive days immediately prior to the Day –14 screening visit and must document current use on the day of the initial screening visit

CIU diagnosis for ≥ 6 months

- Willing to give written informed consent, adhere to the visit schedules and meet study requirements

For those patients below the legal age of consent, the child must be willing to give written informed assent and the parent(s)/guardian(s) must be willing to give written informed consent.

For patients below the legal age of consent, both child and parent must be able to adhere to dose and visit schedules and meet study requirements.

- Willing and able to complete a daily symptom eDiary for the duration of the study
- Patients must not have any missing eDiary entries in the 7 days prior to randomization

4.1.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Treatment with an investigational agent within 30 days of Day –14
- Weight less than 20 kg (44 lbs)
- Clearly defined underlying etiology for chronic urticarias other than CIU (main manifestation being physical urticaria). This includes the following urticarias:

Acute, solar, cholinergic, heat, cold, aquagenic, delayed pressure or contact

As well as the following diseases as these diseases may have symptoms of urticaria or angioedema:

Urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary or acquired angioedema, lymphoma, leukemia, or generalized cancer

- Evidence of parasitic infection defined as having the following three items:

Risk factors for parasitic disease (living in an endemic area, chronic GI symptoms, travel within the last 6 months to an endemic area and/or chronic immunosuppression)

AND

An absolute eosinophil count more than twice the upper limit of normal
AND

Evidence of parasitic colonization or infection on stool evaluation for ova and parasites. Note that stool ova and parasite evaluation will only be conducted in patients with both risk factors and an eosinophil count more than twice the upper limit of normal

- Atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus or other skin disease associated with itch
- Previous treatment with omalizumab within a year prior to Day –14
- Routine (daily or every other day during 5 or more consecutive days) doses of the following medications within 30 days prior to Day –14: systemic or cutaneous (topical) corticosteroids (prescription or over the counter), hydroxychloroquine, methotrexate, cyclosporine, or cyclophosphamide
- IV immunoglobulin G (IVIG), or plasmapheresis within 30 days prior to Day –14
- Regular (daily/every other day) doxepin (oral) use within *14 days* prior to Day –14
- Any H2 antihistamine use within 7 days prior to Day –14
- Any LTRA (montelukast or zafirlukast) within 7 days prior to Day –14
- Any H1 antihistamines at greater than approved doses within 3 days prior to Day –14
- Patients with current malignancy, history of malignancy, or currently under work-up for suspected malignancy except non-melanoma skin cancer that has been treated or excised and is considered resolved
- Hypersensitivity to omalizumab or any component of the formulation
- History of anaphylactic shock
- Presence of clinically significant cardiovascular, neurological, psychiatric, metabolic or other pathological conditions that could interfere with the interpretation of the study results and or compromise the safety of the patients
- Medical examination or laboratory findings that suggest the possibility of decompensation of co-existing conditions for the duration of the study. Any items that are cause for uncertainty must be reviewed with the Medical Monitor.
- Inability to comply with study and follow-up procedures
- Evidence of current drug or alcohol abuse

- *Nursing women or women of childbearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they meet the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels >40 mIU/mL or 6 weeks post-surgical bilateral oophorectomy (with or without hysterectomy) or hysterectomy OR are using one or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation, vasectomy), hormonal contraception (implantable, patch, oral), and double-barrier methods (any double combination of: IUD, male or female condom with spermicidal gel, diaphragm, sponge, or cervical cap)*
- *Contraindications to diphenhydramine: Overreactivity against the agent diphenhydramine, other antihistaminic agents, or other components of this agent; acute bronchial asthma; acute angle-closure glaucoma; pheochromocytoma; hyperplasia of the prostate gland with formation of residual urine; epilepsy; hypokalemia; hypomagnesemia; bradycardia; a congenital long QT syndrome or other clinically significant cardiac disorders (especially coronary heart disease, disturbances in conduction, arrhythmias); the simultaneous application of drugs which prolong the QT interval (e.g., antiarrhythmic drugs class IA or III, antibiotics, cisapride, malaria drugs, antihistaminic drugs, neuroleptic drugs) or lead to hypokalemia (e.g., certain diuretic drugs); the simultaneous application of MAO inhibitors; the simultaneous uptake of alcohol*

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

At the Day 1 visit, patients will be randomized to one of 3 doses of omalizumab (75, 150, or 300 mg) or placebo at an approximately 1:1:1 ratio using an IxRS. Patients, all study personnel, the designated evaluating physician(s), the Sponsor and its agents (with the exception of the IxRS service provider, the remote unblinded monitoring staff, the unblinding statistician, the unblinded pharmacists at the sites, the iDMC members and the iDCC personnel) will be blinded to treatment assignment. Only the IxRS provider, the Sponsor's unblinding statistician and the iDCC statistician will have access to the unblinding code during the study.

Study drug supplies will be shipped blinded to each site. Each center will identify an individual responsible (e.g., pharmacist) for the reconstitution procedures. This individual will prepare the study drug for each patient prior to administration. An individual not involved with evaluating the patient must be identified to administer the study drug. To minimize risk of potential bias arising from

access to laboratory results that could potentially unblind treatment assignments (e.g., free IgE levels and serum omalizumab concentrations), access to these results will be restricted to the site and the Sponsor until study completion.

4.3 STUDY TREATMENT

4.3.1 Study Drug

a. Formulation

Omalizumab (Xolair[®]) is a sterile, white, preservative-free, lyophilized powder, contained in a single-use vial that will be reconstituted with sterile water for injection (SWFI), USP, and administered as a subcutaneous injection. Each omalizumab vial contains 202.5 mg of omalizumab, 145.5 mg sucrose, 2.8 mg L-histidine hydrochloride monohydrate, 1.8 mg L-histidine, and 0.5 mg polysorbate 20. Each vial is designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI, USP.

For further details, see the Omalizumab Investigator Brochure.

Placebo

The placebo contains the same ingredients as the omalizumab formulation listed above, excluding omalizumab.

b. Dosage, Administration, and Storage

Patients will receive omalizumab (75, 150 or 300 mg) or placebo administered subcutaneously every 4 weeks at the study center. Missed doses will not be replaced.

Study medication will be supplied as a lyophilized, sterile powder in a single-use, 5-mL vial that is designed to deliver 150 mg of omalizumab or placebo for SC administration upon reconstitution with 1.4 mL Sterile Water for Injection.

Each patient will receive two injections of study medication at every treatment visit. For details regarding each individual's injection, please refer to Appendix G.

Doses of more than 150 mg are divided among more than one injection site to limit injections to not more than 150 mg per site.

The reconstituted vial is to be used for single-dose administration only. Study drug will be administered subcutaneously to patients in the deltoid region of the right or left arm. Alternatively, the injections can be administered in the thigh if medically significant reasons preclude administration in the deltoid region. A curtain or other appropriate method to shield the patients from observing the injection will be used.

Study drug will be supplied in a blinded fashion. Study drug will be packaged in boxes of 1 vial per box and will be shipped at an ambient temperature in the United States and Canada. Two boxes will be provided at each dosing visit for the patient. In countries other than the United States and Canada, study drug will be shipped at 2°C–8°C. Study drug in all countries must be stored in refrigerated conditions (2°C–8°C; 36°F–46°F) in a limited access area and/or a locked refrigerator. Study drug should be stored according to the storage instructions on the box immediately upon receipt but no later than 24 hours after receipt.

Study drug should not be frozen or shaken. Study drug is for single use only and contains no preservatives. The solution should be used for subcutaneous injection within 8 hours following reconstitution if stored in the vial at 2°C–8°C (36°F–46°F), or within 4 hours of reconstitution if stored at room temperature. Reconstituted vials should be protected from direct sunlight. See Appendices F and G for study drug preparation and administration instructions.

Patients should be observed after administration of omalizumab for signs and symptoms of anaphylaxis. In addition, the study staff that administers omalizumab should be prepared to manage anaphylaxis. Patients should also be informed of the signs and symptoms of anaphylaxis and be instructed to seek immediate care should symptoms occur.

For detailed, blinded, study drug administration instructions, please see Appendix G.

c. Dosage Modification

No dosage modification of study drug will be allowed during this study.

4.3.2 Reference Drugs

The long-acting H1 antihistamines and doses allowed during the study are as follows:

- Cetirizine 5 or 10 mg once per day (QD)
- Levocetirizine dihydrochloride 2.5 or 5 mg QD

- Fexofenadine 60 mg twice per day or 180 mg QD
- Loratadine 10 mg QD
- Desloratadine 5 mg QD

4.4 CONCOMITANT AND EXCLUDED THERAPIES

4.4.1 Concomitant Therapy

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF). Patients will be encouraged to use the minimal dose required to control their symptoms.

All patients will be allowed to take study-defined H1 antihistamine medications at approved doses during the screening, treatment, and follow-up periods.

Patients should remain on a stable H1 antihistamine treatment regimen throughout the study period. Diphenhydramine (25 mg) will be provided and used on an as-needed basis (maximum 3 times/day) during screening, treatment and follow-up periods.

Therapies used for the treatment of CIU prior to enrollment will be collected as part of the patient's medical history.

4.4.2 Excluded Therapy

Prior to the screening visit (–14 days) and during the study, the following medications and treatments will be restricted:

- Routine (daily or every other day during 5 or more consecutive days) doses of the following medications within 30 days prior to Day –14: systemic or cutaneous (topical) corticosteroids (prescription or over the counter), hydroxychloroquine, methotrexate, cyclosporine, or cyclophosphamide
- Routine (daily or every other day during 5 or more consecutive days) doses of doxepin within *14 days* prior to Day –14
- Omalizumab within 1 year prior to screening
- Any LTRAs (montelukast or zafirlukast) or H2 blockers within 7 days prior to Day –14
- Any H1 antihistamines at greater than approved doses within 3 days prior to Day –14
- Either intravenous immunoglobulin G (IVIG) or plasmapheresis within 30 days prior to Day –14

Patients who receive any excluded therapy during screening should be considered a screening failure. Patients who receive any excluded therapy after randomization will be discontinued from study treatment; if a patient has received at least one dose of omalizumab following enrollment, the patient should be followed for safety for the remainder of the study.

Patients taking either LTRAs or H2 blockers for diseases other than CIU (e.g., asthma or GERD, respectively) will be permitted to continue their use during the study. These diseases must be recorded as part of the medical history collected during the screening period. Inhaled asthma controllers, including corticosteroids, are also permitted during the study.

4.5 STUDY ASSESSMENTS

The evaluations and procedures performed during the study are detailed in Appendix A-1.

4.5.1 Definitions of Study Assessments

a. Medical History and Concomitant Medications

Comprehensive medical and surgical history will be obtained at the Day –14 visit and concomitant medication usage will be collected at all visits, including unscheduled visits. The Day –14 medical history will include a comprehensive review of the patient's CIU medical history. This will include onset of symptoms, date of diagnosis, and therapies received for CIU.

b. Vital Signs

Vital signs will include measurements of pulse, systolic and diastolic blood pressure while the patient is in a seated position. Vital signs will be assessed as outlined in Appendix A-1 and during other unscheduled study visits when clinically indicated. The patients' height and weight will be measured once during the screening period.

c. Physical Examination

A physical examination will be performed as outlined in Appendix A-1 and during other unscheduled study visits when clinically indicated. The Day –14 visit physical examination should be comprehensive while subsequent examinations may be limited to detect changes in symptoms of CIU as well as directed by patient

complaints regarding adverse events. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

d. Laboratory Assessments

Samples for hematology, serum chemistries, and urinalysis will be analyzed at a central laboratory unless otherwise indicated. All blood draws should be drawn prior to study drug administration.

Laboratory assessments will include the following:

- Hematology (hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent and absolute differential count [neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells])
- Serum chemistries (sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatine phosphokinase, and uric acid)
- Stool ova and parasite evaluation. This test should be conducted in patients who have risk factors for parasitic disease (e.g., living in an endemic area, travel to an endemic area within the last 6 months, chronic GI symptoms or chronic immunosuppression) AND an eosinophil count > 2 times the upper limit of normal. This test should be conducted anytime during the screening period after the Day –14 results are available for applicable patients (test conducted locally).
- All women of childbearing potential (including those who have had a tubal ligation) will have a local urine pregnancy test. Post-menopausal women and women who have had a hysterectomy will not be required to have pregnancy testing. If a local urine pregnancy test shows a positive result, then study drug will not be administered that day. Other study procedures should also be postponed and the result must be confirmed by a serum pregnancy test (test to be conducted by central laboratory) prior to proceeding.
- Urinalysis including protein, glucose, nitrites, specific gravity, ketones, RBCs, WBCs, and microscopic examination including cellular elements and casts

The following laboratory assessments will be conducted to evaluate the mechanism of action of omalizumab in CIU:

- CU index test (IBT laboratories) – test to evaluate the presence of reactive autoantibodies to the IgE high affinity receptor

- Total blood cell histamine assay – test to evaluate histamine as a marker for overall intravascular basophil volume (*North American* sites only)
- Evaluation of basophil high-affinity IgE receptor density by FACS analysis
- Thyroperoxidase antibody

e. PK/PD Assessment

Blood samples will be collected at specified visits for determination of trough serum levels of omalizumab (PK), serum free-IgE (PD), and total-IgE (PD) (see Appendix A-2).

f. Anti-Therapeutic Antibodies Assessment

Blood samples will be collected at specified visits for ATA determination (see Appendix A-2).

g. Exploratory Blood RNA and Serum Biomarker Samples

These samples will be collected at a subset of visits and stored for later use for exploratory research of markers of drug response.

h. In-Clinic Measured Urticaria Activity Score

The In-Clinic Measured UAS is a non-eDiary based, in-clinic measured UAS score based on the patient's condition over 12 hours prior to the visit and will be assessed as outlined in Appendix A-1.

The UAS is a composite score with numeric severity intensity ratings (0=none to 3=intense/severe) for a) the number of wheals (hives); and b) the severity of the itch. The maximum in-clinic measured UAS value is 6 (see Appendix H).

i. Patient eDiary

The eDiary questions will consist of UAS (itch score, number of hives), largest hive size, sleep interference score, activity interference question, diphenhydramine use, angioedema episodes, and calls to doctor or nurse practitioner (see Appendix B). The eDiary is to be completed twice a day by the patient for the duration of the study. The eDiary will be given to the patient at the Day –14 visit.

j. Patient Reported Outcomes (PROs)

- The Medical Outcomes study Sleep Scale (see Appendix C), DLQI (see Appendix D), EQ-5D (see Appendix E), and CU-Q2oL will be performed prior to study drug administration when applicable (see Appendix A-1). Note that some of these PROs (Chronic Urticaria Quality-of-Life Questionnaire [CU-Q2oL]) will not be available in some regions.

- Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) is a 10-item dermatology-specific health-related quality of life measure (Finlay 1994). Patients rate their dermatology symptoms as well as the impact of their skin condition on various aspects of their lives. An overall score will be calculated as well as for the following domains: Symptoms and Feelings, Daily Activities, Leisure, Work and School, Personal Relationships, Treatment. The minimally important difference of the overall DLQI score for patients with CIU has been estimated to be 2.24–3.10 (Shikier et al. 2005).

- Chronic Urticaria Quality-of-Life Questionnaire (CU-Q2oL)

The Chronic Urticaria Quality-of-Life Questionnaire (CU-Q2oL) is a 23-item CIU-specific health-related quality of life questionnaire (Baiardini et al. 2005). Patients rate their CIU symptoms and the impact of their CIU on various aspects of their lives. An overall score will be calculated as well for the following domains: Pruritus, Swelling, Impact on Life Activities, Sleep Problems, Limits, and Looks.

- EuroQoL-5D Questionnaire

The EuroQoL-5D (EQ-5D) questionnaire is a generic preference-based health related quality of life questionnaire that provides a single index value for health status (The EuroQol Group 1990). The EQ-5D questionnaire is designed for self-completion by patients and consists of five questions each with three possible categories (no problems, moderate problems, severe problems) and a visual analogue scale from 0 (worst possible health state) to 100 (best possible health state). Patients are asked to rate the health-related quality of life during the past day. The five questions comprise five dimensions of health (Mobility, Self-care, Usual Activities, Pain/Discomfort, and Anxiety/Depression). A EuroQoL-5D Index Score will be constructed using the five questions and the appropriate population-based weights. The data from the visual analog scale will be summarized in the Health State variable.

- Medical Outcomes Study Sleep Scale (MOS Sleep Scale)

The Medical Outcomes Study Sleep Scale (MOS Sleep Scale) is a 12-item questionnaire asking patients to rate various dimensions of their sleep over the past four weeks (Hays et al., 1992, Spritzer et al. 2003).

Several scores can be derived: Sleep Disturbance, Snoring, Short of Breath, Sleep Adequacy, Somnolence, Sleep Problems Index I, Sleep Problems Index II, Sleep Quantity, and Optimal Sleep.

4.5.2 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations and before restricting medications and treatments. The informed consent process must be documented in the patient's medical chart.

Informed Consent Forms for patients who are not subsequently enrolled will be maintained at the study site.

Screening and pretreatment tests and evaluations will be performed within 14 days preceding Day 1 (defined as the day of first dose of study drug), unless otherwise specified. Extensions to the screening period may be permitted under exceptional circumstances if information concerning eligibility is outstanding. Results of standard-of-care examinations performed prior to obtaining informed consent and within 14 days prior to study entry may be used and do not need to be repeated for screening.

Patients will be instructed on the use and completion of their electronic diaries at screening and the diaries will be reviewed by the study personnel on Day 1 to ensure that they are being completed correctly.

Please see the Study Flowchart provided in Appendix A-1 for the schedule of screening and pretreatment assessments.

4.5.3 Assessments during Treatment

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before the first injection of study drug.

The Week 12 visit should be scheduled on Day 85 (not on Day 84 or earlier). A +3-day window is allowed from the scheduled date.

All assessments will be performed at the time of the specified visit unless a time window is specified. Assessments scheduled on the day of study drug administration should be performed prior to study drug administration, unless otherwise noted.

Please see the Study Flowchart provided in Appendix A-1 for the schedule of treatment period assessments.

4.5.4 Study Completion/Early Termination Visit

Patients withdrawing from study treatment should be encouraged to continue attending the clinic every 4 weeks as per the Study Flowchart provided in Appendices A-1 and A-2 and at minimum will be asked to return to the clinic ≤ 16 weeks after the last dose administered for an early termination visit.

See Section 4.6 for the schedule of assessments to be completed for patient discontinuation.

Please see the Study Flowchart provided in Appendices A-1 and A-2 for assessments to be performed at the early termination visit.

4.5.5 Follow-Up Assessments

Ongoing adverse events thought to be related to omalizumab will be followed until the event has resolved to baseline grade; the event is assessed by the investigator as stable; the patient is lost to follow-up; the patient withdraws consent; or when it has been determined that the study treatment or participation is not the cause of the adverse event.

Please see the Study Flowchart provided in Appendix A-1 for specified follow-up assessments.

4.5.6 Unscheduled Visits

Patients may come in to clinic for unscheduled visits to assess adverse events or serious adverse events that occur during the study. These visits should be recorded and no specific evaluation or diagnostic testing is required on these days. Concomitant medication usage should also be collected.

4.6 PATIENT DISCONTINUATION

The investigator has the right to discontinue a patient from the study for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study; for reasons of noncompliance (e.g., missed doses, missed visits, or missing eDiary entries); if the patient becomes pregnant; or if the investigator determines it is in the best interest of the patient.

See Sections 4.5.4 and 4.5.5 for assessments that are to be performed for patients who prematurely withdraw from the study during the treatment period. Patients who discontinue from the study will not be allowed to re-enter the study.

4.7 STUDY DISCONTINUATION

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Data recording is inaccurate or incomplete
- In addition, the Sponsor may decide to discontinue the study based on the iDMC recommendation.

4.8 POST-STUDY ACCESS

Currently, Genentech does not have any plans to provide omalizumab or other study interventions to patients after the conclusion of the study or upon earlier withdrawal. Genentech will evaluate the appropriateness of continuing to provide omalizumab to study patients after evaluating the primary efficacy outcome measure and safety data gathered in the study.

4.9 ASSAY METHODS

Serum total omalizumab levels as well as total and free IgE levels will be measured in quantitative immunoassays. ATAs will be detected using a fragment ELISA. Samples that screen for positive ATA will be further characterized using an immunodepletion-based assay.

4.10 STATISTICAL METHODS

All analyses of efficacy outcomes from the *treatment period* will include all patients who were randomized and received at least one dose of study drug (mITT: modified intention to treat), unless otherwise specified. The number of patients randomized but not receiving study drug is expected to be very small, if not zero. Patients will be analyzed according to the treatment arm to which they were randomized.

Safety analyses will include all patients who were randomized and received at least one dose of study treatment, with patients analyzed according to the treatment actually received.

Unless otherwise specified, treatment comparisons will be performed between each of the omalizumab groups (75, 150, and 300 mg) and the placebo group. Procedures will be employed to adjust for multiple comparisons in order to maintain a type I error rate for the primary endpoint analysis of $\alpha=0.05$ (two sided). Full details of the Type I error control plan will be provided in a separate document. The statistical test to be employed for each comparison is specified below. Descriptive summaries of continuous data will present the group mean, standard deviation, median, minimum, maximum, and sample size. Descriptive summaries of discrete data will report the number of patients and incidence as a frequency and as a percentage.

The baseline value of any variable will be defined as the last available value prior to the first administration of study drug for the *treatment period* (Day 1), unless otherwise specified.

Full details of the statistical methods will be described in the Statistical Analysis Plan.

4.10.1 Analysis of the Conduct of the Study

The disposition of patients for each study period will be summarized by treatment group with respect to the number of patients randomized, treated, and completing each treatment period. Patient discontinuation and the reason for discontinuation will be summarized by treatment group for each *study* period. The number of patients who complete each scheduled dose will be summarized by treatment group for each treatment period. The number of patients who violate key eligibility

criteria as well as those who have major protocol deviations will be summarized by treatment group for each study period.

4.10.2 Analysis of Treatment Group Comparability

Treatment groups entering the *treatment period* of the study will be assessed for comparability with respect to demographic (i.e., age, sex, race/ethnicity) and baseline characteristics (e.g., body weight, presence of anti-FcεRI autoantibody as detected by CU index test, total IgE levels, UAS7 weekly itch score, weekly hive score, weekly size of the largest hive score, interference with sleep, and the presence of angioedema).

4.10.3 Efficacy Analyses

a. Primary Endpoint

The primary efficacy endpoint is the change in weekly itch score from baseline to Week 12. The analysis of the primary endpoint will consist of treatment comparisons made using analysis of covariance (ANCOVA) controlling for baseline weekly itch score, and baseline weight (<80 kg vs. ≥80 kg).

The ANCOVA model will be based on the MITT patients. Missing Week 12 itch scores will be imputed by carrying forward the patients' baseline scores (BOCF). The Week 12 itch scores for patients who received excluded therapy listed in Section 4.4.2 by Week 12 will also be imputed using their baseline scores.

b. Secondary Endpoints

- Change from baseline in UAS7 at Week 12

The evaluation of this endpoint will consist of treatment comparisons made using ANCOVA controlling for baseline UAS7 and baseline weight (<80 kg vs. ≥80 kg).

- Time to weekly itch score MID response by Week 12

Treatment comparisons of time to first weekly itch score MID response by Week 12 will be performed using the Cox proportional hazards (PH) model stratified by baseline weekly itch score and baseline weight (<80 kg vs. ≥80 kg). Kaplan-Meier estimates of the distribution of time to weekly itch score MID response will be presented graphically.

For the purpose of this analysis, time to weekly itch score response will be censored at the Week 12 visit date for patients who have not achieved MID response by Week 12.

- Proportion of patients with $UAS7 \leq 6$ at Week 12
The Cochran-Mantel-Haenszel test stratified by baseline UAS7 and baseline weight (<80 kg vs. ≥ 80 kg) will be performed to compare the proportions of patients with $UAS7 \leq 6$ at Week 12 in each of the omalizumab groups versus placebo.
- Change from baseline in weekly hive score at Week 12
Treatment comparisons of change from baseline to Week 12 in the weekly hives score will be made using ANCOVA controlling for baseline weekly hives score, and baseline weight (<80 kg vs. ≥ 80 kg).
- Change from baseline in weekly largest hive score at Week 12
The analysis of change from baseline to Week 12 in the weekly largest hive score will consist of treatment comparisons made using ANCOVA controlling for baseline weekly largest hive score, and baseline weight (<80 kg vs. ≥ 80 kg).
- Proportion of weekly itch score MID responders at Week 12
The Cochran-Mantel-Haenszel test stratified by baseline weekly itch score, and baseline weight (<80 kg vs. ≥ 80 kg) will be performed to compare the proportions of weekly itch score MID responders at Week 12 in each of the omalizumab groups versus placebo.
- *Proportion of patients with $UAS7 \leq 6$ at Week 28*
The Cochran-Mantel-Haenszel test stratified by baseline UAS7 and baseline weight (<80 kg vs. ≥ 80 kg) will be performed to compare the proportions of patients with $UAS7 \leq 6$ at Week 28 in each of the omalizumab groups versus placebo.
- Change from baseline in health-related quality-of-life as measured by the DLQI at Week 12
The analysis of change from baseline at Week 12 in DLQI will consist of treatment comparisons made using ANCOVA controlling for baseline DLQI, and baseline weight (<80 kg vs. ≥ 80 kg).
- Proportion of angioedema-free days from Week 4 to Week 12 of therapy
The analysis of the proportion of angioedema-free days from Week 4 to Week 12 will consist of treatment comparisons made using ANCOVA controlling for baseline weight (<80 kg vs. ≥ 80 kg).

c. Additional Analyses of the Primary Endpoint

Sensitivity analyses of the primary endpoint will be performed as follows:

- An ANCOVA model will be fitted which controls for baseline weekly itch score, and baseline weight (< 80 kg vs. ≥ 80 kg) with missing Week 12 weekly itch scores imputed by the method of last observation carried forward (LOCF).
- A mixed effects model will be fitted which includes all available weekly itch scores from baseline to Week 12. All mITT patients will be included in this analysis.
- An ANCOVA model will be fitted which controls for baseline weekly itch score, baseline weight (< 80 kg vs. ≥ 80 kg), and diphenhydramine use during Week 12 (≤ 15 tablets vs. > 15 tablets) with missing Week 12 itch scores imputed by the BOCF method.

d. Type-I Error Control Plan for the Primary and Secondary Endpoints

A type I error control plan will be employed for the testing of the primary endpoint for each of the omalizumab groups versus the placebo group in order to maintain an overall type I error rate of 0.05 (two-sided) across the three omalizumab dose levels. For an omalizumab dose group that is statistically significantly different from the placebo group with regard to the primary endpoint, the statistical tests for treatment differences between the omalizumab group and placebo will be conducted for the secondary endpoints at the 0.05 significance level in the following hierarchical order:

- Change from baseline in UAS7 at Week 12
- Change from baseline in the weekly hive score at Week 12
- Time to weekly itch score MID response at Week 12
- Proportion of patients with UAS7 ≤ 6 at Week 12

The details of Type-I Error control plan will be specified as part of the Statistical Analysis Plan.

e. Exploratory Endpoints

The details of the methods for the analysis of exploratory endpoints listed in Section 3.3.5 will be specified in the Statistical Analysis Plan. For the endpoints used to characterize disease/symptom recurrence, which include but are not limited to the following two outcome measures, descriptive summary statistics for each treatment group will be

provided but no statistical tests will be conducted to compare between treatment groups given that there is no proper comparison group:

- *Proportion of Week 12 responders who maintain their response ($UAS7 \leq 6$) to the Week 28 visit, with Week 12 responders defined as patients who achieve an absolute $UAS7 \leq 6$ at Week 12*
- *Time to relapse in Week 12 responders, with relapse defined as the first time $UAS7 > 6$ after the Week 12 visit*

4.10.4 Safety Analysis

Safety will be assessed through the summary of adverse events, laboratory test results, vital signs, and antibodies to omalizumab. These summaries will be produced for the whole study and separately for the *treatment period* and the *follow-up period*. The following analyses of safety will be conducted for all patients who receive any amount of study drug.

a. Adverse Events

Verbatim descriptions of treatment-emergent adverse events will be coded and summarized by treatment group. Separate summaries will be generated for serious adverse events, deaths, and adverse events leading to discontinuation of study drug.

b. Laboratory Tests

Descriptive summaries of laboratory values at baseline and throughout the study will be generated for selected parameters. For these selected parameters, changes from baseline and the proportion of patients experiencing clinically significant changes relative to baseline will be compared between treatment groups.

c. Vital Signs

Descriptive summaries of vital signs, including the change from baseline for vital signs, will be generated by treatment group. Vital signs include pulse and systolic and diastolic blood pressure.

4.10.5 Pharmacokinetic and Pharmacodynamic Analyses

Total omalizumab, free and total IgE levels will be summarized using descriptive statistics by treatment group for each visit at which these analytes are measured.

4.10.6 Handling of Missing Data

a. Calculation of UAS7 Score

The UAS7 score is the sum of the average daily UAS scores over 7 days each week. The daily UAS scores are calculated based on daily eDiary entries for itch and hives scores. For each of the morning and evening eDiary entries, the UAS score is calculated as the sum of the itch and hives scores. The daily UAS score is then calculated as the average of the morning and evening UAS scores.

When either the morning or evening score is missing, the non-missing UAS score for that day (morning or evening) will be used as the daily score. When one or more of the daily UAS scores are missing, the following principles will be applied to handle the missing data:

- If a patient has at least 4 non-missing daily UAS scores within the 7 days prior to the study visit, the UAS7 score is calculated as the sum of the available eDiary UAS scores in that week, divided by the number of days that have a non-missing diary UAS score, multiplied by 7.
- If there are less than 4 non-missing daily UAS scores within the prior 7 days, then the UAS7 score is missing for the week.

The same principles will be applied to handle the missing data for all of the weekly outcomes.

b. Imputation of Missing Values for Primary Endpoint and Other Weekly Scores

Weekly Itch Score

For the analysis of the weekly itch score change from baseline, patients with a missing score at Week 12 will have the Week 12 weekly itch score imputed by their baseline weekly itch score. This method is considered conservative under the assumption that the majority of patients will withdraw prematurely from the treatment due to a lack of symptom improvement resulting in missing the Week 12 score.

The same imputation methods that are applied to the weekly itch score endpoint will be applied to the following endpoints:

- UAS7 score
- Weekly hives score
- Weekly largest hive score
- DLQI

Response Status

Patients who discontinue from the study or from study treatment prior to Week 12 will be classified as non-responders for the following endpoints:

- Weekly itch score MID responder
- UAS7 ≤ 6 response
- UAS7 MID responder

The same principle will be applied to responder endpoints evaluated at Week 28.

Time to the Weekly Itch Score MID Response

This endpoint will be considered censored at the date of the last non-missing weekly itch score evaluation up to the Week 12 study visit for any patient who fails to achieve an MID response. If a patient discontinues treatment prior to Week 12, without achieving an MID response, this endpoint will be censored as of the day of treatment discontinuation.

4.10.7 Determination of Sample Size

The sample size for this study is primarily based on safety and regulatory considerations. The estimation of power for efficacy assumes a mean change from baseline in the weekly itch score at Week 12 to be 9 points and 3.5 points for the omalizumab and placebo group, respectively, with a common standard deviation of 6 points (based on data from the MYSTIQUE and XCUISITE studies). Assuming an early discontinuation rate of 15% (based on data from the MYSTIQUE and XCUISITE studies) by Week 12, a total of 300 patients (*1:1:1:1 randomization ratio with 75 patients in each treatment group*) will yield approximately 98% power to detect a difference in treatment effect in the primary endpoint at the 0.05 level for any omalizumab group. A multiplicity type-I error control plan will be employed to adjust for the comparisons of multiple omalizumab groups to the placebo group in order to maintain an overall type I error rate of 0.05 (two sided).

4.11 DATA QUALITY ASSURANCE

The data will be collected via Electronic Data Capture (EDC) using eCRFs.

The site will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the

sites will resolve electronically in the EDC system. The CRO will be responsible for the data management of this study, including quality checking of the data.

Genentech will perform oversight of the data management of this study.

Genentech will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central Laboratory data and other electronic data (including eDiary) will be sent directly to Genentech, using Genentech's standard procedures to handle and process the electronic transfer of these data. eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at Genentech and records retention for the study data will be consistent with Genentech's standard procedures.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

The Sponsor or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

The Sponsor or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. The Sponsor or its designee will report other relevant SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central IRBs/ECs (except in the United States where investigators are responsible for reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification.

5.1.1 **Adverse Event**

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with CIU that were not present prior to the AE reporting period (see Section 5.2.1)
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies)
- AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention (e.g., medication washout)
- Preexisting medical conditions (including the condition being studied, CIU) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

5.1.2 **Serious Adverse Event**

An SAE is any AE that is any of the following:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- A congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product(s)
- Considered a significant medical event by the investigator (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

All AEs that do not meet any of the criteria for serious should be regarded as **non-serious AEs**.

The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache). “Serious” is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient’s life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the eCRF.

5.2 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs and SAEs (as defined in Section 5.1) are recorded on the eCRF and reported to the Sponsor in accordance with protocol instructions.

5.2.1 Adverse Event Reporting Period

After informed consent, but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures or medication washout). Patients who undergo screening procedures but do not enroll in the study will not have SAEs recorded in the clinical database.

After initiation of study medications, all AEs and SAEs regardless of attribution will be collected until 140 days (7 drug half-lives) following the last administration of study treatment or study discontinuation/termination, whichever is later.

After this period, investigators should report only SAEs that are felt to be related to prior study treatment (see Section 5.6).

5.2.2 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive questions include:

“How have you felt since your last clinic visit?”

“Have you had any new or changed health problems since you were last here?”

5.2.3 **Assessment of Severity and Causality of Adverse Events**

Investigators will seek information on AEs and SAEs at each patient contact. All AEs and SAEs, whether reported by the patient or noted by authorized study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

For each AE and SAE recorded on the applicable eCRF, the investigator will make an assessment of seriousness (see Section 5.1.2 for seriousness criteria), severity and causality.

Table 2 provides guidance for grading AE severity and Table 3 provides guidance for assessing the causal relationship to the investigational product(s).

The following AE grading (severity) will be used for AE reporting.

Table 2
Adverse Event Grading (Severity) Scale

Mild	Symptoms causing no or minimal interference with usual social and functional activities.
Moderate	Symptoms causing greater than minimal interference with usual social and functional activities.
Severe	Symptoms causing inability to perform usual social and functional activities.

Regardless of severity, some events may also meet the regulatory criteria for “serious”. For definition of SAE, refer to Section 5.1.2.

To ensure consistency of causality assessments, investigators should apply the following general guidelines:

Table 3
Causal Attribution Guidance

Is the AE/SAE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?	
YES	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship possible, AND other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the AE/SAE.
NO	The temporal relationship of the AE/SAE to investigational product administration makes a causal relationship unlikely, OR other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the AE/SAE.

Note: The investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators and applicable regulatory authorities. The causality is to be reported as either yes or no. The investigator should assess the event as best as possible at the time of its occurrence. Should they need to update the causality assessment in the future, they can. The causality assessment is required for every event the patient experiences. Causality assessment must be provided each time an AE report is made. If the need to reassess causality for an AE arises, an updated report can be made at any time.

5.3 PROCEDURES FOR RECORDING ADVERSE EVENTS

5.3.1 Recording Adverse Events on the eCRF

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the eCRF. Avoid colloquialisms and abbreviations.

There is one eCRF page for recording AEs or SAEs.

Only one medical concept should be recorded in the event field on the Adverse Event eCRF.

a. Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

c. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the eCRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on the Adverse Event eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on Adverse Event eCRF.

d. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5× the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the eCRF, unless their severity, seriousness, or etiology changes.

e. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.2.1), regardless of attribution, will be recorded on an Adverse Event eCRF and expeditiously reported to the Sponsor. This includes death attributed to progression of CIU.

When recording a death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “Unexplained Death” on the eCRF.

If the death is attributed to progression of CIU, record “chronic idiopathic urticaria progression” as the SAE term on the eCRF.

f. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

g. Worsening of Chronic Idiopathic Urticaria

Chronic idiopathic urticaria should be recorded as an AE or SAE only if judged by the investigator to have unexpectedly worsened in severity and/or frequency or changed in nature any time during the study. When recording an unanticipated worsening of chronic idiopathic urticaria on an Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “accelerated chronic idiopathic urticaria”).

h. Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol.

There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

i. Pregnancy

If a female patient becomes pregnant while receiving investigational therapy or within 9 months after the last dose of investigational product, a Pregnancy Report eCRF should be completed and submitted via the EDC system within 24 hours of learning of the pregnancy.

Abortion, whether therapeutic or spontaneous, should always be classified as serious (as the Sponsor considers these medically significant), recorded on an AE eCRF, and expeditiously reported to the Sponsor.

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to the investigational product should be recorded and reported as an SAE.

In the event the EDC system is unavailable, a Pregnancy Report worksheet and Pregnancy Fax Coversheet should be completed and faxed to the Sponsor's Drug Safety Department or its designee at the fax numbers listed in Section 5.4.2.

For U.S. Sites only:

Any pregnancy that occurs in a patient known to receive omalizumab should be reported per study reporting guidance and the patient should be referred to the Xolair Pregnancy Registry at 1-888-4XOLAIR (496-5247), option 3.

During the conduct of the study, a treatment assignment should be unblinded only in the event of a life-threatening medical emergency that requires immediate unblinding/unmasking, or in the event of an unexpected serious adverse event judged by the investigator as related to study drug, for FDA safety reporting. In such cases, unblinding will be implemented following standard procedures, and only following agreement by both the investigator and Medical Monitor that unblinding is necessary.

5.4 EXPEDITED REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS

5.4.1 Reporting Requirements for Fatal/Life-Threatening SAEs Related to Investigational Product

Any life-threatening (i.e., imminent risk of death) or fatal AE that is attributed by the investigator to the investigational product will be telephoned to the Medical Monitor immediately, followed by submission of written case details on an eCRF within 24 hours as described in Section 5.4.2.

Medical Monitor Contact Information for sites in the United States:

Medical Monitor:	Edward Conner, M.D.
Telephone No.:	(650) 467-1661
Alternate Telephone No.:	(888) 835-2555

Table 4
Serious Adverse Event Reporting Contact Numbers
for Countries Outside of the United States

Country	Fax	Phone
Australia	1 800 122 898	1 800 121 020
Canada	1 800 69 66 306	1 800 696 58 64
Denmark	800 18513	800 18503
France	0 800 90 64 78	0 800 906 485
Germany	0 800 1 818 909	0 800 1 820 510
Italy	800 8 74 751	800 8 747 41
New Zealand	0 800 44 95 92	0 800 44 95 91
Poland	00 800 353 1 204	00 800 353 1 203
Russia	AT&T access code 363 2400 (Moscow) or 8 pause 495 363 2400 (Outside Moscow) or 8 pause 812 363 2400 (Outside St. Petersburg) or 8 + pause + 10-800-110-1011 (all other places) + Pause + Fax # : 877 264 10 39	AT&T access code 363 2400 (Moscow) or 8 pause 495 363 2400 (Outside Moscow) or 8 pause 812 363 2400 (Outside St. Petersburg) or 8 + pause + 10-800-110-1011 (all other places) + Pause + Phone # : 877 264 10 40
Singapore	AT&T access code 800 0111 111 + Pause + Fax # : 877 264 10 39	AT&T access code 800 0111 111 + Pause + Phone # : 877 264 10 40
Spain	900 943 531	900 943 530
Switzerland	0 800 55 97 67	0 800 55 97 63
Turkey	AT&T access code 0811 288 0001 + Pause + Fax # : 877 264 10 39	AT&T access code 0811 288 0001 + Pause + Phone # : 877 264 10 40
United Kingdom	0 800 132 079	0 800 834 450

5.4.2 Reporting Requirements for All SAEs

Investigators will submit reports of all SAEs, regardless of attribution to Sponsor or designee within 24 hours of learning of the events. For initial SAE reports, investigators should record all case details that can be gathered within 24 hours on an AE eCRF and submit the report via the EDC system. A report will be generated and sent to Sponsor's Drug Safety or designee by the EDC system. In the event the EDC system is unavailable, or an SAE occurs during screening, a completed SAE Report worksheet and fax coversheet should be faxed immediately upon completion to Sponsor's Drug Safety Department or its designee at the fax numbers indicated below. Once the EDC system is available, or the patient is randomized to treatment, all information will need to be entered and submitted via the EDC system.

Sites in the United States:

Fax No.: (650) 225-4682

Alternate Fax No.: (650) 225-5288

Sites Outside of the United States:

See Table 4 for a country specific list of contact phone numbers for SAE reporting.

Relevant follow-up information should be submitted to Sponsor's Drug Safety Department or its designee as soon as it becomes available and/or upon request.

5.5 TYPE AND DURATION OF FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

The investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized, the patient is lost to follow up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification (SDV).

For some SAEs, the Sponsor or its designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

5.6 POST-STUDY ADVERSE EVENTS

At the last scheduled visit, the investigator should instruct each patient to report to the investigator any subsequent SAEs that the patient's personal physician believes could be related to prior study treatment.

The investigator should notify the study Sponsor of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation if felt to be related to prior study treatment. The Sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in this study. The investigator should report these events to Sponsor's Drug Safety or designee on the Adverse Event eCRF. If the EDC system is no longer available, the investigator should report the event directly to Sponsor's Drug Safety or designee via phone at 1-888-835-2555.

6. INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study and any study-related procedures at a specific site, the following documents must be on file with Sponsor or a Sponsor representative:

- U.S. FDA Form 1572 for each site (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator

The names of any sub-investigators must appear on this form.

Investigators must also complete all regulatory documentation as required by local and national regulations.

- Current curricula vitae and evidence of licensure of the Principal Investigator and all sub-investigators
- Complete financial disclosure forms for the Principal Investigator and all sub-investigators listed on the U.S. FDA Form 1572
- U.S. sites only: Federalwide Assurance number or IRB statement of compliance
- Written documentation of IRB/EC approval of the protocol (identified by protocol number or title and date of approval) and Informed Consent Form (identified by protocol number or title and date of approval)
- A copy of the IRB/EC-approved Informed Consent Form

The Sponsor or its designee must review any proposed deviations from the sample Informed Consent Form.

- Current laboratory certification of the laboratory performing the analysis (if other than a Sponsor-approved central laboratory), as well as current references ranges for all laboratory tests
- A Clinical Research Agreement signed and dated by the study site
- Investigator Brochure Receipt signed and dated by the Principal Investigator
- Certified translations of an approved Informed Consent Form, and any other written information to be given to the patient (when applicable), IRB/EC approval letters, and pertinent correspondence
- A Protocol Acceptance Form signed and dated by the Principal Investigator
- Canada only when applicable: original Qualified Investigator Undertaking Form, signed by each Canadian investigator involved in the study
- Documents as appropriate for additional countries

6.2 STUDY COMPLETION

The following data and materials are required by the Sponsor or its designee before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from Day –14 through the end of the study follow-up period
- All laboratory certifications for laboratories performing the analysis (is other than Sponsor-approved central laboratory), as well as current normal laboratory ranges for all laboratory tests
- eCRFs (including queries) properly completed by appropriate study personnel and electronically signed and dated by the investigator
- Completed Drug Accountability Records (Retrieval Record, Drug Inventory Log, and Inventory of Returned Clinical Material forms)
- Copies of protocol amendments and IRB/EC approval/notification, if appropriate
- A summary of the study prepared by the Principal Investigator (IRB summary close letter is acceptable)
- All essential documents (e.g., curriculum vitae for each Principal Investigator and sub-investigator, U.S. FDA Form 1572 for each site)
- A signed and dated Protocol Amendment Acceptance Form(s) [if applicable]
- Updated financial disclosure forms for the Principal Investigator and all sub-investigators listed on the U.S. FDA Form 1572 (applicable for 1 year after the last patient has completed the study)

6.3 INFORMED CONSENT FORM

Sponsor's Sample Informed Consent Form (and sample Child's Assent) will be provided to each site. Sponsor or its designee must review and approve any proposed deviations from the Sample Informed Consent Form [and Child's Assent, if applicable] or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. Patients must be re-consented to the most current version of the Consent Forms during their participation in the study. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for regulatory purposes.

The Consent Forms must be signed by the patient or the patient's legally authorized representative before his or her participation in the study. The case history for each patient shall document the informed consent process and that

written informed consent was obtained prior to participation in the study. A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The Informed Consent Form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised Consent Forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised Consent Form for continued participation in the study. The final revised IRB/EC-approved Informed Consent Form must be provided to Sponsor or designee for regulatory purposes.

If the site utilizes a separate Authorization Form for patient authorization to use and disclose personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations, the review, approval, and other processes outlined above apply except that IRB/IEC review and approval may not be required per study site policies.

In the United States, each Informed Consent Form may also include authorization allowing the institution, investigator, sub-investigator and the Sponsor(s) to use and disclose Personal Health information in compliance with the HIPAA of 1996.

Signed and dated Informed Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

6.4 COMMUNICATION WITH THE INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator for review and approval before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol changes or amendments and of any unanticipated problems involving risk to human patients or others.

In addition to the requirements to report protocol-defined AEs to the Sponsor, investigators are required to promptly report to their respective IRB/EC all unanticipated problems involving risk to human patients. Some IRBs/ECs may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study treatment, and are unexpected. Investigators may receive written IND safety reports or other safety-related communications from Sponsor or designee. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB/EC and archived in the site's Study File.

6.5 STUDY MONITORING REQUIREMENTS

Site visits will be conducted by an authorized Sponsor representative or designee to inspect study data, patients' medical records, and eCRFs. The Principal Investigator will permit Sponsor monitors/representatives and collaborators, the U.S. FDA, other regulatory agencies, Institutional Review Boards, and the respective national or local health authorities to inspect facilities and records relevant to this study.

6.6 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using the Medidata Rave EDC system. Sites will receive training and a manual for appropriate eCRF completion. eCRFs will be submitted electronically to Sponsor and designee and should be handled in accordance with instructions from Sponsor or designee.

All eCRFs should be completed by designated, trained examining personnel or the study coordinator as appropriate. The eCRF should be reviewed and electronically signed and dated by the investigator.

In addition, at the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records.

6.7 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing SDV to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents are where patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in a clinical study.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must never be obliterated or destroyed.

To facilitate SDV, the investigator(s) and institution(s) must provide the Sponsor direct access to applicable source documents and reports for study-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable regulatory authorities.

6.8 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with FDA requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system (for clinical research purposes) would be one that (1) allows data entry only by authorized individuals; (2) prevents the deletion or alteration of previously entered data and provides an audit trail for such data changes (e.g., modification of file); (3) protects the database from tampering; and (4) ensures data preservation.

In collaboration with the study monitor, Sponsor's Quality Assurance group or its designee may assist in assessing whether electronic records generated from computerized medical record systems used at investigational sites can serve as source documents for the purposes of this protocol.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the eCRFs can be verified.

6.9 STUDY MEDICATION ACCOUNTABILITY

All study drug required for completion of this study will be provided by the Sponsor. The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug received at, dispensed from, returned to and disposed of by the study site should be recorded by using the Drug Inventory Log.

Study drug will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to Sponsor or designee with the appropriate documentation, as determined by the study site. If the study site chooses to destroy study drug, the method of destruction must be documented.

Sponsor or designee must evaluate and approve the study site's drug destruction standard operating procedure prior to the initiation of drug destruction by the study site.

Study drug from the ex-US sites, will be destroyed at each country's selected facility.

6.10 DISCLOSURE OF DATA

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other regulatory agencies, national and local health authorities, Sponsor monitors/representatives and collaborators, and the IRB/EC for each study site, if appropriate.

6.11 RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including eCRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

No records should be disposed of without the written approval of Sponsor or designee. Written notification should be provided to Sponsor or designee for transfer of any records to another party or moving them to another location.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the U.S. FDA IND regulations and the relevant national and local health authorities, whichever is longer.

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APPENDIX A-1 Study Flowchart

	Screening ^k		Treatment Period				Follow-Up Period				ET
Day	Day –14	Day –7	Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	
Week			Week 0	Week 4	Week 8	Week 12 ^a	Week 16	Week 20	Week 24	Week 28	
Visit #	1	2	3	4	5	6	7	8	9	10	
Visit window (days)	–4/ +2			±3	±3	+3	±3	±3	±3	±3	
Informed consent	x										
Inclusion/exclusion criteria	x	x	x								
Demographic data	x										
Medical/surgical history	x										
Vital signs (blood pressure and pulse)	x		x	x	x	x	x	x	x	x	x
Physical exam ⁱ	x		x	x	x	x	x	x	x	x	x
Weight/height	x										
Urine pregnancy test ^b	x		x	x	x	x	x	x			
Concomitant medication usage	x	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x
Study drug/placebo administration			x	x	x						
Site to contact IxRS	x		x	x	x						x
PROs											
Patients' eDiary ^c	x	x	x	x	x	x	x	x	x	x	x
CuQ2-OL ^d			x	x		x				x	x
EQ-5D ^d			x			x				x	x

APPENDIX A-1 (cont'd)

Study Flowchart

	Screening ^k		Treatment Period				Follow-Up Period				ET
Day	Day -14	Day -7	Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	
Week			Week 0	Week 4	Week 8	Week 12 ^a	Week 16	Week 20	Week 24	Week 28	
Visit #	1	2	3	4	5	6	7	8	9	10	
Visit window (days)	-4/ +2			±3	±3	+3	±3	±3	±3	±3	
MOS sleep scale ^d			x	x		x				x	x
DLQI ^d			x	x		x				x	x
Physician's (in-clinic) assessment of UAS score ^d	x	x	x	x	x	x	x	x	x	x	x
Laboratory tests											
Hematology ^{e, f}	x		x	x	x	x	x	x	x	x	x
Stool ova and parasite evaluation ^j		x									
Chemistry ^g	x										
Urinalysis ^h	x										
Thyroperoxidase antibody	x										
Sample collection											
Total blood cell histamine ^f (U.S. sites only)			x			x				x	x
CU Index	x										
Basophil FCεRI expression assay ^f			x			x				x	x
Serum sample for biomarker ^f			x			x				x	x
Blood RNA ^f			x			x				x	x

APPENDIX A-1 (cont'd)

Study Flowchart

DLQI=dermatology life quality index; ET=early termination; IxRS=interactive voice and web response systems; MOS=medical outcomes study; UAS=urticaria activity score.

NOTE: Unless otherwise indicated, all assessments should be preformed pre-study drug administration.

- ^a The Week 12 visit should be scheduled on Day 85 (not Day 84) in order to collect eDiary data of Day 84. A 3-day window is allowed.
- ^b All women of childbearing potential (including those who have had a tubal ligation) will have a urine pregnancy test at screening and prior to study drug administration. If the urine pregnancy test results are positive, dosing should be held and a serum pregnancy test performed by the central laboratory. Urine pregnancy tests will be performed at the site.
- ^c Includes UAS7 (itch score, number of hives), largest size of hives, sleep interference score, activity interference question, rescue medication (diphenhydramine) use, angioedema episodes, number of calls to doctor or nurse. Daily diary completed twice a day by the patient. The eDiary will be given to patients on Day –14.
- ^d The MOS Sleep Scale, DLQI, CuQ2-OL, EQ-5D and physician's (in-clinic) assessment of UAS score (itch score + number of hives score) must be completed prior to administration of study drug.
- ^e Hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells).
- ^f Blood draw for all visits will be done pre-dose.
- ^g Sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatine phosphokinase, and uric acid.
- ^h Urinalysis to include protein, glucose, nitrites, specific gravity, ketones, RBCs, WBCs, and microscopic examination includes cellular elements, microorganisms, crystals and casts.
- ⁱ Physical exam on Day –14 is comprehensive but subsequent physical exams may be limited (as specified in section 4.5.1.c).
- ^j Note that stool ova and parasite examination should be performed on Day –7 in patients with an eosinophil count > 2 times the upper limit of normal on Day –14 AND risk factors for parasitic disease. Stool ova and parasite examination will be performed by a local laboratory.
- ^k The screening period is 12 to 18 days prior to Day 1. Day –14 and Day –7 are provided for reference. Day –14 should be conducted 18 to 12 days prior to Day 1. Complete diary information must be collected on 7 consecutive days prior to the Day 1 visit. The Day –7 visit is intended for review of screening labs collected on Day –14, assessment of in-clinic UAS score, evaluation of patients eDiary use and additional eDiary training if necessary. The Day –7 visit can occur up to 10 days prior to the Day 1 visit.

APPENDIX A-2
Study Flowchart: Pharmacokinetics/Pharmacodynamics^a

	Screening		Treatment Period				Follow-Up Period				ET
Day	Day -14	Day -7	Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	
Week			Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	
Visit #	1	2	3	4	5	6	7	8	9	10	
Visit window (days)	-4/ +2			±3	±3	+3	±3	±3	±3	±3	
PK serum sample (serum omalizumab) ^a			x			x				x	x
PD serum samples (serum free IgE and total IgE) ^a			x			x				x	x
ATA serum sample ^a			x							x	x

ATA=anti-therapeutic antibody; PD=pharmacodynamic; PK=pharmacokinetic.

^a On dosing day, PK/PD, and ATA blood draws will be performed pre-dose.

APPENDIX B
Patient Diary

General Instructions

Please answer each question to the best of your ability.

There are no right or wrong answers.

For each question, please choose the response that describes your experience.

Please pay close attention to the timeframe of interest. Some questions ask about the **past 12 hours**, while others ask about the **past 24 hours**.

**Instructions for Counting the Number of Hives
and Measuring the Size of the Largest Hive**

Count each hive separately even if you have more than one hive grouped together with other hives.

Please use the ruler that you have been given to measure the size of your largest hive. If you need help, please have someone else take this measurement for you. **Please do not measure a group of hives as one hive.**

APPENDIX B (cont'd)
Patient Diary

Today's Date

		-				-				
Day			Month			Year				

Please complete this section every morning throughout the duration of the study. (Please circle only one response.)

1. Thinking about the **past 12 hours**, please record the severity of itch and the number of hives you may have had associated with your skin condition. **Please count each hive separately** even if you have more than one hive grouped together with other hives.

Itch (severity)	Hives (number)
0 = none 1 = mild 2 = moderate 3 = severe	0 = none 1 = between 1 and 6 hives 2 = between 7 and 12 hives 3 = greater than 12 hives

This next question asks you to estimate the size of your largest hive in centimeters (cm). Please use the ruler that you have been provided with to make this measurement. If your largest hive is located on your back or in a place that is hard to reach, please have someone else take this measurement for you. When measuring the largest hive size, **please do not measure a group of hives as one hive.**

Largest Hive (size)
0 = none 1 = less than 1.25 centimeters (cm) 2 = between 1.25 centimeter (cm) and 2.5 centimeters (cm) 3 = greater than 2.5 centimeters (cm)

APPENDIX B (cont'd)
Patient Diary

Today's Date

		-				-				
Day			Month			Year				

Please complete this section every evening throughout the duration of the study. (Please circle only one response.)

2. Thinking about the **past 12 hours**, please record the severity of itch and the number of hives you may have had associated with your skin condition. **Please count each hive separately** even if you have more one than one hive grouped together with other hives.

Itch (severity)	Hives (number)
0 = none 1 = mild 2 = moderate 3 = severe	0 = none 1 = between 1 and 6 hives 2 = between 7 and 12 hives 3 = greater than 12 hives

This next question asks you to estimate the size of your largest hive in centimeters (cm). Please use the ruler that you have been provided with to make this measurement. If your largest hive is located on your back or in a place that is hard to reach, please have someone else take this measurement for you. When measuring the largest hive size, **please do not measure a group of hives as one hive.**

Largest Hive (size)
0 = none 1 = less than 1.25 centimeters (cm) 2 = between 1.25 centimeter (cm) and 2.5 centimeters (cm) 3 = greater than 2.5 centimeters (cm)

APPENDIX B (cont'd)
Patient Diary

Today's Date

		-				-				
--	--	---	--	--	--	---	--	--	--	--

Day

Month

Year

Please complete this section once each day throughout the duration of the study (preferably at the same time each day).

(Please circle only one response.)

3. Please rate how much your hives or itch interfered with your sleep during the **past 24 hours**.

- 0 No interference
- 1 Mild, little interference with sleep
- 2 Moderate, awoke occasionally, some interference with sleep
- 3 Substantial, woke up often, severe interference with sleep

4. Please rate how much your hives or itch interfered with your daily activities during **the past 24 hours**. This could include work, school, sports, hobbies, and activities with friends and family.

- 0 No interference
- 1 Mild, little interference with daily activities
- 2 Moderate, some interference with daily activities
- 3 Substantial, severe interference with daily activities

APPENDIX B (cont'd)
Patient Diary

These next questions are about your symptoms and how you managed them during the past 24 hours.

5. During the **past 24 hours**, how many pills of diphenhydramine 25 mg did you use in order to control symptoms of your skin condition such as itch or hives?

0 = 0 pills

1 = 1 pill

2 = 2 pills

3 = 3 pills

6a. During the **past 24 hours**, did you have any rapid swelling on your face, (especially your eyelids or lips), inside your mouth (including your throat or tongue), or elsewhere on your body? This rapid swelling, also called angioedema, is at a deeper level under your skin than hives.

0 = No (**GO TO Question 7**)

1 = Yes

6b. If Yes, how did you treat this rapid swelling? (**Circle all that apply.**)

0 Did nothing (**GO TO Question 7**)

1 Took some prescription or non-prescription medication

2 Called my doctor, nurse or nurse practitioner

3 Went to see my doctor, nurse or nurse practitioner

4 Went to the emergency room at the hospital

5 Was hospitalized

7. During the **past 24 hours**, did you or someone else call your doctor, nurse or nurse practitioner because of your skin condition?

0 = No

1 = Yes

APPENDIX C
Sleep Scale from the Medical Outcomes Study

Sleep Scale from the Medical Outcomes Study

1. How long did it usually take for you to fall asleep during the past 4 weeks?

(Circle One)

0-15 minutes.....1

16-30 minutes.....2

31-45 minutes.....3

46-60 minutes.....4

More than 60 minutes 5

2. On the average, how many hours did you sleep each night during the past 4 weeks?

Write in number
of hours per night:

--	--

How often during the past 4 weeks did you...

(Circle One Number On Each Line)

	All of the Time ▼	Most of the Time ▼	A Good Bit of the Time ▼	Some of the Time ▼	A Little of the Time ▼	None of the Time ▼
3. feel that your sleep was not quiet (moving restlessly, feeling tense, speaking, etc., while sleeping)?	1	2	3	4	5	6
4. get enough sleep to feel rested upon waking in the morning?	1	2	3	4	5	6
5. awaken short of breath or with a headache?	1	2	3	4	5	6
6. feel drowsy or sleepy during the day?	1	2	3	4	5	6
7. have trouble falling asleep?	1	2	3	4	5	6
8. awaken during your sleep time and have trouble falling asleep again?	1	2	3	4	5	6
9. have trouble staying awake during the day?	1	2	3	4	5	6
10. snore during your sleep?	1	2	3	4	5	6
11. take naps (5 minutes or longer) during the day?	1	2	3	4	5	6
12. get the amount of sleep you needed?	1	2	3	4	5	6

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Hays, R. D., & Stewart, A. L. (1992). Sleep measures. In A. L. Stewart & J. E. Ware (eds.), Measuring functioning and well-being: The Medical Outcomes Study approach (pp. 235-259), Durham, NC: Duke University Press.

APPENDIX D
Dermatology Life Quality Index

DERMATOLOGY LIFE QUALITY INDEX

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☐ one box for each question.

- | | | | |
|-----|---|--|---------------------------------------|
| 1. | Over the last week, how itchy, sore, painful or stinging has your skin been? | Very much ☐
A lot ☐
A little ☐
Not at all ☐ | |
| 2. | Over the last week, how embarrassed or self conscious have you been because of your skin? | Very much ☐
A lot ☐
A little ☐
Not at all ☐ | |
| 3. | Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden ? | Very much ☐
A lot ☐
A little ☐
Not at all ☐ | Not relevant ☐ |
| 4. | Over the last week, how much has your skin influenced the clothes you wear? | Very much ☐
A lot ☐
A little ☐
Not at all ☐ | Not relevant ☐ |
| 5. | Over the last week, how much has your skin affected any social or leisure activities? | Very much ☐
A lot ☐
A little ☐
Not at all ☐ | Not relevant ☐ |
| 6. | Over the last week, how much has your skin made it difficult for you to do any sport ? | Very much ☐
A lot ☐
A little ☐
Not at all ☐ | Not relevant ☐ |
| 7. | Over the last week, has your skin prevented you from working or studying ? | Yes ☐
No ☐ | Not relevant ☐ |
| | If "No", over the last week how much has your skin been a problem at work or studying ? | A lot ☐
A little ☐
Not at all ☐ | |
| 8. | Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives ? | Very much ☐
A lot ☐
A little ☐
Not at all ☐ | Not relevant ☐ |
| 9. | Over the last week, how much has your skin caused any sexual difficulties ? | Very much ☐
A lot ☐
A little ☐
Not at all ☐ | Not relevant ☐ |
| 10. | Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time? | Very much ☐
A lot ☐
A little ☐
Not at all ☐ | Not relevant ☐ |

Please check you have answered EVERY question. Thank you.

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APPENDIX E

EuroQoL-5D



Health Questionnaire
(English version for the US)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- | | |
|---------------------------------------|--------------------------|
| I have no problems in walking about | ☐ |
| I have some problems in walking about | ☐ |
| I am confined to bed | ☐ |

Self-Care

- | | |
|---|--------------------------|
| I have no problems with self-care | ☐ |
| I have some problems washing or dressing myself | ☐ |
| I am unable to wash or dress myself | ☐ |

Usual Activities (*e.g. work, study, housework, family or leisure activities*)

- | | |
|--|--------------------------|
| I have no problems with performing my usual activities | ☐ |
| I have some problems with performing my usual activities | ☐ |
| I am unable to perform my usual activities | ☐ |

Pain/Discomfort

- | | |
|------------------------------------|--------------------------|
| I have no pain or discomfort | ☐ |
| I have moderate pain or discomfort | ☐ |
| I have extreme pain or discomfort | ☐ |

Anxiety/Depression

- | | |
|--------------------------------------|--------------------------|
| I am not anxious or depressed | ☐ |
| I am moderately anxious or depressed | ☐ |
| I am extremely anxious or depressed | ☐ |

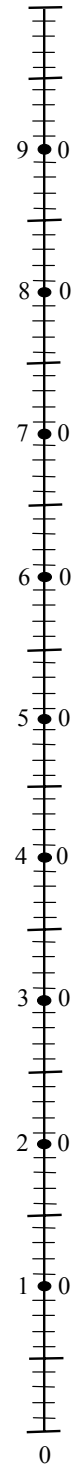
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own
health state
today**

Best
imaginable
health state

100



Worst
imaginable
health state

APPENDIX F

Study Drug Dosing and Scheduling Table

Blinded Study Drug Dosing Schedule (Number of Injections and Total Injection Volumes)

Dose (mg)	Number of Injections	Total Volume Injected (mL) ^a
75	2 injections: 0.6 mL omalizumab + 0.6 mL placebo	1.2
150	2 injections: 1.2 mL omalizumab + 1.2 mL placebo	2.4
300	2 injections: 1.2 mL omalizumab + 1.2 mL omalizumab	2.4
Placebo	2 injections: 1.2 mL placebo + 1.2 mL placebo	2.4

^a 1.2 mL maximum delivered volume per vial.

APPENDIX G

Study Drug Preparation and Administration

An unblinded pharmacist or other qualified designated individual will prepare the study drug (omalizumab or placebo) injection as outlined below. Study drug for subcutaneous (SC) administration should be prepared using Sterile Water for Injection (SWFI), USP only.

Study drug is for single use only and contains no preservatives. The solution should be used for SC administration within 8 hours following reconstitution when stored in the vial at 2°C–8°C (36°F–46°F), or within 4 hours of reconstitution when stored at room temperature.

The lyophilized product will take 15–20 minutes to dissolve. The fully reconstituted product will appear clear or slightly opalescent and may have a few small bubbles or foam around the edge of the vial. The reconstituted product is somewhat viscous; in order to obtain the full 1.2 mL dose, ALL OF THE PRODUCT MUST BE WITHDRAWN from the vial before expelling any air or excess solution from the syringe.

Administration

1. Draw 1.4 mL SWFI, USP into a 3-cc syringe equipped with a 1-inch, 18-gauge needle.
2. Place the vial upright on a flat surface and, using standard aseptic technique, insert the needle and inject the SWFI directly onto the product.
3. Keeping the vial upright, gently swirl the upright vial for approximately 1 minute to evenly wet the powder. Do not shake.
4. Gently swirl the vial for 5–10 seconds approximately every 5 minutes in order to dissolve any remaining solids. Vials typically take 10–20 minutes to solubilize. Longer reconstitution times may be required. Continue to swirl the vial occasionally during this time to aid in solubilization. There should be no visible gel-like particles in the solution. Do not use if foreign particles are present.
Note: It is acceptable to have small bubbles or foam around the edge of the vial. Do not use if the contents of the vial do not dissolve completely in 40 minutes.

APPENDIX G (cont'd)
Study Drug Preparation and Administration

5. Invert the vial for 15 seconds to allow the solution to drain toward the stopper. Using a new 3-cc syringe equipped with a 1-inch, 18-gauge needle, insert the needle into the inverted vial. Position the needle tip at the very bottom of the solution in the vial stopper when drawing the solution into the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel to remove all of the solution from the inverted vial.
6. Replace the 18-gauge needle with a 25-gauge needle for SC administration.
7. Expel air, large bubbles, and any excess solution to obtain the required 0.6–1.2 mL dose. A thin layer of small bubbles may remain at the top of the solution in the syringe. Because the solution is slightly viscous, the injection may take 5–10 seconds to administer.
8. A vial delivers 1.2 mL (150 mg) of study drug. For a 75 mg dose, draw up all contents of the vial and dispel the contents of the syringe until only 0.6 mL of the contents remains in the syringe.
9. Cap the syringe. Label the syringe with the patient number, *kit number details* (*Kit #1 or #2*), and the protocol number (Q4882g). The syringe is now ready for use.

APPENDIX H

In-Clinic Urticaria Activity Score (Max 6)

The physician or the person he or she designates will provide the sum of the score of the patient's urticaria lesions (number of hives) and pruritus (itch) reflective of the patient's condition over the 12 hours prior to the visit using the following rating scale:

Pruritus:

0= None

1= Mild – minimal awareness, easily tolerated

2= Moderate – definite awareness, bothersome but tolerable

3= Severe – difficult to tolerate

Number of Hives:

0 = none

1= 1–6

2= 7–12

3= >12

STATISTICAL ANALYSIS PLAN

TITLE: A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, DOSE-RANGING, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, RESPONSE DURATION AND SAFETY OF XOLAIR® (OMALIZUMAB) IN PATIENTS WITH CHRONIC IDIOPATHIC URTICARIA (CIU) WHO REMAIN SYMPTOMATIC DESPITE ANTIHISTAMINE TREATMENT (H1)

PROTOCOL NUMBER: Q4882g

STUDY DRUG: XOLAIR® (Omalizumab)

IND NUMBER: 101,612

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: Shannon Bradley, M.S.
Hsin-Ju Hsieh, Ph.D.

DATE FINAL: 21 December 2011

SAP APPROVAL

Plan Number / Version: Q4882g / A

Date: See last date in electronic signature manifestation below.
Plan approved by: See electronic signature manifestation below.

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1. BACKGROUND

The main purpose of the ASTERIA II study (Q4882g) is to demonstrate the efficacy and safety of Xolair® (omalizumab), compared with placebo, as an add-on therapy in patients, aged 12 to 75 years who remain symptomatic despite H1 antihistamine (anti-H1) therapy. In addition, the study is designed to evaluate the appropriate dose of omalizumab and the time to onset of clinical effect in patients with chronic idiopathic urticaria (CIU), as well as to provide information regarding disease recurrence after study treatment is withdrawn.

The weekly itch severity score was chosen as the primary outcome measure for this study, based on feedback from both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA). Initially, the Urticaria Activity Score (UAS7), a composite score including both itch severity and number of hives recorded twice daily over 7 days, was proposed as the primary endpoint. The regulatory agencies stated that although the use of the UAS7 was acceptable as a primary outcome, a statistically significant difference from placebo would be required for the itch severity component as well. Because itch is the most worrisome symptom to patients with CIU, the weekly itch severity score was designated as the primary efficacy outcome measure and the UAS7 and number of hives weekly scores were designated as supportive secondary efficacy outcome measures for this study.

The FDA suggested during the End of Phase II meeting that the more conservative approach of baseline-carry-forward (BOCF) be used for imputation of missing data for the primary endpoint rather than proposed last-observation-carry-forward (LOCF) method. On the basis of this suggestion, the BOCF imputation method will be used for the primary analysis.

Several of the secondary outcome measures were chosen based on suggestions or requests from the EMA during a Scientific Advice meeting. The EMA requested efficacy data on the frequency and/or severity of angioedema as well as an analysis of response frequency. Secondary outcome measures have been defined to address these requests.

The FDA also requested that an attempt be made to gain an insight into the mechanism of action of omalizumab in the patient population under study. To this end, basophil high-affinity IgE receptor density is being evaluated by fluorescence-activated cell sorter analysis and descriptions of the proposed summaries are included in the exploratory analysis section of this document.

The statistical methods described in this Statistical Analysis Plan supersede the analysis methods described in the study protocol.

2. STUDY DESIGN

The study is a global Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of omalizumab administered subcutaneously as an add-on therapy for the treatment of adolescent and adult patients aged 12 to 75 who have been diagnosed with refractory CIU and who remain symptomatic despite approved-dose H1 antihistamine treatment. The study will enroll approximately 300 patients (75 per treatment arm) at approximately 70 study sites globally.

The study will consist of three distinct study periods over a time period of 30 weeks, as outlined below (also, see Figure 1):

- Screening Period: Day -14 to Day -1
- Treatment Period: Day 1 to Day 85 (Week 12)
- Follow-up Period: Day 85 to Day 197 (Week 12 to Week 28)

Patients will have the 2-week screening period to establish their eligibility for the study and baseline symptom scores. For the duration of the screening period, patients must maintain stable doses of their pre-screening H1 antihistamine treatment. To be eligible for the study, patients must have no missing eDiary entries, a UAS7 symptom score (range 0–42) of ≥ 16 (equivalent to moderate to severe CIU symptoms for at least 4 out of the 7 days in a week), and a weekly itch severity score (a component of the UAS7 with range 0–21) of ≥ 8 for the 7 days prior to randomization.

On Day 1, eligible patients will be randomly assigned (in a 1:1:1:1 ratio using an Interactive Voice and Web Response System [IxRS]) to receive omalizumab (75, 150, or 300 mg) or placebo by subcutaneous (SC) injection every 4 weeks during the 12-week double-blind treatment period. Randomization to treatment groups will be stratified by baseline weekly itch severity score (< 13 vs. ≥ 13), baseline weight (< 80 kg vs. ≥ 80 kg), and study site. A hierarchical dynamic randomization scheme will be used to achieve overall balance between treatment groups and within strata. Efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) data will be collected. The last dose of study drug will be given at the Day 57 (Week 8) visit. The primary endpoint will be measured at Week 12. For the 12 weeks of the treatment period, patients must maintain stable doses of their pre randomization H1 antihistamine treatment.

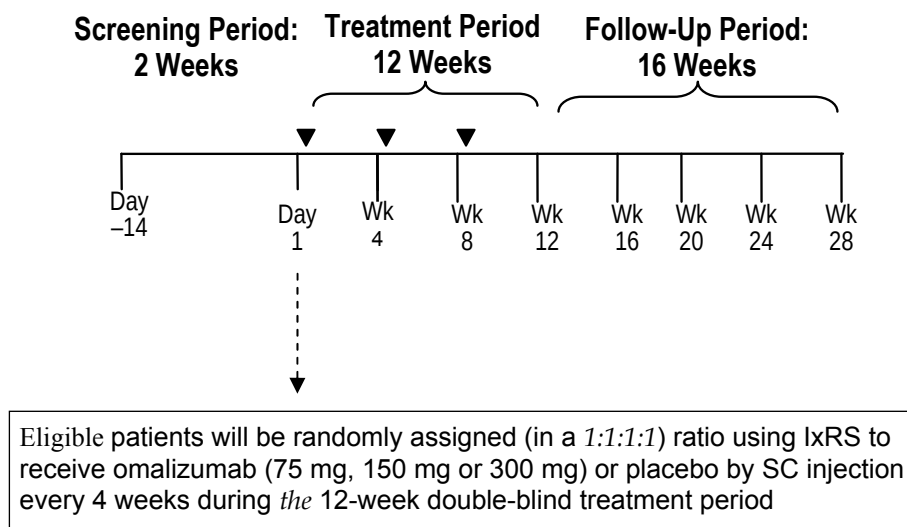
After completion of the 12-week treatment period, all patients will enter a 16-week follow-up period to allow for further characterization of the pharmacokinetics and pharmacodynamics of omalizumab, collection of additional efficacy and safety data, and evaluation of the presence of anti-therapeutic antibodies (ATAs). Patients will continue to visit the study center at 4-week intervals. No study treatment will be given during the follow-up period. During the follow-up period, patients may add up to one additional H1 antihistamine therapy (refer to Protocol Section 4.3.2). Increasing the

dose of each antihistamine treatment above the approved dose is not permitted. The goal of allowing additional H1 antihistamine therapy after the primary endpoint has been assessed is to reduce patient dropout for improved safety evaluation.

The blind will be maintained among patients and study site personnel for the full 28 weeks of the study (post randomization). For the duration of the study, all patients will be provided with diphenhydramine (25 mg) for itch relief on an as-needed basis (up to a maximum of three doses in 24 hours or less based on local regulations).

The end of the study is defined as the last enrolled patient's last visit.

Figure 1: Study Schema



IxRS=interactive voice and web response system; SC=subcutaneous.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Study Flowchart in Appendix 2.

2.2 OUTCOME MEASURES

2.2.1 PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is the change from baseline in weekly itch severity score at Week 12.

2.2.2 SECONDARY EFFICACY ENDPOINTS

The secondary efficacy endpoints include the following:

- Change from baseline in UAS7 at Week 12
- Change from baseline in weekly number of hives score at Week 12
- Time to minimally important difference (MID) response in weekly itch severity score by Week 12
- Proportion of patients with UAS7 ≤ 6 at Week 12
- Proportion of weekly itch severity score MID Responders at Week 12
- Change from baseline in weekly size of the largest hive score at Week 12
- Change from baseline in health-related quality-of-life as measured by the Dermatology Life Quality Index (DLQI) (see Appendix 3) at Week 12
- Proportion of angioedema-free days from Week 4 to Week 12 of therapy

2.2.3 EXPLORATORY EFFICACY ENDPOINTS

The exploratory efficacy endpoints include the following:

- Proportion of patients with UAS7 ≤ 6 at Week 28
- Time to UAS7 MID response by Week 12
- Proportion of Week 12 responders who maintain their response (UAS7 ≤ 6) to the Week 28 visit
- Time to relapse in Week 12 responders
- Change from baseline in health-related quality-of-life as measured by the Chronic Urticaria Quality-of-Life Questionnaire (CU-Q₂₀L) (see Appendix 4) at Week 12 and Week 28
- Change from baseline in health-related quality-of-life as measured by the DLQI at Week 28
- Change from baseline in the number of itch-free days and/or hive-free days at Week 12
- Change in number of tablets/week of sedating H1 antihistamine (diphenhydramine) for itch relief from baseline to Week 12
- Change from baseline in weekly sleep interference score (derived from patient daily diary data) at Week 12
- Change from baseline in weekly interference with daily activities score at Week 12

- Change from baseline in health utility as measured by the EuroQoL-5D (EQ-5D) (see Appendix 5) at Week 12 and Week 28
- Change from baseline in Medical Outcomes Study (MOS) sleep score (see Appendix 6) at Week 12
- Summary of healthcare utilization (calling a doctor, nurse or nurse practitioner) based on patient daily diary data
- Summary of action(s) taken in response to angioedema based on patient daily diary data
- Correlation between basophil high-affinity IgE receptor density and change from baseline in weekly itch severity score at Week 12 and Week 28

2.2.4 PHARMACOKINETIC/PHARMACODYNAMIC ENDPOINT

The following PK and PD endpoint will be reported:

- Summary trough serum levels of omalizumab, total and free IgE

2.2.5 SAFETY OUTCOME MEASURES

The safety of omalizumab will be assessed using the following safety outcome measures:

- Incidence and severity of adverse events and serious adverse events
- Changes in vital signs
- Clinical laboratory evaluations
- ATA evaluation at the end of the follow-up period

2.3 DETERMINATION OF SAMPLE SIZE

The sample size for this study is primarily based on safety and regulatory considerations. The estimation of power for efficacy assumes a mean change from baseline in the weekly itch severity score at Week 12 to be 9 points and 3.5 points for the omalizumab and placebo group, respectively, with a common standard deviation of 6 points (based on data from the MYSTIQUE and XCUISITE studies). Assuming an early discontinuation rate of 15% (based on data from the MYSTIQUE and XCUISITE studies) by Week 12, a total of 300 patients (1:1:1:1 randomization ratio with 75 patients in each treatment group) will yield approximately 98% power to detect a difference in treatment effect in the primary endpoint at the 0.05 level for any omalizumab group. A multiplicity type I error control plan will be employed to adjust for the comparisons of multiple omalizumab groups to the placebo group in order to maintain an overall type I error rate of 0.05 (two sided) for testing of the primary endpoint.

2.4 ANALYSIS TIMING

The primary analysis for the study will take place when all patients have completed their Week 28 visit or discontinued early from the study and all study data are in the database and have been cleaned and verified and the database is locked.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Patient randomization and the study drug kit number assignments have been handled by an interactive voice and web response system (IxRS) provided by Bracket. A dynamic randomization scheme is used to obtain an approximately 1:1:1:1 ratio across the four treatment arms. The levels in this hierarchy are overall study treatment balance, treatment balance within the baseline weekly itch severity score strata (< 13 vs. ≥ 13), treatment balance within the body weight strata (< 80 kg vs. ≥ 80 kg), and balance within each study center. A biased-coin assignment is used when the imbalance at a given level exceeded the specified threshold. The dynamic randomization parameters (i.e., imbalance thresholds at each level and biased coin used) and programming details will be provided in the Clinical Study Report.

To ensure the randomization algorithm is carried out correctly at least one and up to five audit(s) will be conducted during the study by Axio Research, LLC. The Sponsor will not have access to unblinded results of this audit at any time during the study. Details of the audit results will be provided as part of the Clinical Study Report.

3.2 DATA MONITORING

The independent Data Monitoring Committee (iDMC) shares with the Sponsor the responsibility for regularly monitoring the overall safety of the patients in the studies. By carefully reviewing summaries of adverse events (AEs), serious adverse events (SAEs), deaths, and other specified safety events, the iDMC will help the Sponsor minimize patient exposure to unnecessary risk. The iDMC will meet periodically to review unblinded safety summaries prepared by an external independent Data Coordinating Center (iDCC). While the iDMC will be reviewing unblinded safety information, the Sponsor will remain blinded until formal study unblinding takes place.

The iDMC will be responsible for the following:

- Ongoing review of reports of suspected unexpected serious adverse reactions (SUSARs)
- Quarterly safety monitoring for SAEs
- Reviewing safety data approximately every 6 months

The iDMC will be responsible for ensuring a timely review of the data provided by the iDCC and to make recommendations, if necessary, to the Sponsor regarding changes in study conduct, including early study termination. There is no intent to stop these studies for efficacy at any of the iDMC reviews.

Details of the roles and responsibilities of the iDMC for this study are specified in the study iDMC charter.

4. STATISTICAL METHODS

Unless otherwise specified, treatment comparisons will be performed between each of the omalizumab groups (75, 150, and 300 mg) and the placebo group. A separate analysis will be performed for the comparison of each omalizumab dose level versus placebo. Procedures will be employed to adjust for multiple comparisons in order to maintain a type I error rate for the primary endpoint analysis of $\alpha=0.05$ (two sided). The statistical test to be employed for each comparison is specified below. Descriptive summaries of continuous data will present the group mean, standard deviation, median, minimum, maximum, and sample size. Descriptive summaries of discrete data will report the number of patients and incidence as a frequency and as a percentage.

4.1 ANALYSIS POPULATIONS

Four analysis populations are defined for this study: randomized population, modified intention-to-treat (mITT) population, safety-evaluable population, and pharmacokinetic-evaluable population.

4.1.1 RANDOMIZED POPULATION

The randomized population will include all randomized patients regardless of whether they received any study drug. Treatment groups for this population will be defined according to the treatment assigned at randomization by the IxRS.

4.1.2 MODIFIED INTENTION TO TREAT (MITT) POPULATION

This population will include all patients randomized in the study who received at least one dose of study drug. The treatment group for this population will be defined according to the treatment assigned at randomization by the IxRS. This analysis population will be used for efficacy analysis unless otherwise specified.

4.1.3 PHARMACOKINETIC EVALUABLE POPULATION

Pharmacokinetic-evaluable patients will include randomized patients who have received at least one dose of study drug and have provided at least one serum sample for determination of omalizumab concentration.

4.1.4 SAFETY POPULATION

This population includes patients who received at least one dose of study drug. Treatment groups for this population will be defined according to the actual treatment received during the treatment period as follows:

- Placebo: Patients who received only placebo injections (i.e., no active treatment) during the treatment period
- 75-mg omalizumab: Patients who received at least one 75-mg omalizumab injection but no higher active dose level (i.e., 150-mg or 300-mg) injections during the treatment period
- 150-mg omalizumab: Patients who received at least one 150-mg omalizumab injection but no higher active dose level (i.e., 300-mg) injections during the treatment period
- 300-mg omalizumab: Patients who received at least one 300-mg omalizumab injection during the treatment period

If there are no differences between the IxRS assignment and actual treatment received during the treatment period, the mITT and the safety population will be the same population. This analysis population will be used for analysis of all safety endpoints.

4.2 ANALYSIS OF STUDY CONDUCT

The number of patients randomized will be tabulated by country, center, and treatment group. The disposition of patients will be summarized with respect to patients who 1) are randomized; 2) are randomized and treated with at least one dose of study drug; 3) have completed treatment period; and 4) have completed each study period. The number of patients who complete each scheduled dose will be summarized by treatment group. The number of patients in each analysis population will be summarized by treatment group, when applicable. Eligibility criteria exceptions and major protocol deviations will be summarized. For patients who discontinued from treatment or from the study early, reasons for discontinuation will be summarized.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Treatment groups entering the treatment period of the study will be assessed for comparability with respect to baseline and demographic characteristics such as age, sex, race/ethnicity, body weight, presence of anti-FcεRI autoantibody as detected by CU index test, the presence of thyroperoxidase antibody, total IgE levels, UAS7, weekly itch severity score, weekly number of hives score, weekly size of the largest hive score, interference with sleep interference with daily activities, the presence of angioedema, and the types of previous therapies received for CIU. The assessments of treatment group comparability will be

done using descriptive statistics. Baseline characteristics will be summarized by treatment group using mean, standard deviation, median, and range for continuous variables and proportions for categorical variables, as appropriate.

4.4 EFFICACY ANALYSIS

Unless otherwise specified, all analyses of efficacy outcomes from the treatment period will be based on the mITT population (defined in Section 4.1.2) and a separate analysis will be performed for the comparison of each omalizumab dose level versus placebo. Patients will be analyzed according to the treatment arm to which they were randomized. Treatment comparisons will be performed between each of the omalizumab groups (75, 150, and 300 mg) and the placebo group. All statistical tests will be two-sided with overall 0.05 of significance level and adjustment for multiple comparisons will be performed according to the type I error control plan detailed in Section 4.8.

A number of efficacy outcome measures (weekly itch severity score, weekly number of hives score, UAS7, weekly size of largest hive score, number of tablets per week of diphenhydramine use, weekly sleep interference score and weekly interference with daily activities score) are in the form of weekly scores derived from patient daily diary data. The study weeks are defined (see Table 1) based on the study days starting with Day 1, which is the day the patient receives the first study treatment.

Table 1: Study Week Definitions Based on Protocol-Scheduled Visits

Study Week	Study Day	Study Week	Study Day
1	1–7	15	99–105
2	8–14	16*	106–112
3	15–21	17	113–119
4*	22–28	18	120–126
5	29–35	19	127–133
6	36–42	20*	134–140
7	43–49	21	141–147
8*	50–56	22	148–154
9	57–63	23	155–161
10	64–70	24	162–168
11	71–77	25	169–175
12*	78–84	26	176–182
13	85–91	27	183–189
14	92–98	28	190–196

* Indicates week prior to a study treatment visits after Day 1. For example, the Week 4 study visit occurs on Day 29, and Week 4 weekly scores are based on Days 22 to 28.

Furthermore, the baseline week is comprised of the 7 days prior to Day 1 (Day -7 to Day -1).

Table 1 summarizes the time period (in study days) over which the data are used in the calculation of each weekly score. For most study weeks, weekly scores will be based on the 7 study days given in Table 1. However, in situations where a study treatment visit occurs before or after the protocol-specified visit day, the following algorithm(s) will be applied to determine from which study days the data will be used to compute the weekly scores:

- Weeks prior to a study treatment visit after Day 1 (Week 4, Week 8):
The time period of the study week starts from the first study day of that week (see Table 1) and ends at the earlier of a) the last study day of the week (see Table 1); or b) the day before the study treatment visit. For example, if the Week 8 visit occurs on or after Day 57, then data from study Days 50 to 56 will be used for the calculation of the Week 8 weekly scores. Alternatively, if a patient's Week 8 visit occurs on Day 55, then the Week 8 weekly scores will be calculated using daily scores from Days 50 to 54.
- Weeks immediately following a study treatment visit (Week 1, Week 5, Week 9): The time period of the study week starts from the latter of a) the first study day of the week (see Table 1); or b) the study day on which the treatment visit occurred and ends on the last study day of the week (see Table 1). For example, if the Week 4 visit occurs on or before Day 29, then Days 29 to 35 are used for the calculation of the Week 5 weekly scores. Alternatively, if a patient's Week 4 visit occurs on Day 30, then the Week 5 weekly scores will be calculated using data from Days 30 to 35.

Illustrations of the above definitions are shown in Appendix 7. The table (see Table 2) below shows an example of patient visits and the study days used to calculate the weekly scores. The treatment visit days are shaded in grey, where the Week 4 visit occurs at Day 31, and the Week 8 visit occurs at Day 55. For each day, the number in the "Week" row indicates the study weekly score for which the diary data from that day will be used. For example, data from Day 31 to Day 35 will be used in the Week 5 weekly score calculations. For study days where "-" appears in the week row, data from that day will not be used in any weekly score calculations.

Table 2: An Example of Study Week Definition when Study Visits Do Not Follow Protocol-Specified Visit Days

Day	1	2-7	8-14	15-21	22-28	29-30	31	32-35	36-42	43-49	50-54	55	56	57-63	64-70	71-77	78-83	84
Week	1	2	3	4	-	5		6	7	8	-	-	9	10	11	12	-	

4.4.1 PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is the change from baseline in weekly itch severity score at Week 12, defined as the Week 12 weekly itch severity score minus the baseline weekly itch severity score. Changes from baseline in weekly itch severity score for other study weeks are calculated similarly.

Itch severity is recorded twice daily (morning and evening) in the patients' eDiaries, on a scale of 0 (none) to 3 (severe). A daily itch severity score is calculated as the average of the morning and evening scores. When either the morning or evening score is missing, the non-missing itch severity score for that day (morning or evening) will be used as the daily itch severity score, and when both the morning and evening itch scores are missing, the daily itch score will be missing. A weekly itch severity score is calculated as the sum of the daily itch severity scores over the study days that make up a given study week (as described in Section 4.4). When one or more of the daily itch scores are missing or if a given study week is <7 days (i.e., the study week following a treatment visit which occurred late), the following principles will be applied to handle the missing data:

- If a patient has at least 4 non-missing daily itch severity scores included in the calculation of the weekly score (as defined in Section 4.4), the weekly itch severity score is defined as the sum of the available daily itch severity scores in that week, divided by the number of days that have a non-missing daily itch severity score, multiplied by 7.
- If there are less than 4 non-missing daily itch severity scores included in the calculation of the weekly score (as defined in Section 4.4), then the weekly itch severity score is missing for that week.

Every effort should be made to continue to follow patients who discontinue from study treatment every 4 weeks for the duration of the treatment and follow-up study periods. Patients who discontinue prematurely from study treatment or who receive excluded therapy during the treatment period (listed in Protocol Section 4.4.2) will be encouraged to remain in the study and enter the 16-week follow-up period.

These patients will be considered discontinued from study treatment as of the earlier of a) the protocol-specified visit day of the first *missed* treatment; or b) the date they started taking the excluded therapy. Subsequent daily diary scores will be deemed missing for the purposes of the efficacy analyses. For example, if a patient receives study treatment at the Week 4 visit and is subsequently discontinued from treatment, the patient would be considered discontinued from treatment as of study Day 57 (the protocol-specified Week 8 study visit day), and their weekly scores starting from Week 9 will be missing for the purposes of efficacy analyses. This principle will be applied to other efficacy outcomes which are in the form of weekly scores derived from the patient daily diary data.

Missing Week 12 weekly itch severity scores will be imputed by carrying forward the baseline weekly itch severity score (BOCF). For summaries by study week, the weekly itch severity scores will be presented with using BOCF.

The mean and standard deviation of the change from baseline in weekly itch severity scores for each treatment group will be presented by study week. The analysis of the change from baseline in weekly itch severity score at Week 12 will consist of treatment comparisons between each of the omalizumab groups (75, 150, and 300 mg) and the placebo group using analysis of covariance (ANCOVA) controlling for baseline weekly itch severity score (<13 vs ≥ 13), and baseline weight (<80 kg vs. ≥ 80 kg). A separate ANCOVA model will be run for each omalizumab dose group versus placebo. The least squares means (LSM) and the corresponding 95% confidence intervals of the differences between each of the omalizumab groups and the placebo group will be presented along with the p-values for treatment differences resulting from the ANCOVA model.

Refer to Section 4.8 for details regarding management of type I error.

4.4.2 SECONDARY EFFICACY ENDPOINTS

4.4.2.1 Change from Baseline in UAS7 at Week 12

The UAS (0–6) is a composite score of 1) the number of hives; and 2) the Intensity of the itch, each with numeric severity intensity ratings on a scale of 0–3 (0=none to 3=intense/severe), measured twice daily (morning and evening) via eDiary. The daily UAS is a sum of the daily itch score and the daily hive score. If either the daily itch score or the daily hive score are missing, the corresponding daily UAS will be missing. The UAS7 is the sum of the daily UAS scores over the study days which make up a given study week (as described in Section 4.4).

The calculation of UAS7 scores when one or more of the daily UAS are missing or if a given study week is <7 days (i.e., the study week following a treatment visit which occurred late), as well as weekly scores for patients who discontinue study treatment will be handled using the same principles as described for the primary endpoint in Section 4.4.1.

Change from baseline in UAS7 at Week 12 is the Week 12 UAS7 minus the Baseline UAS7. Changes from baseline in UAS7 for other study weeks are calculated similarly.

The mean and standard deviation of the change from baseline in UAS7 for each treatment group will be presented by study week. The analysis of the change from baseline in UAS7 at Week 12 will consist of treatment comparisons between each of the omalizumab groups (75-mg, 150-mg and 300-mg) and the placebo group using ANCOVA controlling for baseline UAS7 (<median vs. ≥ median) and baseline weight (<80 kg vs. ≥80 kg). A separate ANCOVA model will be run for each omalizumab dose group versus placebo. The LSM and the corresponding 95% confidence intervals of the differences between each of the omalizumab groups and the placebo group will be presented along with the p-values for treatment differences resulting from the ANCOVA model.

Refer to Section 4.8 for details regarding management of type I error.

4.4.2.2 Change from Baseline in Weekly Number of Hives Score at Week 12

The number of hives is measured twice daily (morning and evening), on a scale of 0 (none) to 3 (>12). The daily number of hives score is the average of the morning and evening scores, and the weekly number of hives score is the sum of the daily number of hives scores over the study days which make up a given study week (as described in Section 4.4).

The calculation of weekly number of hives scores when one or more of the daily number of hives scores are missing or if a given study week is <7 days (i.e., the study week following a treatment visit which occurred late), as well as weekly scores for patients who discontinue study treatment will be handled using the same principles as described for the primary endpoint in Section 4.4.1.

Change from baseline in weekly number-of-hives score at Week 12 is the Week 12 weekly number-of-hives score minus the baseline weekly number-of-hives score. Changes from baseline in weekly number of hives score for other study weeks are calculated similarly.

The mean and standard deviation of the change from baseline in weekly number of hives score for each treatment group will be presented by study week. The analysis of the change from baseline in weekly number of hives score at Week 12 will consist of treatment comparisons between each of the omalizumab groups (75-mg, 150-mg and 300-mg) and the placebo group using ANCOVA controlling for baseline weekly number of hives score (<median vs. ≥ median) and baseline weight (<80 kg vs. ≥80 kg). A separate ANCOVA model will be run for each omalizumab dose group versus placebo. The LSM and the corresponding 95% confidence intervals of the differences between the omalizumab groups and the placebo group will be presented along with the p-values for the treatment differences resulting from the ANCOVA model.

Refer to Section 4.8 for details regarding management of type I error.

4.4.2.3 Time to Minimally Important Difference (MID) Response in Weekly Itch Severity Score by Week 12

Weekly itch severity score MID response is defined as a reduction from baseline in weekly itch severity score of ≥ 5 points (Mathias et al., in press). Time to weekly itch severity score MID response is the time (in weeks) from Day 1 to the study week when weekly itch severity score MID response is first achieved; that is, the study week for which the change from baseline in weekly itch severity score is ≤ -5 .

This endpoint will be considered censored at the date of the last non-missing weekly itch severity score evaluation up to the Week 12 study visit for any patient who fails to achieve an MID response. If a patient discontinues treatment prior to Week 12 without achieving an MID response, this endpoint will be censored as of the day of treatment discontinuation (as specified in Section 4.4.1) if they had not already achieved MID.

Kaplan-Meier estimates of the distribution of time to first weekly itch severity score MID response will be presented graphically. The median of the time to first weekly itch severity score MID response and the corresponding 95% confidence interval will be presented for each treatment group. The treatment comparisons will be performed using the Cox proportional hazards (PH) model stratified by baseline weekly itch severity score (< 13 vs. ≥ 13) and baseline weight (< 80 kg vs. ≥ 80 kg). A separate Cox PH model will be run for each omalizumab dose group versus placebo.

Refer to Section 4.8 for details regarding management of type I error.

4.4.2.4 Proportion of Patients with UAS7 ≤ 6 at Week 12

The Week 12 UAS7 will be defined as in Section 4.4.2.1. Patients will be classified as non-responders at Week 12 (i.e., did not achieve UAS7 ≤ 6 at Week 12) if they have a missing UAS7 at Week 12.

The proportions of patients who achieve UAS7 ≤ 6 at Week 12 for each treatment group will be presented. The Cochran-Mantel-Haenszel test stratified by baseline UAS7 ($< \text{median}$ vs. $\geq \text{median}$) and baseline weight (< 80 kg vs. ≥ 80 kg) will be performed to compare the proportions of patients with UAS7 ≤ 6 at Week 12 in each of the omalizumab groups versus placebo.

Refer to Section 4.8 for details regarding management of type I error.

4.4.2.5 Proportion of Weekly Itch Severity Score MID Responders at Week 12

Weekly itch severity score MID response is defined as a reduction from baseline in weekly itch severity score of ≥ 5 points. Patients will be classified as non-responders at Week 12 (i.e., did not achieve a change from baseline in weekly itch severity score ≤ -5 at Week 12) if they have a missing weekly itch severity score at Week 12.

The proportions of patients who achieve weekly itch severity score MID at Week 12 for each treatment group will be presented. The Cochran-Mantel-Haenszel test stratified by baseline weekly itch severity score (< 13 vs. ≥ 13) and baseline weight (< 80 kg vs. ≥ 80 kg) will be performed to compare the proportions of weekly itch severity score MID responders at Week 12 in each of the omalizumab groups versus placebo.

4.4.2.6 Change from Baseline in Weekly Size of Largest Hive Score at Week 12

The size of the largest hive is measured twice daily, on a scale of 0 (none) to 3 (> 2.5 cm). The daily size of largest hive score is the average of the morning and evening scores, and the weekly size of largest hive score is the sum of the daily scores over the study days which make up a given study week (as described in Section 4.4).

The calculation of weekly size of largest hive scores when one or more of the daily size of largest hive scores are missing or if a given study week is < 7 days (i.e., the study week following a treatment visit that occurred late), as well as weekly scores for patients who discontinue study treatment, will be handled using the same principles as described for the primary endpoint in Section 4.4.1.

Change from baseline in weekly size of largest hive score at Week 12 is the Week 12 weekly size of largest hive score minus the baseline weekly size of largest hive score. Changes from baseline in weekly size of largest hive score for other study weeks are calculated similarly.

The mean and standard deviation of the change from baseline in weekly size of largest hive score for each treatment group will be presented by study week. The analysis of the change from baseline in weekly size of largest hive score at Week 12 will consist of treatment comparisons between each of the omalizumab groups (75-mg, 150-mg and 300-mg) and the placebo group using ANCOVA controlling for baseline weekly size of largest hive score ($< \text{median}$ vs. $\geq \text{median}$) and baseline weight (< 80 kg vs. ≥ 80 kg). A separate ANCOVA model will be run for each omalizumab dose group versus placebo. The LSM and the corresponding 95% confidence intervals of the differences between the omalizumab groups and the placebo group will be presented along with the p-values for the treatment differences resulting from the ANCOVA model.

4.4.2.7 Change from Baseline in Health-Related Quality of Life as Measured by the Dermatology Life Quality Index at Week 12

The Dermatology Life Quality Index (DLQI) is a 10-item dermatology-specific health-related quality of life measure (Finlay and Khan 1994). Patients rate their dermatology symptoms as well as the impact of their skin condition on various aspects of their lives over the last week. An overall score will be calculated as well as for the following domains: Symptoms and Feelings, Daily Activities, Leisure, Work and School, Personal Relationships, and Treatment.

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. The scoring of each question is as follows:

- | | |
|--|--|
| • Very much | Scored 3 |
| • A lot | Scored 2 |
| • A little | Scored 1 |
| • Not at all | Scored 0 |
| • Not relevant | Scored 0 |
| • Question unanswered | Scored 0 |
| • If leading Question 7 response is Yes | Scored 3 |
| • If leading Question 7 response is <u>not</u> Yes | Scored as above using follow-up Question 7 |

The six DLQI domain scores are scored as follows:

- | | | |
|--------------------------|-------------------|-----------------|
| • Symptoms and feelings | Questions 1 and 2 | Score maximum 6 |
| • Daily activities | Questions 3 and 4 | Score maximum 6 |
| • Leisure | Questions 5 and 6 | Score maximum 6 |
| • Work and School | Question 7 | Score maximum 3 |
| • Personal relationships | Questions 8 and 9 | Score maximum 6 |
| • Treatment | Question 10 | Score maximum 3 |

The baseline and Week 12 overall DLQI scores as well as the domain scores will be derived from questionnaire assessed at the Day 1 and Week 12 visits, respectively.

Changes from baseline in the overall and domain DLQI scores at Week 12 are defined as the Week 12 score minus the baseline score. Changes from baseline for other timepoints are calculated similarly.

The mean and standard deviation of the change from baseline in the overall and domain DLQI scores at Week 12 for each treatment group will be presented. The analysis will consist of treatment comparisons on overall score between each of the omalizumab groups (75-mg, 150-mg and 300-mg) and the placebo group using ANCOVA controlling for baseline DLQI (<median vs. ≥ median), and baseline weight (<80 kg vs. ≥80 kg). A separate ANCOVA model will be run for each omalizumab dose group versus placebo. The LSM and the corresponding 95% confidence intervals of the differences between the omalizumab groups and the placebo group will be presented along with the p-values for the treatment differences resulting from the ANCOVA models.

No imputation will be performed for missing Week 12 overall DLQI scores.

4.4.2.8 Proportion of Angioedema-Free Days from Week 4 to Week 12 of Therapy

The occurrence of angioedema is recorded once daily (evening) in the patients' eDiaries. The proportion of angioedema-free days from Week 4 to Week 12 will be defined as the number of days for which the patient indicated a "No" response 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 prior to the Week 12 visit date. Patients who withdraw before the Week 4 visit or who have missing responses for >40% of the daily diary entries between the Week 4 study visit and the Week 12 study visit will not be included in this analysis. No imputations will be made for missing data. The mean, median and standard deviation of the proportion of angioedema-free days from Week 4 to Week 12 for each treatment group will be presented. The treatment comparison will be conducted using a Van Elteren's test (stratified Wilcoxon rank-sum test), stratified by presence of angioedema at baseline (Yes vs No) and baseline weight (<80 kg vs. ≥80 kg) (van Elteren 1960). The presence of angioedema at baseline will be Yes if the patient indicated a "Yes" response to the angioedema question in the daily diary on any of the 7 days prior to the Day 1 study visit (study days -7 to -1). Likewise, the presence of angioedema at baseline will be No if the patient indicated a "No" response to the angioedema question in the daily diary on all of the 7 days prior to the Day 1 study visit.

4.4.3 EXPLORATORY EFFICACY ENDPOINTS

4.4.3.1 Change from Baseline Endpoints

The following exploratory endpoints are based on change from baseline measurements and will be analyzed in a similar way. The mean and standard deviation of the change from baseline for each treatment group will be presented. The separate treatment comparisons will be between each omalizumab dose group versus placebo made using ANCOVA controlling for baseline score (<median vs. ≥ median) and baseline weight (<80 kg vs. ≥80 kg). A separate ANCOVA model will be run for each omalizumab dose group versus placebo.

The LSM and the corresponding 95% confidence intervals for the differences between the omalizumab groups and the placebo group will be presented along with the p-values for the treatment differences resulting from the ANCOVA models.

4.4.3.1.1 Change from Baseline in the Chronic Urticaria Quality-of-Life Questionnaire (CU-Q_{2oL}) at Week 12 and Week 28

The Chronic Urticaria Quality-of-Life Questionnaire (CU-Q_{2oL}) is a 23-item CIU-specific health-related quality-of-life questionnaire where patients rate their CIU symptoms and the impact of their CIU on various aspects of their lives. An overall score will be calculated as well for the following domains: Pruritus, Swelling, Impact on Life Activities, Sleep Problems, Limits, and Looks.

Each item is assessed on a 5-point scale ranging from 1 (Not at all) to 5 (Extremely). Questions and scores were formulated such that the higher the score, the worse the QoL.

The overall raw score and the 7 domain raw scores are scored as follows (please see below, Table 3).

Table 3: CU-Q_{2oL} Overall Score and Domain Scores Definitions

Score	Items	Minimum	Maximum
Overall	1 to 23	23	115
Pruritus	1 and 2	2	10
Swelling	3 and 4	2	10
Impact on Life Activities	5 to 10	6	30
Sleep Problems	11 to 15	5	25
Limits	16, 17, and 22	3	15
Looks	18 to 21 and 23	5	25

To compute the overall CU-Q_{2oL} and domain scores, the following formula is used to convert the raw scores to 0-100 point scores:

$$[(\text{Sum of items} - \text{minimum}) / (\text{maximum} - \text{minimum})] \times 100$$

The baseline, Week 12, and Week 28 overall CU-Q_{2oL} scores as well as the domain scores will be derived from questionnaires assessed at the Day 1, Week 12, and Week 28 visits, respectively.

No imputation will be performed for missing Week 12 or Week 28 CU-Q_{2oL} scores.

Changes from baseline in the overall and domain CU-Q_{2oL} scores at Week 12 are defined as the Week 12 score minus the Baseline score. Changes from baseline for Week 28 are calculated similarly (Baiardini et al. 2005).

4.4.3.1.2 Change from Baseline in DLQI at Week 28

This is defined in Section 4.4.2.8. No imputation will be performed for missing Week 28 DLQI scores.

4.4.3.1.3 Change from Baseline in the Proportion of Itch-Free Days and/or Hive-Free Days at Week 12

The proportion of itch-free days is defined by the number of days a patient has a daily itch score of 0 over the study days which make up a given study week (as described in Section 4.4). Similarly, the proportion of hive-free days is defined by the number of days a patient has a daily hive score of 0 over the study days which make up a given study week. The number of itch-free and hive-free days is defined as the number of days that both the daily itch and the daily hive score are 0 over the study days which make up a given study week. This analysis will include only patients who have non-missing weekly itch and hive scores at Week 12.

4.4.3.1.4 Change in Number of Tablets/Week of Sedating H1 Antihistamine (Diphenhydramine) for Itch Relief from Baseline to Week 12

Diphenhydramine use is recorded on the eDiary once daily (0–9). The number of tablets/week of sedating H1 antihistamine (diphenhydramine) for itch relief is defined as the sum of daily use of diphenhydramine over the study days which make up a given study week (as described in Section 4.4). The change in number of tablets/week of sedating H1 antihistamine (diphenhydramine) for itch relief from baseline to Week 12 is the Week 12 number of tablets/week minus the baseline number of tablets/week.

4.4.3.1.5 Change from Baseline in Weekly Sleep Interference Score at Week 12

The sleep interference score is recorded on the eDiary once daily (0-3). The weekly sleep interference score is defined by the sum of daily sleep interference score over the study days which make up a given study week (as described in Section 4.4). Changes from baseline to Week 12 are calculated similarly to other outcomes.

4.4.3.1.6 Change from Baseline in Weekly Interference with Daily Activities Score at Week 12 and Week 28

The daily activity interference score is recorded on the eDiary once a day (0-3). The weekly interference with daily activities score is defined by the sum of daily interference score over the study days which make up a given study week (as described in Section 4.4). Changes from baseline to Week 12 are calculated similarly to other outcomes.

4.4.3.1.7 Change from Baseline in Health Utility as Measured by the EuroQoL-5D at Week 12 and Week 28

The EQ-5D questionnaire is a generic preference-based health related quality-of-life questionnaire that provides a single index value for health status (The EuroQol Group 1990). The EQ-5D questionnaire is designed for self-completion by patients and will be administered at baseline, Week 12, and at the end of the study (Week 28).

The EQ-5D questionnaire consists of five questions each with three possible categories (no problems, moderate problems, severe problems) and a visual analogue scale from 0 (worst possible health state) to 100 (best possible health state). The five questions comprise five dimensions of health (mobility self-care, usual activities, pain/discomfort, and anxiety/depression). An EQ-5D index score will be constructed using the five questions and U.K. population-based weights as implemented by Kind et al. (1998). No imputation will be performed for missing Week 12 or Week 28 EQ-5D scores.

Each question will be summarized separately by treatment group for each timepoint using proportions. The visual analogue scale will also be summarized by treatment group using mean, standard deviation, median, and range. The EQ-5D index score will also be summarized by treatment groups for each timepoint.

Changes from baseline in EQ-5D index score at Week 12 and Week 28 are calculated similarly to other outcomes.

4.4.3.1.8 Change from Baseline in MOS Sleep Score at Week 12

The MOS Sleep Scale is a 12-item questionnaire asking patients to rate various dimensions of their sleep over the past four weeks (Hays and Stewart 1992). Several scores can be derived: Sleep Disturbance, Snoring, Short of Breath, Sleep Adequacy, Somnolence, Sleep Problems Index I, Sleep Problems Index II, Sleep Quantity, and Optimal Sleep. Derivations of the scores are detailed in Spritzer and Hays (2003).

The baseline and Week 12 MOS domain scores will be derived from questionnaires assessed at the Day 1 and Week 12 visits, respectively. No imputation will be performed for missing Week 12 MOS domain scores. Changes from baseline in the MOS domain scores are calculated similarly to other outcomes.

4.4.3.2 Endpoints that Consist of Proportion of Responders

4.4.3.2.1 Proportion of Patients with UAS7 $\leq$ 6 at Week 28

The Week 28 UAS7 will be defined as in Section 4.4.2.1. Patients will be classified as non-responders at Week 28 (i.e., did not achieve UAS7 $\leq$ 6 at Week 28) if they have a missing UAS7 at Week 28.

The proportions of patients who achieve $\text{UAS7} \leq 6$ at Week 28 for each treatment group will be presented. The treatment comparisons will be made using the Cochran-Mantel-Haenszel test stratified by baseline UAS7 ($< \text{median}$ vs. $\geq \text{median}$) and baseline weight ($< 80 \text{ kg}$ vs. $\geq 80 \text{ kg}$) will be performed to compare the proportions of patients with $\text{UAS7} \leq 6$ at Week 28 in each of the omalizumab groups versus placebo.

4.4.3.2.2 Proportion of Week 12 Responders who Maintain their Response ($\text{UAS7} \leq 6$) to the Week 28 Visit

This analysis will be restricted to patients who achieve $\text{UAS7} \leq 6$ at Week 12. The proportions of those patients with Week 12 $\text{UAS7} \leq 6$ who maintain $\text{UAS7} \leq 6$ through Week 28 will be presented for each treatment group. Patients with a missing UAS7 for any week from Week 13 to Week 28 will be classified as not maintaining the response to the Week 28 visit. This endpoint is used solely to characterize disease/symptom recurrence. Given that there is no proper comparison group, descriptive summary statistics for each treatment group will be provided but no statistical tests will be conducted to compare between treatment groups.

4.4.3.3 Endpoints that Consist of Time to First Event (Response/Relapse)

4.4.3.3.1 Time to MID Response in UAS7 by Week 12

This endpoint will be considered censored at the date of the last non-missing UAS7 evaluation up to the Week 12 study visit for any patient who fails to achieve an MID response.

Kaplan-Meier estimates of the distribution of time to first UAS7 MID response will be presented graphically. The median of the time to first UAS7 MID response and the corresponding 95% confidence interval will be presented for each treatment group. The treatment comparisons will be performed using the Cox PH model stratified by baseline UAS7 ($< \text{median}$ vs. $\geq \text{median}$) and baseline weight ($< 80 \text{ kg}$ vs. $\geq 80 \text{ kg}$). A separate Cox PH model will be run for each omalizumab dose group versus placebo.

4.4.3.3.2 Time to Relapse in Week 12 Responders

This analysis will be restricted to patients who achieve $\text{UAS7} \leq 6$ at Week 12. The time to relapse is defined as the time (in weeks) from the Week 12 visit to the first week where $\text{UAS7} > 6$.

This endpoint will be considered censored at the date of the last non-missing UAS7 evaluation after the Week 12 visit for any patient who maintains a $\text{UAS7} \leq 6$.

Kaplan-Meier estimates of the distribution of time to first relapse will be presented graphically. The median of the time to first relapse and the corresponding 95% confidence interval will be presented for each treatment group. No statistical tests will be conducted to compare between treatment groups given that no proper comparison group exists.

4.4.3.4 Other Endpoints

Healthcare utilization (calling a doctor, nurse, or nurse practitioner) based on patient daily diary data will be summarized for each treatment group.

For patients reporting angioedema, the action(s) taken in response to their angioedema based on patient daily diary data will be summarized for each treatment group.

The correlation between basophil high-affinity IgE receptor down-regulation and the change from baseline in weekly itch severity score will be summarized for each treatment group at Week 12 and Week 28.

4.4.4 SENSITIVITY ANALYSES

Sensitivity analyses of the primary endpoint will be performed to compare each omalizumab dose group to placebo as follows:

- An ANCOVA model will be fitted which is similar to the primary analysis but imputes missing Week 12 weekly itch severity scores by the method of LOCF. That is, for patients who have a missing Week 12 weekly itch severity score, the Week 12 weekly itch severity score will be imputed by the last non-missing weekly. As in the primary analysis, the ANCOVA model will control for baseline weekly itch severity score (< 13 vs. ≥ 13) and baseline weight (< 80 kg vs. ≥ 80 kg), and a separate ANCOVA model will be run for each omalizumab dose group versus placebo.
- A mixed effects model will be fitted which includes all observed weekly itch severity scores from baseline to Week 12. No imputation will be applied to those weeks with a missing weekly itch severity score. The baseline weekly itch severity score (< 13 vs. ≥ 13), baseline weight (< 80 kg vs. ≥ 80 kg), treatment group (omalizumab vs placebo), and time will be included as covariates in the model, and a separate model will be run for each omalizumab dose group versus placebo.

- An ANCOVA model will be fitted, which is similar to the primary analysis but imputes the Week 12 weekly itch severity score by carrying forward the baseline weekly itch severity score (BOCF) for patients who received any systemic steroids for any reason during the 2 weeks prior to the Week 12 visit (study days 71 to 84). As in the primary analysis, the ANCOVA model will control for baseline weekly itch severity score (< 13 vs. ≥ 13) and baseline weight (< 80 kg vs. ≥ 80 kg), and a separate ANCOVA model will be run for each omalizumab dose group versus placebo.

4.4.5 SUBGROUP ANALYSES

Subgroup analyses will be performed by categories of the following demographic and baseline variable categories to evaluate consistency of the primary efficacy results. Subgroup analyses are considered supportive.

- Gender (Male vs. Female)
- Age (< 18 , 18–64, ≥ 65 years)
- Race (White, Black or African-American, all other races)
- Region (U.S., non-U.S.)
- Baseline weekly itch severity score (< 13 , ≥ 13)
- Baseline UAS7 ($< \text{median}$, $\geq \text{median}$)
- Body weight (< 80 kg, ≥ 80 kg)
- Presence of anti-FcεRI autoantibody as detected by CU index test (Yes, No)
- Presence of angioedema at baseline (Yes, No)
- Previous use of systemic steroids for CIU (Yes, No)
- Presence of thyroperoxidase antibody at baseline (Positive, Negative)
- Duration of disease prior to baseline (< 2 , 2–10, > 10 years)
- Previous number of CIU medications (≤ 2 , 3–5, > 5)

The mean and standard deviation of the change from baseline in weekly itch severity scores at Week 12 by treatment group will be presented for each subgroup level. In addition, the ANCOVA model specified in Section 4.4.1 will be applied separately to each subgroup level.

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Total omalizumab levels will be summarized using descriptive statistics. Free IgE and total IgE will be summarized using mean and standard deviations by treatment group at each visit at which they are measured. The summaries will include the raw data as well as change from baseline.

4.6 SAFETY ANALYSES

Safety will be assessed through the summary of adverse events, laboratory test results, vital signs, and antibodies to omalizumab. Separate summaries will be produced for the whole study, the 12-week treatment period, and the 16-week follow-up period. Safety analyses will include the safety-evaluable patients. Patients will be analyzed according to the actual treatment received.

4.6.1 EXPOSURE OF STUDY MEDICATION

The number of doses and the total dose (mg) of study drug administered during the study will be summarized by treatment group. The duration of study drug exposure will also be summarized by treatment group. The duration of study drug exposure will be defined as the date of the last treatment visit—the date of the first study drug administration + 1 + 4 weeks (28 days). If a patient received study medication after their last scheduled treatment visit as an error, the date of the last dose of study medication will be taken as the treatment end date.

4.6.2 ADVERSE EVENTS

Verbatim descriptions of adverse events will be coded and analyzed using appropriate thesaurus terms. A treatment-emergent adverse event is defined as any adverse event reported on or after the first dose of study drug.

Treatment-emergent adverse events will be summarized by treatment group for each of the following:

- All adverse events
- All adverse events by severity (mild, moderate, severe)
- Serious adverse events
- Adverse events leading to discontinuation of study drug
- Deaths

Narratives for all reported serious adverse events and pregnancies will also be provided.

Adverse events listed below are of special interest for omalizumab treatment. The number of patients with study-emergent adverse events of special interest will be summarized by treatment group.

- Anaphylaxis
- Churg-Strauss syndrome
- Hypersensitivity
- Injection-site reaction
- Malignancy
- Serum sickness syndrome
- Skin rash
- Thrombocytopenia and bleeding-related disorders
- Hematopoietic cytopenias
- Arterial thrombotic events (ATEs)
- Asthma/bronchospasm
- Liver-related investigations, signs and symptoms

4.6.3 LABORATORY DATA

Descriptive summaries of serum chemistry and urinalysis baseline values will be generated by treatment group. Hematology values will be summarized at baseline and throughout the study by treatment group. Changes from baseline in clinical laboratory values and the proportion of patients experiencing changes relative to baseline based on normal ranges for the specific tests will be presented by treatment group.

The baseline value of any variable will be defined as the last available value prior to the first administration of study drug for the treatment period (Day 1), unless otherwise specified.

4.6.4 VITAL SIGNS

A patient listing of vital signs will be generated. Vital signs include pulse and systolic and diastolic blood pressure.

4.6.5 ANTI-THERAPEUTIC ANTIBODIES

Anti-Therapeutic antibody data will be reported for each treatment group at the end of the follow-up visit (Week 28), along with an estimate of the proportion of patients with treatment-emergent positive ATAs at Week 28.

4.7 MISSING DATA

The following sub-sections summarize the principles described in Section 4.4.

4.7.1 CALCULATION OF THE DIARY-BASED DAILY SCORES

The following scores are recorded twice daily (morning and evening) in the patient eDiary: the itch score, the hive score, and the largest hive score. The daily scores for these assessments are calculated as the average of the morning and evening scores. When either the morning or evening score is missing, the non-missing score for that day (morning or evening) will be used as the daily score and when both the morning and evening scores are missing, the daily score will be missing. No imputation will be conducted for missing daily scores.

The daily UAS is a sum of the daily itch score and the daily hive score. If either the daily itch score or the daily hive score are missing, the corresponding daily UAS will be missing.

The following scores are recorded once daily (morning or evening) in the patient eDiary: number of diphenhydramine tablets for itch relief (evening), presence of angioedema (evening), sleep interference score (morning) and daily activities interference score (evening). The daily scores for these assessments are based on the one entry made per day. When a morning or evening diary entry is not completed, the result will be a missing daily score for the once daily assessment(s) corresponding to that diary entry. No imputation will be conducted for missing daily scores.

4.7.2 CALCULATION OF THE DIARY-BASED WEEKLY SCORES

The diary-based weekly score is calculated as the sum of the daily scores over the study days which make up a given study week (as described in Section 4.4).

When one or more of the daily scores are missing or if a given study week is <7 days (i.e., the study week following a treatment visit which occurred late), the following principles will be applied to handle the missing data:

- If a patient has at least 4 non-missing daily scores included in the calculation of the weekly score, the weekly score is defined as the sum of the available daily scores in that week, divided by the number of days that have a non-missing daily score, multiplied by 7.
- If there are less than 4 non-missing daily scores included in the calculation of the weekly score, then the weekly score is defined as missing for that week.

4.7.3 IMPUTATION OF MISSING DATA

For change from baseline weekly score endpoints (weekly itch severity score, weekly number of hives score, UAS7, weekly size of largest hive score, proportion of itch-free and/or hive-free days, number of diphenhydramine tablets/week, weekly sleep interference score, and weekly daily activities interference score) analyzed at particular timepoints (e.g., Week 12 or Week 28), missing post-baseline weekly scores will be imputed using the baseline weekly score (BOCF). In addition, for summaries by study week, the weekly scores will be imputed using BOCF.

For endpoints that consist of proportions of responders (UAS7 ≤ 6 response, weekly itch severity score MID responder, UAS7 MID responder) analyzed at a particular time point (e.g., Week 12 or Week 28), patients with missing weekly scores for the given week will be classified as non-responders.

For time to the first event endpoints (time to the first weekly itch severity score MID response, time to the first UAS7 MID response, time to the first relapse in Week 12 responders), the endpoint will be considered censored at the week of the last non-missing weekly score in the absence of the event. In addition, it will be assumed that an event did not occur during a week with a missing weekly score that occurs between baseline and a study week with a non-missing weekly score.

4.7.4 OTHER PATIENT-REPORTED OUTCOMES

With respect to the scoring of the CuQ2-OL, EQ-5D, MOS sleep scale, and DLQI, missing data will be handled as detailed in the appropriate instrument-specific instrument manuals. No imputation will be performed for missing scores at a given study visit.

In order to examine the robustness of the results based on non-missing scores, sensitivity analyses will be performed with missing scores imputed using the BOCF method.

4.8 TYPE I ERROR CONTROL PLAN

4.8.1 PRIMARY EFFICACY ENDPOINT

In order to maintain an overall type I error rate of 0.05 (two-sided) across the three omalizumab dose levels, the testing of the primary endpoint will be conducted in the following hierarchical order:

- Stage 1: Omalizumab 300-mg group vs. placebo
If there is no statistically significant difference found between the omalizumab 300mg group and the placebo group at the significance level of 0.05, then the test for the next stage will not be considered statistically significant regardless of the p-value.
- Stage 2: Omalizumab 150-mg group vs. placebo
If there is 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 will not be considered statistically significant regardless of the p-value.
- Stage 3: Omalizumab 75-mg group vs. placebo
The statistical test will be conducted at a significance level of 0.05.

4.8.2 SECONDARY EFFICACY ENDPOINT

A hierarchical analysis of the following secondary endpoints will be performed for each dose found to be significant in the primary endpoint (Dmitrienko et al. 2003). All tests will be conducted at a 0.05 significance level. A p-value that is less than 0.05 can only be claimed statistically significant if statistical significance has been claimed at the previous stage. The hierarchical analysis of the secondary endpoints will be independent between different dose levels. In other words, failure to claim statistical significance for a secondary endpoint at any omalizumab dose level does not affect the testing of any secondary endpoint at another dose level.

- 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 itch severity score MID response at Week 12
- Stage 4: Proportion of patients with $\text{UAS7} \leq 6$ at Week 12
- Stage 5: Proportion of weekly itch severity score 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 (DLQI) at Week 12
- Stage 8: Proportion of angioedema-free days from Week 4 to Week 12 of therapy

5. REFERENCES

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Appendix 1

Protocol Synopsis

PROTOCOL SYNOPSIS

<u>TITLE:</u>	A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, DOSE-RANGING, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY, RESPONSE DURATION AND SAFETY OF XOLAIR® (OMALIZUMAB) IN PATIENTS WITH CHRONIC IDIOPATHIC URTICARIA (CIU) WHO REMAIN SYMPTOMATIC DESPITE ANTIHISTAMINE TREATMENT (H1)
<u>PROTOCOL NUMBER:</u>	Q4882g
<u>Eudract Number:</u>	2010-022785-27
<u>STUDY DRUG:</u>	XOLAIR® (Omalizumab)
<u>PHASE:</u>	III
<u>INDICATION:</u>	Chronic idiopathic urticaria
<u>IND:</u>	101,612
<u>SPONSOR:</u>	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990 U.S.A.
<u>DATE FINAL:</u>	24 September 2010
<u>DATE AMENDED:</u>	11 January 2011

Objectives

Primary Objective

- To evaluate the efficacy of omalizumab compared with placebo in patients with refractory chronic idiopathic urticaria (CIU) receiving concomitant H1 antihistamine therapy

Secondary Objectives

- To evaluate the safety of omalizumab therapy in patients with refractory CIU
- To evaluate onset of clinical effect of omalizumab therapy in CIU
- To evaluate the dose of omalizumab therapy in patients with refractory CIU
- *To evaluate duration of response after withdrawal of omalizumab in patients with refractory CIU*
- To evaluate the quality-of-life benefit of omalizumab therapy in patients with refractory CIU

Study Design

The study is a global Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of omalizumab administered subcutaneously as an add-on therapy for the treatment of adolescent and adult patients aged 12–75 who have been diagnosed with refractory CIU and who remain symptomatic despite standard-dosed H1 antihistamine treatment. The study will enroll approximately 300 patients at approximately 70 study sites globally.

The study will consist of *three* distinct study periods over a time period of 30 weeks, as outlined below (see also Figure 1):

Appendix 1

Protocol Synopsis (cont'd)

- Screening period: Day –14 to Day –1
- Treatment Period: Day 1 to Day 85 Pre-dose (Week 0 to Week 12)
- Follow-Up Period: Day 85 to Day 197 (Week 12 to Week 28)

The screening period will consist of visits at Day –14 and Day –7. Patients must meet all of the following criteria to enter the screening period:

- Non-electronic diary based UAS of ≥ 4 established in the clinic based on the patient's condition over 12 hours prior to either Day –14, Day –7, or Day 1 despite being on H1 antihistamine therapy
- Use of an approved dose of an H1 antihistamine for CIU at Day –14 and for at least the 3 consecutive days immediately prior to Day –14 (see Section 4.3.2 for list of H1 antihistamines available for use in this study)
- Willing and able to complete a symptom electronic diary (eDiary) twice daily throughout the screening period to establish the patient's UAS7 score

Patients will have the 2-week screening period to establish their eligibility for the study and baseline symptom scores. For the duration of the screening period, patients must maintain stable doses of their pre-screening H1 antihistamine treatment. To be eligible for the study, patients must have no missing eDiary entries, a UAS7 symptom score of ≥ 16 (equivalent to moderate to severe CIU symptoms for at least 4 out of the 7 days in a week), and a weekly itch score (a component of the UAS7) of ≥ 8 for the 7 days prior to randomization.

Only in exceptional circumstances, when information concerning eligibility is outstanding (e.g., pending laboratory data) will a longer screening period be permitted. Upon approval from the Medical Monitor, patients may be re-screened. Circumstances that may permit re-screening include, but are not limited to, an in-clinic UAS score or laboratory test results that do not meet eligibility requirements.

On Day 1, eligible patients will be randomly assigned (in a 1:1:1:1 ratio using Interactive Voice and Web Response System [IxRS]) to receive omalizumab (75, 150, or 300 mg) or placebo by subcutaneous (SC) injection every 4 weeks during the 12-week double-blind treatment period. There will be approximately 75 patients in *each of* the 75, 150, and 300 mg omalizumab treatment arms and in the placebo arm. Randomization to treatment groups will be stratified by baseline weekly itch score, baseline weight, and study site. A hierarchical dynamic randomization scheme will be used to achieve overall balance between treatment groups and within strata. Efficacy, safety, *pharmacokinetic (PK)*, and *pharmacodynamic (PD)* data will be collected. For the duration of the *treatment period*, patients must maintain stable doses of their pre-randomization CIU H1 antihistamine treatment. The last dose of study drug during the *treatment period* will be given at the Day 57 (Week 8) study visit. *The primary endpoint will be measured at Week 12. In the follow-up period, patients may add up to one additional H1 antihistamine therapy (refer to Section 4.3.2). Increasing the dose of antihistamine above the approved dose is not permitted. The goal of allowing additional H1 antihistamine therapy after the primary endpoint has been assessed is to reduce patient dropout for improved safety evaluation.*

After completion of the 12-week *treatment period*, all patients will enter a 16-week follow-up period to allow for further characterization of the pharmacokinetics (PK) and pharmacodynamics (PD) of omalizumab, collection of additional efficacy and safety data, and evaluation of the presence of anti-therapeutic antibodies (ATAs). Patients will continue to visit the study center at 4-week intervals. No study treatment will be given; patients must maintain stable doses of their pre-randomization CIU H1 antihistamine treatment.

The blind will be maintained for the full 28 weeks of the study (post-randomization). For the duration of the study, all patients will be provided with diphenhydramine (25 mg) for itch relief on an as-needed basis (up to a maximum of three doses in 24 hours or less based on local regulations).

Appendix 1

Protocol Synopsis (cont'd)

Outcome Measures

Primary Efficacy Outcome Measure

The primary efficacy outcome measure is the change from baseline in weekly itch score (a component of the UAS7) at Week 12 (see Table 1). The itch score will be recorded twice daily (morning and evening) in the patient eDiary, on a scale of 0 (none) to 3 (severe). The daily itch score is the average of the morning and evening scores. The baseline weekly itch score is the sum of the daily itch scores over the 7 days prior to randomization (Day 1 visit), and the weekly itch score at Week 12 is the sum of daily itch scores over the 7 days prior to the Week 12 visit (Day 85). The same principles of calculating baseline and Week 12 weekly scores will be applied to the following weekly outcomes unless otherwise stated.

Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures are as follows:

- Change from baseline in UAS7 at Week 12

The UAS is a composite eDiary-recorded score with numeric severity intensity ratings on a scale of 0–3 (0 = none to 3 = intense/severe) for 1) the number of wheals (hives); and 2) the intensity of the itch (see Table 1), measured twice daily (morning and evening). The daily UAS is the average of the morning and evening scores and the UAS7 is the sum of the daily UAS scores over 7 days.

Table 1 Twice Daily Assessment of Disease Activity in Patients with CIU (UAS Scale)		
Score	Wheals (Hives)	Pruritus (Itch)
0	None	None
1	Mild (1–6 hives/12 hour)	Mild
2	Moderate (7–12 hives/12 hour)	Moderate
3	Intense (> 12 hives/12 hour)	Severe

CIU = chronic idiopathic urticaria.

- Change from baseline in weekly hives score at Week 12
The number of hives is measured twice daily (morning and evening), on a scale of 0 (none) to 3 (> 12). The daily hives score is the average of the morning and evening scores, and the weekly hives score is the sum of the daily hives scores over 7 days.
- Time to weekly itch score minimally important difference (MID) response by Week 12
Weekly itch score MID response is defined as a reduction from baseline in weekly itch score of ≥ 5 points. Time to weekly itch score MID response is the time (in weeks) from the date of the first dose to the date where weekly itch score MID response is first achieved.
- Proportion of patients with UAS7 ≤ 6 at Week 12
UAS7 ≤ 6 identifies patients with an excellent clinical response who may be considering discontinuing therapy as they have minimal or no symptoms.
- Change from baseline in weekly largest hive score at Week 12
The largest hive score is measured twice daily, on a scale of 0 (none) to 3 (> 2.5 cm). The daily largest hive score is the average of the morning and evening scores, and the weekly largest hive score is the sum of the daily scores over 7 days.
- Proportion of weekly itch score MID Responders at Week 12
Weekly itch score MID responders are defined as patients who achieve a weekly itch score MID response at the Week 12 visit.

Appendix 1

Protocol Synopsis (cont'd)

- *Proportion of patients with UAS7 ≤ 6 at Week 28*
- Change from baseline in health-related quality-of-life as measured by the Dermatology Life Quality Index (DLQI) at Week 12
- Proportion of angioedema-free days from Week 4 to Week 12 of therapy

Safety Outcome Measures

The safety of omalizumab will be assessed using the following safety outcome measures:

- Incidence and severity of adverse events and serious adverse events
- Changes in vital signs
- Clinical laboratory evaluations
- ATA evaluation at the end of the follow-up period

Pharmacokinetic/Pharmacodynamic Outcome Measures

The following PK and PD outcome measures will be reported:

- Summary trough serum levels of omalizumab, total and free IgE

Exploratory Outcome Measures

The following exploratory *efficacy* outcome measures will be assessed:

- Proportion of patients with UAS7 ≤ 6 at Week 28
- Time to UAS7 minimally important difference (MID) response by Week 12
UAS7 MID response is defined as a reduction from baseline in UAS7 score of ≥ 11 points. Time to UAS7 MID response is the time (in weeks) from the date of the first dose to the date where UAS7 MID response is first achieved.
- *Proportion of Week 12 responders who maintain their response (UAS7 ≤ 6) to the Week 28 visit*
Week 12 responders are defined as patients who achieve an absolute UAS7 ≤ 6 at Week 12.
- *Time to relapse in Week 12 responders*
Time to relapse is defined as the date of the Week 12 visit to the date where UAS7 > 6 .
- Change from baseline in health-related quality-of-life as measured by the Chronic Urticaria Quality-of-Life Questionnaire (CU-Q2oL) at Week 12 *and* Week 28
- *Change from baseline in health-related quality-of-life as measured by the DLQI at Week 28*
- Change from baseline in the number of itch-free days and/or hive-free days at Week 12
- Change in number of tablets/week of sedating H1 antihistamine (diphenhydramine) for itch relief from baseline to Week 12
- Change from baseline in weekly sleep interference score at Week 12
The sleep interference score is measured daily, on a scale of 0 (No interference) to 3 (substantial, woke up often, severe impact on sleep). The weekly sleep interference score is the sum of the daily scores over 7 days.
- Change from baseline in weekly interference with daily activities score at Week 12
The daily activities interference score is measured daily on a 0 (No interference) to 3 (Substantial, severe interference with daily activities) scale. The weekly interference with daily activities score is the sum of the daily scores over 7 days.
- Change from baseline in health utility as measured by the EQ-5D at Week 12 *and* Week 28
- Change from baseline in MOS sleep score at Week 12

A number of laboratory investigations will be conducted to gain an insight into the mechanism of action of omalizumab in the patient population under study.

Appendix 1

Protocol Synopsis (cont'd)

Safety Plan

Omalizumab is currently approved for marketing in approximately 52 countries for patients 6 years and above (including, but not limited, to the European Union, New Zealand and Russia). In some regions the indicated age is limited to 12 years and above (including, but not limited to the U.S., Canada, and Australia). Each individual country basic prescribing information may vary, but in general, it is for the prevention of asthma exacerbations and control of asthma symptoms when given as add-on therapy for adult and adolescent patients with moderate to severe persistent allergic asthma who remain inadequately controlled. Consult the local prescribing information for more information.

Patient injections will be administered by a qualified healthcare professional, and patients will be monitored for an appropriate period of time after each dosing event. Patients will be instructed to recognize the signs and symptoms of any severe hypersensitivity reaction, and to contact a healthcare provider in case of any such symptoms.

Patients with CIU can have angioedema as part of their symptoms. When that angioedema poses a risk to the airway, the emergent use of systemic corticosteroids is indicated. Patients who need to be treated with systemic corticosteroids will be discontinued from study treatment and followed for safety for the remainder of the study. Patients will be provided emergency contact information and advised to contact a physician during the entire study, in case of angioedema.

During the conduct of the study, a treatment assignment should be unblinded only in the event of a life-threatening medical emergency that requires immediate unblinding/unmasking, or in the event of an unexpected serious adverse event judged by the investigator as related to study drug, for FDA safety reporting. In such cases, unblinding will be implemented following standard procedures, and only following agreement by both the investigator and Medical Monitor that unblinding is necessary.

Safety data including serious and non-serious adverse events and laboratory test results will be reviewed internally on a periodic basis during the conduct of the study. See Section 5 (Assessment of Safety) for complete details of the safety evaluation for this study.

An independent Data Monitoring Committee (iDMC) will review blinded and unblinded safety data provided to them by an independent Data Coordinating Center (iDCC) every 6 months for the duration of the study.

Please refer to the Omalizumab Investigator Brochure for additional information on safety risks.

Study Treatment

Patients will receive omalizumab (75 ,150, or 300 mg) or placebo administered subcutaneously every 4 weeks at the study center.

Study medication will be supplied as a lyophilized, sterile powder in a single-use, 5-mL vial that is designed to deliver 150 mg of omalizumab or placebo for SC administration upon reconstitution with 1.4 mL Sterile Water for Injection.

Each patient will receive two injections of study medication. For details regarding each individual's injection, please refer to Appendix H.

Concomitant Therapy and Clinical Practice

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use. All concomitant medications should be reported to the investigator and recorded on the appropriate electronic Case Report Form (eCRF). Patients will be encouraged to use the minimal dose required to control their symptoms.

All patients will be allowed to take study-defined H1 antihistamine medications at approved doses during the screening, treatment, and follow-up periods. Patients should remain on a stable H1 antihistamine treatment regimen throughout the study period. Diphenhydramine (25 mg) will be provided and used on an as-needed basis (maximum 3 times/day) during screening, treatment and

Appendix 1

Protocol Synopsis (cont'd)

follow-up periods. *Therapies used for the treatment of CIU prior to enrollment will be collected as part of the patient's medical history.*

Excluded Therapy

Prior to the screening visit (-14 days) and during the study, the following medications and treatments will be restricted:

- Routine (daily or every other day during 5 or more consecutive days) doses of the following medications within 30 days prior to Day -14: systemic or cutaneous (topical) corticosteroids (prescription or over the counter), hydroxychloroquine, methotrexate, cyclosporine, or cyclophosphamide
- Routine (daily or every other day during 5 or more consecutive days) doses of doxepin within 14 days prior to Day -14
- Omalizumab within 1 year prior to screening
- Any LTRAs (montelukast or zafirlukast) or H2 blockers within 7 days prior to Day -14
- Any H1 antihistamines at greater than approved doses within 3 days prior to Day -14
- Either intravenous immunoglobulin G (IVIG) or plasmapheresis within 30 days prior to Day -14

Patients who receive any excluded therapy during screening should be considered a screening failure. Patients who receive any excluded therapy after randomization will be discontinued from study treatment; if a patient has received at least one dose of omalizumab following enrollment, the patient should be followed for safety for the remainder of the study.

Patients taking either LTRAs or H2 blockers for diseases other than CIU (e.g. asthma or GERD, respectively) will be permitted to continue their use during the study. These diseases must be recorded as part of the medical history collected during the screening period. Inhaled asthma controllers, including corticosteroids, are also permitted during the study.

Statistical Methods

Primary Efficacy Analysis

The primary efficacy endpoint is the change in weekly itch score from baseline to Week 12. The analysis of the primary endpoint will consist of treatment comparisons made using analysis of covariance (ANCOVA) controlling for baseline weekly itch score, and baseline weight (<80 kg vs. ≥80 kg). The ANCOVA model will be based on the mITT patients. Missing Week 12 itch scores will be imputed by carrying forward the patients' baseline scores (BOCF). The Week 12 itch scores for patients who received excluded therapy listed in Section 4.4.2 by Week 12 will also be imputed using their baseline scores.

Determination of Sample Size

The sample size for this study is primarily based on safety and regulatory considerations. The estimation of power for efficacy assumes a mean change from baseline in the weekly itch score at Week 12 to be 9 points and 3.5 points for the omalizumab and placebo group, respectively, with a common standard deviation of 6 points (based on data from the MYSTIQUE and XCUISITE studies). Assuming an early discontinuation rate of 15% (based on data from the MYSTIQUE and XCUISITE studies) by Week 12, a total of 300 patients (1:1:1:1 randomization ratio *with 75 patients in each treatment group*) will yield approximately 98% power to detect a difference in treatment effect in the primary endpoint at the 0.05 level for any omalizumab group. A multiplicity type-I error control plan will be employed to adjust for the comparisons of multiple omalizumab groups to the placebo group in order to maintain an overall type I error rate of 0.05 (two sided).

Appendix 2 Study Flowchart

	Screening ^k		Treatment Period				Follow-Up Period				ET
Day	Day -14	Day -7	Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	
Week			Week 0	Week 4	Week 8	Week 12 ^a	Week 16	Week 20	Week 24	Week 28	
Visit #	1	2	3	4	5	6	7	8	9	10	
Visit window (days)	-4/ +2			±3	±3	+3	±3	±3	±3	±3	
Informed consent	x										
Inclusion/exclusion criteria	x	x	x								
Demographic data	x										
Medical/surgical history	x										
Vital signs (blood pressure and pulse)	x		x	x	x	x	x	x	x	x	x
Physical exam ⁱ	x		x	x	x	x	x	x	x	x	x
Weight/height	x										
Urine pregnancy test ^b	x		x	x	x	x	x	x			
Concomitant medication usage	x	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x
Study drug/placebo administration			x	x	x						
Site to contact IxRS	x		x	x	x						x
PROs											
Patients' eDiary ^c	x	x	x	x	x	x	x	x	x	x	x
CuQ2-OL ^d			x	x		x				x	x
EQ-5D ^d			x			x				x	x

Appendix 2 Study Flowchart (cont'd)

	Screening ^k		Treatment Period				Follow-Up Period				ET
Day	Day -14	Day -7	Day 1	Day 29	Day 57	Day 85	Day 113	Day 141	Day 169	Day 197	
Week			Week 0	Week 4	Week 8	Week 12 ^a	Week 16	Week 20	Week 24	Week 28	
Visit #	1	2	3	4	5	6	7	8	9	10	
Visit window (days)	-4/ +2			±3	±3	+3	±3	±3	±3	±3	
MOS sleep scale ^d			x	x		x				x	x
DLQI ^d			x	x		x				x	x
Physician's (in-clinic) assessment of UAS score ^d	x	x	x	x	x	x	x	x	x	x	x
Laboratory tests											
Hematology ^{e, f}	x		x	x	x	x	x	x	x	x	x
Stool ova and parasite evaluation ^j		x									
Chemistry ^g	x										
Urinalysis ^h	x										
Thyroperoxidase antibody	x										
Sample collection											
Total blood cell histamine ^f (U.S. sites only)			x			x				x	x
CU Index	x										
Basophil FCεRI expression assay ^f			x			x				x	x
Serum sample for biomarker ^f			x			x				x	x
Blood RNA ^f			x			x				x	x

Appendix 2

Study Flowchart (cont'd)

DLQI=dermatology life quality index; ET=early termination; IxRS=interactive voice and web response systems; MOS=medical outcomes study; UAS=urticaria activity score.

NOTE: Unless otherwise indicated, all assessments should be preformed pre-study drug administration.

- ^a The Week 12 visit should be scheduled on Day 85 (not Day 84) in order to collect eDiary data of Day 84. A 3-day window is allowed.
- ^b All women of childbearing potential (including those who have had a tubal ligation) will have a urine pregnancy test at screening and prior to study drug administration. If the urine pregnancy test results are positive, dosing should be held and a serum pregnancy test performed by the central laboratory. Urine pregnancy tests will be performed at the site.
- ^c Includes UAS7 (itch score, number of hives), largest size of hives, sleep interference score, activity interference question, rescue medication (diphenhydramine) use, angioedema episodes, number of calls to doctor or nurse. Daily diary completed twice a day by the patient. The eDiary will be given to patients on Day –14.
- ^d The MOS Sleep Scale, DLQI, CuQ2-OL, EQ-5D and physician's (in-clinic) assessment of UAS score (itch score+number of hives score) must be completed prior to administration of study drug.
- ^e Hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells).
- ^f Blood draw for all visits will be done pre-dose.
- ^g Sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatine phosphokinase, and uric acid.
- ^h Urinalysis to include protein, glucose, nitrites, specific gravity, ketones, RBCs, WBCs, and microscopic examination includes cellular elements, microorganisms, crystals and casts.
- ⁱ Physical exam on Day –14 is comprehensive but subsequent physical exams may be limited (as specified in section 4.5.1.c).
- ^j Note that stool ova and parasite examination should be performed on Day –7 in patients with an eosinophil count > 2 times the upper limit of normal on Day –14 AND risk factors for parasitic disease. Stool ova and parasite examination will be performed by a local laboratory.
- ^k The screening period is 12 to 18 days prior to Day 1. Day –14 and Day –7 are provided for reference. Day –14 should be conducted 18 to 12 days prior to Day 1. Complete diary information must be collected on 7 consecutive days prior to the Day 1 visit. The Day –7 visit is intended for review of screening labs collected on Day –14, assessment of in-clinic UAS score, evaluation of patients eDiary use and additional eDiary training if necessary. The Day –7 visit can occur up to 10 days prior to the Day 1 visit.

Appendix 3

Dermatology Life Quality Index

DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Instructions for use and scoring

The Dermatology Life Quality Index questionnaire is designed for use in adults, i.e. patients over the age of 16. It is self explanatory and can be simply handed to the patient who is asked to fill it in without the need for detailed explanation. It is usually completed in one to two minutes.

Scoring

The scoring of each question is as follows:

Very much	scored 3
A lot	scored 2
A little	scored 1
Not at all	scored 0
Not relevant	scored 0
Question unanswered	scored 0
Question 7: "prevented work or studying"	scored 3

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. The DLQI can also be expressed as a percentage of the maximum possible score of 30.

Detailed analysis of the DLQI

The DLQI can be analysed under six headings as follows:

Symptoms and feelings	Questions 1 and 2	Score maximum 6
Daily activities	Questions 3 and 4	Score maximum 6
Leisure	Questions 5 and 6	Score maximum 6
Work and School	Question 7	Score maximum 3
Personal relationships	Questions 8 and 9	Score maximum 6
Treatment	Question 10	Score maximum 3

The scores for each of these sections can also be expressed as a percentage of either 6 or 3.

Reference

A.Y. Finlay, G.K. Khan. Dermatology Life Quality Index (DLQI): A simple practical measure for routine clinical use. *Clinical and Experimental Dermatology* 1994; 19: 210-216.

Copyright

Please note that the Dermatology Life Quality Index (DLQI) is protected under copyright. However, the authors will usually give permission for the DLQI to be used for academic purposes. Please contact:

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Appendix 4

Chronic Urticaria Quality-of-Life Questionnaire

Chronic Urticaria Quality of Life Questionnaire (CU-Q₂₀L)

How bothered have you been by the following symptoms in the last two weeks?

1 Itching

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

2 Hives

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

3 Swelling of the eyes

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

4 Swelling of the lips

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

Please indicate if urticaria has limited you in the following daily activities during the last two weeks.

5 Work

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

6 Physical activity

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

7 Sleep

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

8 Free time

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

9 Relationships with other people

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

10 Eating

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

Answer the following questions regarding difficulties and problems that you may have experienced in association with urticaria (in the last two weeks).

11 Do you have difficulty falling asleep?

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

12 Do you wake up during the night?

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

13 Are you tired during the day due to a lack of sleep at night?

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

14 Do you have difficulty concentrating?

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

15 Do you feel nervous?

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

16 Do you feel down?

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

17 Do you have to limit your choice of foods?

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

18 Are you embarrassed by the marks that appear on your body due to urticaria?

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

19 Are you embarrassed to go out in public?

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

20 Do you have difficulty using cosmetics (for example, perfumes, creams, lotions, bubble bath, makeup)?

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

21 Is your choice of clothing affected?

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

22 Do you limit your sports activities because of urticaria?

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

23 Are you bothered by side effects from the medication you take for urticaria?

☐ Not at all ☐ A little ☐ Moderately ☐ Very much ☐ Extremely

Appendix 5

EuroQoL-5D



EQ-5D-3L User Guide

Basic information on how to use the EQ-5D-3L instrument

Version 4.0

April 2011

Prepared by:

Rosalind Rabin

Mandy Oemar

Mark Oppe

EuroQol Group Executive Office

On behalf of the EuroQol Group



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1. Introduction

This guide has been developed in order to give users basic information on how to use EQ-5D. Topics include administering the instrument, setting up a database for data collected using EQ-5D as well as information about how to present the results. Also included are several frequently asked questions dealing with common issues regarding the use of EQ-5D and a list of currently available EuroQol Group products.

1.1. The EuroQol Group

- The EuroQol Group is a network of international multidisciplinary researchers devoted to the measurement of health status. Established in 1987, the EuroQol Group originally consisted of researchers from Europe, but nowadays includes members from North America, Asia, Africa, Australia, and New Zealand. The Group is responsible for the development of EQ-5D, a preference based measure of health status that is now widely used in clinical trials, observational studies and other health surveys.
- The EuroQol Group has been holding annual scientific meetings since its inception in 1987.
- The EuroQol Group can be justifiably proud of its collective scientific achievements over the last 20 years. Research areas include: valuation, EQ-5D use in clinical studies and in population surveys, experimentation with the EQ-5D descriptive system, computerized applications, interpretation of EQ-5D ratings and the role of EQ-5D in measuring social inequalities in self-reported health.
- The EuroQol Group's website (www.euroqol.org) contains detailed information about EQ-5D, guidance for users, a list of available language versions, EQ-5D references and contact details.

1.2. EQ-5D

EQ-5D is a standardised measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal¹. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys (Figure 1).

EQ-5D is designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics, and in face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire.

1.2.1. EQ-5D-3L

The EQ-5D 3 level version (EQ-5D-3L) was introduced in 1990. The EQ-5D-3L essentially consists of 2 pages - the EQ-5D descriptive system (page 2) and the EQ visual analogue scale (EQ VAS) (page 3). The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the

¹ EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208

respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. **It should be noted that the numerals 1-3 have no arithmetic properties and should not be used as a cardinal score.**

Figure 1: EQ-5D-3L (UK English sample version)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problem with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

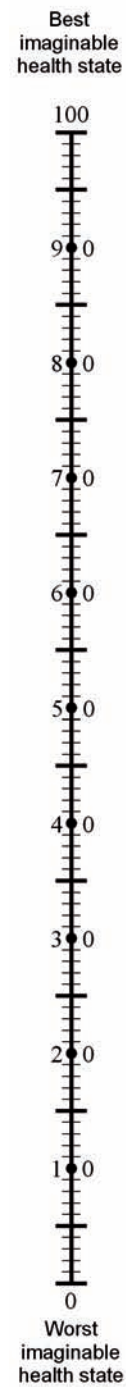
Anxiety/Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own
health state
today**



1.3. What is a health state?

Each of the 5 dimensions comprising the EQ-5D descriptive system is divided into 3 levels of perceived problems:

Level 1: indicating no problem

Level 2: indicating some problems

Level 3: indicating extreme problems

A unique health state is defined by combining 1 level from each of the 5 dimensions.



A total of 243 possible health states is defined in this way. Each state is referred to in terms of a 5 digit code. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 11223 indicates no problems with mobility and self care, some problems with performing usual activities, moderate pain or discomfort and extreme anxiety or depression.

Note: Two further states (unconscious and death) are included in the full set of 245 EQ-5D health states, but information on these states is not collected via self-report.

2. Scoring the EQ-5D-3L descriptive system

The EQ-5D-3L descriptive system should be scored as follows:

By placing a tick in one box in each group, please indicate which statements best describe your health today.

Mobility

I have no problems in walking about ☒

I have some problems in walking about ☐

I am confined to bed ☐

Self-Care

I have no problems with self-care ☒

I have some problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ☒

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☒

Anxiety/Depression

I am not anxious or depressed ☒

I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

Levels of perceived problems are coded as follows:

☒ Level 1 is coded as a '1'

☐ Level 2 is coded as a '2'

☐ Level 3 is coded as a '3'

☒

NB: There should be only one response for each dimension.

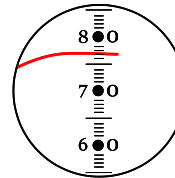
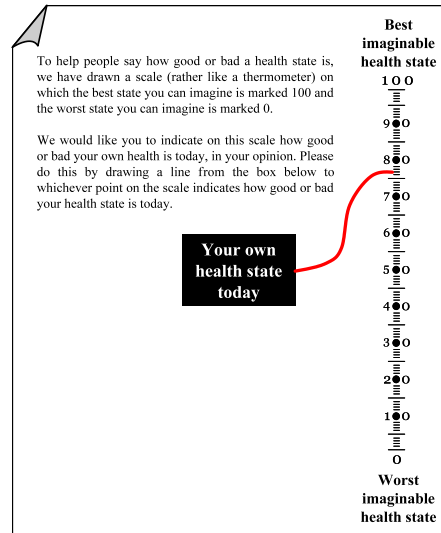
This example identifies the state 11232.

NB: Missing values can be coded as '9'.

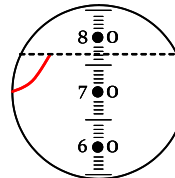
NB: Ambiguous values (e.g. 2 boxes are ticked for a single dimension) should be treated as missing values.

3. Scoring the EQ VAS

The EQ VAS should be scored as follows:



For example this response should be coded as 77



Even though the line does not cross the VAS this response can still be scored by drawing a horizontal line from the end point of the response to the VAS. In this example the response should be coded as 77

NB: Missing values should be coded as '999'.

NB: Ambiguous values (e.g. the line crosses the VAS twice) should be treated as missing values.

4. Converting EQ-5D states to a single summary index

EQ-5D health states, defined by the EQ-5D descriptive system, may be converted into a single summary index by applying a formula that essentially attaches values (also called weights) to each of the levels in each dimension. The index can be calculated by deducting the appropriate weights from 1, the value for full health (i.e. state 11111). Information in this format is useful, for example, in cost utility analysis.

Value sets have been derived for EQ-5D in several countries using the EQ-5D visual analogue scale (EQ-5D VAS) valuation technique or the time trade-off (TTO) valuation technique. The list of currently available value sets with the number of respondents and valuation technique applied is presented in table 1. Most of the EQ-5D value sets have been obtained using a representative sample of the general population, thereby ensuring that they represent the societal perspective. For anyone working with EQ-5D data, an essential guide to the Group's available value sets can be found in: EuroQol Group Monograph series: Volume 2: EQ-5D value sets: inventory, comparative review and user guide, recently published by Springer (see section 8 for more information).

Table 1: List of available value sets (references available on the website)

Country	N	Valuation method
Belgium	722	EQ-5D VAS
Denmark	1686	EQ-5D VAS
Denmark	1332	TTO
Europe	8709	EQ-5D VAS
Finland	1634	EQ-5D VAS
France	443	VAS/TTO
Germany	339	EQ-5D VAS
Germany	339	TTO
Japan	621	TTO
Netherlands	309	TTO
New Zealand	1360	EQ-5D VAS
Slovenia	733	EQ-5D VAS
Spain	300	EQ-5D VAS
Spain	1000	TTO
Thailand	1324	TTO
UK	3395	EQ-5D VAS
UK	3395	TTO
US	4048	TTO
Zimbabwe	2440	TTO

In development:

Canada, Chile, Italy and Singapore

Documents containing the scoring algorithms, information on the valuation studies, tables of values for all 243 health states and SPSS and SAS syntax files can be ordered from the EuroQol Executive Office (userinformationservice@euroqol.org).

5. Organising EQ-5D-3L data

Data collected using EQ-5D-3L can be entered in a database according to the following schema:

Variable name	ID	COUNTRY	YEAR	MOBILITY	SELFCARE	ACTIVITY	PAIN	ANXIETY
Variable description	patient ID number			1=No Problems, 2=Some problems, 3=Extreme problems, 9=Missing value	1=No Problems, 2=Some problems, 3=Extreme problems, 9=Missing value	1=No Problems, 2=Some problems, 3=Extreme problems, 9=Missing value	1=No Problems, 2=Some problems, 3=Extreme problems, 9=Missing value	1=No Problems, 2=Some problems, 3=Extreme problems, 9=Missing value
Data row 1	1001	UK	2006	2	1	2	2	1
Data row 2	1002	UK	2006	1	1	1	1	1

Variable name	STATE	EQ_VAS	SEX	AGE	EDU	METHOD	SOC ECON
Variable description		999= Missing value	1=male, 2=female, 9=Missing value	999= Missing value	1=low, 2=medium, 3=high, 9=Missing value	0=postal, 1=interview, 2=telephone, 9=Missing value	1=employed, 2=retired, ..., 9=Missing value
Data row 1	21221	80	1	43	1	0	1
Data row 2	21111	90	2	24	2	0	4

NB: The variable names are just examples. However, the variables for the 5 dimensions of the EQ-5D descriptive system should be named 'mobility', 'self-care', 'activity', 'pain', and 'anxiety'. If they are given different names the syntax codes containing the value sets that are distributed by the EuroQol Group will not work properly.

6. Presenting EQ-5D-3L results

Data collected using EQ-5D-3L can be presented in various ways. A basic subdivision can be made according to the structure of the EQ-5D-3L:

1. Presenting results from the descriptive system as a health profile
2. Presenting results of the EQ VAS as a measure of overall self-rated health status
3. Presenting results from the EQ-5D-3L index value

The way results can be presented is determined both by the data and by what message you, as a researcher, wish to convey to your audience.

6.1. Health profiles

One way of presenting data as a health profile is by making a table with the frequency or the proportion of reported problems for each level for each dimension. These tables can be broken down to include the proportions per subgroup, such as age, before vs. after treatment, treatment vs. comparator, etc.

Sometimes it is more convenient to dichotomise the EQ-5D levels into 'no problems' (i.e. level 1) and 'problems' (i.e. levels 2 and 3), thereby changing the profile into frequencies of reported problems. This can be the case, for example, in a general population survey where the numbers of reported level 3 problems are very low. Tables 2 and 3 are examples of how to present EQ-5D data in tabulated form. The data for the tables originates from a general population survey in the UK².

Table 2: Proportion of levels 1, 2 and 3 by dimension and by age group

EQ-5D DIMENSION		AGE GROUPS							TOTAL
		18-29	30-39	40-49	50-59	60-69	70-79	80+	
MOBILITY	Level 1	95.4	92.2	89.7	78.1	70.7	60.2	43.3	81.6
	Level 2	4.6	7.6	9.9	21.9	29.3	39.8	56.7	18.3
	Level 3	0.0	0.1	0.4	0.0	0.0	0.0	0.0	0.1
SELF-CARE	Level 1	99.1	98.4	95.8	94.8	94.3	92.6	83.7	95.7
	Level 2	0.9	1.5	4.0	5.2	5.5	7.1	15.6	4.1
	Level 3	0.0	0.1	0.2	0.0	0.2	0.2	0.7	0.1
USUAL ACTIVITIES	Level 1	93.3	91.4	89.2	78.1	75.3	73.7	56.0	83.7
	Level 2	6.3	7.9	9.4	18.8	21.6	22.1	38.3	14.2
	Level 3	0.4	0.7	1.5	3.0	3.1	4.2	5.7	2.1
PAIN / DISCOMFORT	Level 1	83.9	80.7	74.1	56.3	53.8	44.0	39.7	67.0
	Level 2	15.8	17.7	22.8	38.1	40.6	48.4	49.6	29.2
	Level 3	0.3	1.6	3.1	5.6	5.6	7.6	10.6	3.8
ANXIETY / DEPRESSION	Level 1	86.5	82.6	81.3	72.8	72.0	74.7	75.2	79.1
	Level 2	12.6	16.4	16.9	24.4	25.1	22.6	24.1	19.1
	Level 3	0.9	1.0	1.8	2.8	2.9	2.7	0.7	1.8

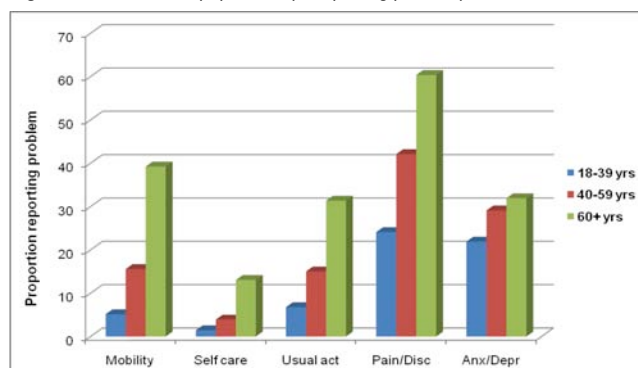
²Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey *Bmj* 1998;316 (7133): 736-41.

Table 3: Frequency of reported problems by dimension and age group

EQ-5D DIMENSION		AGE GROUPS							TOTAL
		18-29	30-39	40-49	50-59	60-69	70-79	80+	
MOBILITY	No problems	643	631	489	362	339	246	61	2770
	Problems	31	53	56	101	140	162	81	625
SELF-CARE	No problems	668	673	522	439	452	378	119	3251
	Problems	6	11	23	24	27	30	23	144
USUAL ACTIVITIES	No problems	629	625	486	362	361	301	80	2842
	Problems	45	59	59	101	118	107	62	553
PAIN / DISCOMFORT	No problems	566	552	404	261	258	179	56	2275
	Problems	108	132	141	202	221	229	86	1120
ANXIETY / DEPRESSION	No problems	583	565	443	337	345	305	107	2684
	Problems	91	119	102	126	134	103	35	711

In addition to presenting the results in tabulated form, you can also use graphical presentations. Two or 3 dimensional bar charts can be used to summarise the results in 1 graph, (see figure 2). Figure 2 shows the sum of the proportion of reported level 2 and level 3 problems for each of the 5 EQ-5D-3L dimensions for 3 distinct age groups. Older people reported more problems on all dimensions but the effect of age was strongest for mobility and weakest for anxiety/depression.

Figure 2: Profile of the population (% reporting problem)



6.2. EQ VAS

In order to present all aspects of the EQ VAS data, you should present both a measure of the central tendency and a measure of dispersion. This could be the mean values and the standard deviation or, if the data is skewed, the median values and the 25th and 75th percentiles. An example is presented in table 4. The data for the table originates from a general population survey in the UK³.

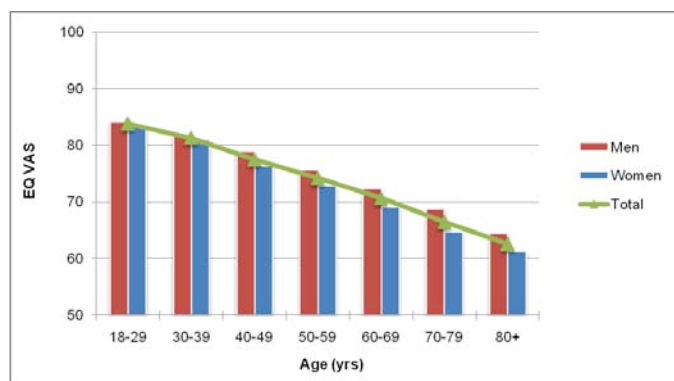
³ Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey *Bmj* 1998;316 (7133): 736-41.

Table 4: EQ VAS values by age – mean + standard deviation and median + percentiles

EQ VAS	AGE GROUPS							TOTAL
	18-29	30-39	40-49	50-59	60-69	70-79	80+	
Mean	87.0	86.2	85.1	81.3	79.8	75.3	72.5	82.8
- Std dev	13.8	14.6	15.5	46.8	17.5	18.5	18.2	23.1
Median	90	90	90	86	85	80	75	90
- 25th	80	80	80	70	70	65	60	75
- 75th	98	95	95	95	93	90	88	95

You can present a graphical representation of the data by using bar charts, line charts, or both (see figure 3). Figure 3 shows the mean EQ VAS ratings reported by men, women and both for 7 distinct age groups. The mean EQ VAS ratings are seen to decrease with increasing age. Also, men of all age groups reported higher EQ VAS ratings than women.

Figure 3: Mean population EQ VAS ratings by age group and sex



6.3. EQ-5D index

Information about the EQ-5D index can be presented in much the same way as the EQ VAS data. This means that for the index, you can present both a measure of the central tendency and a measure of dispersion. This could be the mean values and the standard deviation (or standard error). If the data is skewed, the median values and the 25th and 75th percentiles could be presented. Tables 5 and 6 and figures 4 and 5 contain 2 examples of how to present EQ-5D index results. Table 5 and figure 4 present the results from a study where the effect of a treatment on health status is investigated. Table 6 and figure 5 show results for a patient population and 3 subgroups (the tables and figures are based on hypothetical data and for illustration purposes only).

Table 5: EQ-5D-3L index values before and after treatment

EQ-Index	Before treatment	After treatment
Mean	0,59	0,76
- Std error	0,012	0,015
Median	0,60	0,70
- 25th	0,50	0,65
- 75th	0,70	0,80
N	120	110

Table 6: EQ-5D-3L index values for the total patient population and the 3 subgroups

EQ-Index	All patients	Subgroup 1	Subgroup 2	Subgroup 3
Mean	0,66	0,45	0,55	0,90
- Std error	0,010	0,013	0,015	0,010
Median	0,55	0,40	0,55	0,95
- 25th	0,50	0,30	0,50	0,80
- 75th	0,70	0,50	0,60	1,00
N	300	100	75	125

Figure 4: EQ-5D-3L index values before and after treatment: mean values and 95% confidence intervals

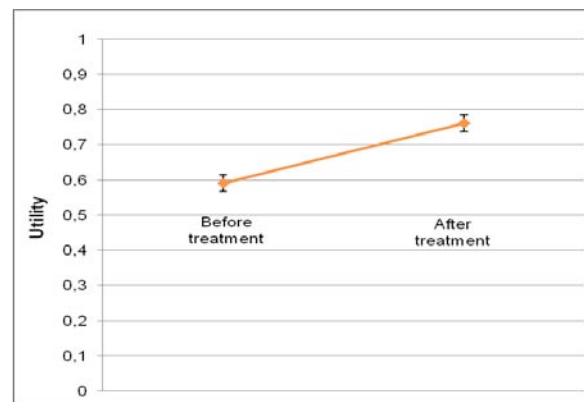
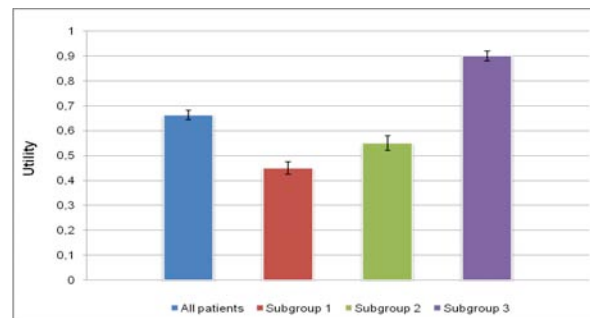


Figure 5: Mean EQ-5D-3L index values and 95% confidence intervals for the total patient population and 3 subgroups.



7. EQ-5D Products

7.1. EQ-5D-3L Translations and other formats



The EQ-5D-3L (EQ-5D 3 level) self complete paper version is currently translated in **more than 150** language versions. If you want to know whether an EQ-5D-3L language version exists for your country, please consult the website (www.euroqol.org).

Likewise, although the EQ-5D-3L was also primarily designed as a pen-and-paper self-complete instrument, it is now available in alternative formats and modes of administration, and in multiple translations e.g.

- Tablet and web-based versions
- PDA versions
- IVR
- Proxy versions
- Versions for telephone and face-to-face interviews

If you are interested in using one of these alternative formats or modes of administration, please contact the EuroQol Executive Office

7.2. Other EQ-5D Products

7.2.1. EQ-5D-5L Translations and formats



The **EQ-5D-5L** self-complete paper version is currently available in **more than 50** different language versions. If you want to know whether an EQ-5D-5L version exists for your country, please consult the website (www.euroqol.org).

Likewise, although the EQ-5D-5L was primarily designed as a pen-and-paper, self-complete instrument, it will increasingly become available in alternative formats and modes of administration. These include:

- Tablet and web-based versions
- PDA versions
- IVR
- Proxy versions
- Versions for telephone and face-to-face interviews

7.2.2. EQ-5D-Y Translations



The **EQ-5D-Y** is an EQ-5D-3L self complete youth version for children and adolescents aged 7-12 years. At present, this version is available in **9** different languages. If you want to know if there is an EQ-5D-Y version appropriate for your country, please consult the website (www.euroqol.org).

7.3. Translation process

All translation/adaptations of EQ-5D are produced using a standardized translation protocol that conforms to internationally recognized guidelines. These guidelines aim to ensure equivalence to the English 'source' version and involve a forward/backward translation process and cognitive debriefing. Only the EuroQol Executive Office can give permission for a translation to be performed and translations can only be stamped as official if they are performed in cooperation with EuroQol Group reviewers.

7.4. How to obtain EQ-5D?

All self-report and alternative modes of self-report versions in different languages must be obtained exclusively from the EuroQol Executive Office. IVR, web, tablet and PDA versions are exclusively provided via the EuroQol Group's preferred vendors. Normally only the language(s) appropriate to the country where the research request originates will be supplied. Licensing fees are determined by the EuroQol Executive Office on the basis of information provided by the user. Whether a fee is appropriate depends upon the type of study, size and/or number of patients/respondents and requested languages.

8. FAQ's

1. **For what period of time does EQ-5D-3L record health status?**

Self-reported health status captured by EQ-5D-3L relates to the respondent's situation at the time of completion. No attempt is made to summarise the recalled health status over the preceding days or weeks, although EQ-5D-3L has been tested in recall mode. An early decision taken by the EuroQol Group determined that health status measurement ought to apply to the respondent's immediate situation - hence the focus on 'your own health state today'.

2. **Can I use only the EQ-5D-3L descriptive system or only the EQ VAS?**

We cannot advise this. EQ-5D-3L is a 2-part instrument so if you only use 1 part you cannot claim to have used EQ-5D-3L in your publications.

3. **How long should the EQ VAS be?**

Officially, for paper versions, the EQ VAS scale should be 20cms. All methodological and developmental work has been carried using this length. To ensure that you print the correct length, make sure your paper size is set at A4 and the box in your printing instructions labelled 'scale to paper size' is set at 'no scaling'.

4. **Can I publish our study using EQ-5D?**

Yes, you are free to publish your results. If you are reproducing the EQ-5D in an appendix we request that you use the sample version of EQ-5D-3L and that the following text is included in the footer: © 1990 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group.

5. **What is the difference between the EQ-5D-3L descriptive system and the EQ VAS?**

The descriptive system can be represented as a health state, e.g. health state 11212 represents a patient who indicates some problems on the usual activities and anxiety/depression dimensions. These health states can be converted to a single index value using (one of) the available EQ-5D-3L value sets. These value sets have been derived using VAS or TTO valuation techniques, and reflect the opinion of the general population. The EQ VAS scores are patient-based and are therefore not representative of the general population. The EQ VAS self-rating records the respondent's own assessment of their health status. The EQ VAS scores however are anchored on 100 = best imaginable health and 0 = worst imaginable health, whereas the value sets are anchored on 11111 = 1 and dead = 0 and can therefore be used in QALY calculations.

6. What is the difference between the VAS and TTO techniques?

The difference between the value sets based on TTO and those based on VAS is that the techniques used for the elicitation of the values on which the models are based differ. In the TTO task, respondents are asked, for example, to imagine they live in a health state (e.g. 22222) for 10 years and then asked to specify the amount of time they are willing to give up to live in full health instead (i.e. 11111). For example, someone might find 8 years in 11111 equivalent to 10 years in 22222. The VAS technique on the other hand, asks people to indicate where, on a vertical thermometer-like scale ranging from best imaginable health to worst imaginable health, they think a health state should be positioned.

7. General population value sets vs patient population value sets

If you want to undertake a utility analysis you will need to use a value set. Generally speaking utility analysis requires a general population-based value set (as opposed to a patient-based set). The rationale behind this is that the values are supposed to reflect the preferences of local taxpayers and potential receivers of healthcare. Additionally, patients tend to rate their health states higher than the general population because of coping etc, often underestimating their need for healthcare. The EQ-5D-3L value sets are therefore based on the values of the general population.

8. Multinational clinical trials

Information relating to EQ-5D health states gathered in the context of multinational trials may be converted into a single summary index using one of the available EQ-5D-3L value sets. There are different options available to do this using appropriate value sets-however the choice depends on the context in which the information will be used by researchers or decision makers. In cases where data from an international trial are to be used to inform decision makers in a specific country, it seems reasonable to expect decision makers to be interested primarily in value sets that reflect the values for EQ-5D-3L health states in that specific country. So for example, if applications for reimbursement of a drug are rolled out from country to country, country-specific value sets should be applied and reported in each pharmaco-economic report. This is no different from the requirement to use country-specific costs. In the absence of a country-specific value set, the researcher should select another set of values for a population that most closely approximates that country. Sometimes however, information about utilities is required to inform researchers or decision makers in an international context. In these instances, 1 value set applied over all EQ-5D health states data is probably more appropriate. The decision about which value set to use will also depend on whether the relevant decision making body in each country specifies any requirements or preferences in regard to the methodology used in different contexts (e.g. TTO, standard gamble (SG), VAS or discrete choice modelling (DCM)). These guidelines are the topic of an

international ongoing debate but the EuroQol Group website is planning to provide a summary of health care decision-making bodies internationally, and their stated requirements regarding the valuation of health states. Detailed information regarding the valuation protocols, guidelines on which value set to use and tables of all available value sets has recently been published by Springer in: EuroQol Group Monograph series: Volume 2: EQ-5D value sets: inventory, comparative review and user guide' (see section 8 for more information). Chapter 4 by Nancy Devlin and David Parkin will be of special interest to researchers pondering the issue of which value set to use.

9. Additional information

9.1. Key EuroQol Group references

1. The EuroQol Group (1990). EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy* 16(3):199-208.
2. Brooks R (1996). EuroQol: the current state of play. *Health Policy* 37(1):53-72.
3. Dolan P (1997). Modeling valuations for EuroQol health states. *Med Care* 35(11):1095-108.
4. Roset M, Badia X, Mayo NE (1999). Sample size calculations in studies using the EuroQol 5D. *Qual Life Res* 8(6):539-49.
5. Greiner W, Weijnen T, Nieuwenhuizen M, et al. (2003). A single European currency for EQ-5D health states. Results from a six country study. *Eur J Health Econ*; 4(3):222-231.
6. Shaw JW, Johnson JA, Coons SJ (2005). US valuation of the EQ-5D health states: development and testing of the D1 valuation model. *Med Care*; 43(3): 203-220.

9.2. Referring to the EQ-5D instrument in publications

When publishing results obtained with the EQ-5D, the following references can be used:

1. The EuroQol Group (1990). EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy* 16(3):199-208.
2. Brooks R (1996). EuroQol: the current state of play. *Health Policy* 37(1):53-72.

If you used a value set in your study you can also include a reference to the publication regarding that value set. The appropriate references for the value sets can be found in the EQ-5D Value Sets Monograph and in the value set summary documents that can be ordered from the EuroQol Executive Office.

9.3. EQ-5D Books

The Measurement and valuation of health status using EQ-5D: A European perspective. Eds Brooks R, Rabin R, de Charro F. Kluwer Academic Publishers, 2005

This book reports on the results of the European Union-funded EQ-net project which furthered the development of EQ-5D in the key areas of valuation, application and translation. The book can be obtained from Springer at www.springeronline.com at a cost of € 107.95.

EQ-5D concepts and methods: a developmental history. Eds Kind P, Brooks R, Rabin R. Springer, 2005.

This book is a collection of papers representing the collective intellectual enterprise of the EuroQol Group and can be obtained from Springer at www.springeronline.com at a cost of € 85.00.

EQ-5D value sets: Inventory, comparative review and user guide. Eds. Szende A, Oppe M, Devlin N. EuroQol Group Monographs Volume 2. Springer, 2006.

This book provides an essential guide to the use of the EuroQol Group's value sets for anyone working with EQ-5D data and can be obtained from Springer at www.springeronline.com at a cost of € 49.95.



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Appendix 6

Medical Outcomes Study Sleep Scale

MOS Sleep Scale:
A Manual for Use and Scoring, Version 1.0
Karen L. Spritzer and Ron D. Hays
November 2003

The following citation is suggested when referencing this manual:

Spritzer, K. L. & Hays, R. D. (2003, November). MOS Sleep Scale: A Manual for Use and Scoring, Version 1.0. Los Angeles, CA.

SCORING RULES

Scoring the MOS Sleep Survey is a two-step process:

- First, original numeric values from the survey are recoded following the scoring rules outlined in Table 1. All items are scored so that a high score reflects more of the attribute implied by the scale name. Each item is then converted to a 0 to 100 possible range so that the lowest and highest possible scores are set at 0 and 100, respectively. In this format, scores represent the achieved percentage of the total possible score. For example, a score of 50 represents 50% of the highest possible score.
- Second, items within each scale are averaged together to create the 7 scale scores. Table 2a indicates which items contribute to each scale. Scales with at least one item answered can be used to generate a scale score. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Scores represent the average for all items in the scale that the respondent answered.

Two additional measures are based on the average number of hours sleep each night during the past 4 weeks and are described in table 2b.

Table 1. Scoring Key: Recoding of Items

ITEM NUMBERS	Original response category	To recoded value of
(not reversed) 4 ^(†) , 12 ^(†)	<1 ----> 1 ----> 2 ----> 3 ----> 4 ----> 5 ----> 6 ----> >6 ---->	. 0 20 40 60 80 100 . bigger ↑ problem
(not reversed) 1	<1 ----> 1 ----> 2 ----> 3 ----> 4 ----> 5 ----> >5 ---->	. 0 25 50 75 100 . bigger ↓ problem
(reversed) 3, 5, 6, 7, 8, 9, 10, 11	<1 ----> 1 ----> 2 ----> 3 ----> 4 ----> 5 ----> 6 ----> >6 ---->	. 100 80 60 40 20 0 . bigger ↑ problem
(reversed) 4 ^(†) , 12 ^(†)	<1 ----> 1 ----> 2 ----> 3 ----> 4 ----> 5 ----> 6 ----> >6 ---->	. 100 80 60 40 20 0 . bigger ↓ problem

^(†)Note that items 4 and 12 are scored differently depending upon which scale they are used in. When used in the sleep adequacy scale, a higher score reflects less of a problem. When used in the sleep problems index, a higher score reflects more of a problem.

Table 2a: Averaging Items to Generate Sleep Scales

Scale		Number of Items	After Recoding Per Table 1, Average the Following Items
SLPD4	sleep disturbance	4	1, 3(R), 7(R), 8(R)
SLPSNR1	snoring	1	10(R)
SLPSOB1	sleep short of breath or headache	1	5(R)
SLPA2	sleep adequacy	2	4(R), 12(R)
SLPS3	sleep somnolence	3	6(R), 9(R), 11(R)
SLP6	sleep problems index I	6	4, 5(R), 7(R), 8(R), 9(R), 12
SLP9	sleep problems index II	9	1, 3(R), 4, 5(R), 6(R), 7(R), 8(R), 9(R), 12

(R) refers to a reversed item.

Table 2b: 3 Additional measures based on average number of hours sleep each night during the past 4 weeks

SLPQRAW Sleep Quantity (raw scores): use item 2 as is.

SLPQRAW=MOS2;

SLPOP1 Optimal Sleep (dichotomy):

MOS2	SLPOP1
<1	. (out-of-range)
1-6	0
7-8	1
9-23	0
24+	. (out-of-range)

Table 3: Central Tendency, variability (including floor and ceiling effects), and reliability of sleep scales[‡]

Measure		Mean	Standard Deviation	% Floor	% Ceiling	Internal Consistency Reliability
SLPD4	sleep disturbance	29.20	23.37	8.56	0.56	0.84
SLPSNR1	snoring	30.89	30.25	32.52	6.00	NA
SLPSOB1	sleep short of breath or headache	13.29	21.82	64.23	0.87	NA
SLPA2	sleep adequacy	60.67	25.38	3.00	5.83	0.75
SLPS3	sleep somnolence	26.41	19.82	9.42	0.32	0.75
SLPQRAW	sleep quantity (raw)	6.93	1.40	0.06	0.03	NA
SLPOP1	optimal sleep (dichot)	0.54	0.50	45.58	54.42	NA
SLP6	sleep problems index I	28.31	18.09	2.32	0.03	0.78
SLP9	sleep problems index II	29.15	18.04	1.17	0.06	0.85

[‡] Data is from the Medical Outcomes Study (MOS), n=3445.

NA - Not applicable for a single-item measure.

APPENDIX

- MOS Sleep Survey (see separate attachment).
- Crosswalk of item numbering between MOS Sleep survey and original Hays/Stewart paper:

MOS Sleep Survey	Hays/Stewart Paper
1	2
2	7
3	3
4	8
5	6
6	10
7	1
8	4
9	11
10	5
11	12
12	9

- Reference for Hays/Stewart paper:

Hays, R. D. & Stewart, A. L. (1992). Sleep measures. In A. L. Stewart & J. E. Ware (eds.), Measuring functioning and well-being: The Medical Outcomes Study approach (pp 235-259), Durham, NC: Duke University Press.

- SAS 8.02® Code for creating Sleep Scales:

```

*-----
* sleep12-1.sas:
*
* SAS(tm) program to create scale scores and produce
* descriptive statistics for MOS Sleep Scale 1.0
* measures.
*
* Written by Karen Spritzer, 11/25/2003.
*-----
*
* This program assumes that your SLEEP items are in a
* dataset named "temp" and have variable names that
* correspond to the survey: MOS1-MOS12
* and rescores them according to the rules found in the
* MOS Sleep Scale scoring manual:
* Spritzer, K. L. & Hays, R. D. (2003, November). MOS
* Sleep Scale: A Manual for Use and Scoring, Version 1.0.
* Los Angeles, CA.
*
* See http://gim.med.ucla.edu/FacultyPages/Hays/SLEEP.htm
* for scoring manual.
*-----

*****
data temp; set temp;

* recode out of range values for individual sleep items to missing;

IF MOS1 NOT IN(1,2,3,4,5) THEN MOS1=.;

ARRAY PT6 MOS3-MOS12;
DO OVER PT6;
IF PT6 NOT IN (1,2,3,4,5,6) THEN PT6=.;
END;

IF MOS2 < 1 OR MOS2 > 23 THEN MOS2=.;

/* COMPUTING NEW SLEEP SCALES */

* REVERSE ITEMS WHEN NECESSARY AND PUT ON 0-100 SCALE;

array orig1 MOS3 MOS4 MOS5 MOS6 MOS7 MOS8 MOS9 MOS10 MOS11 MOS12 ;
array rev1 rMOS3 rMOS4 rMOS5 rMOS6 rMOS7 rMOS8 rMOS9 rMOS10 rMOS11 rMOS12;
do over orig1;
rev1=(7-orig1-1)*20;
end;

MOS1 =(MOS1-1)*25;
MOS4 =(MOS4-1)*20;
MOS12=(MOS12-1)*20;

```

```

label
rMOS3      = "rev Q610A Feel that your sleep was not quiet"
rMOS4      = "rev Q610B Get enough sleep to feel rested up"
rMOS5      = "rev Q610C Awaken short of breath or with a h"
rMOS6      = "rev Q610D Feel drowsy or sleepy during the d"
rMOS7      = "rev Q610E Have trouble falling asleep - How "
rMOS8      = "rev Q610F Awaken during your sleep time and "
rMOS9      = "rev Q610G Have trouble staying awake during "
rMOS10     = "rev Q610H Snore during your sleep - How ofte"
rMOS11     = "rev Q610I Take naps of 5 minutes or longer d"
rMOS12     = "rev Q610J Get the amount of sleep you needed";

```

```

* CREATE SCALES by averaging items;

```

```

* Sleep Disturbance;

```

```

SLPD4 = mean(of MOS1, rMOS3, rMOS7, rMOS8);
label SLPD4 = "Sleep Disturbance Scale";

```

```

* Snoring;

```

```

SLPSNR1 = rMOS10;
label SLPSNR1 = "Snoring Scale";

```

```

* Short of Breath;

```

```

SLPSOB1 = rMOS5;
label SLPSOB1 = "Short of Breath Scale";

```

```

* Sleep Adequacy;

```

```

SLPA2 = mean(of rMOS4, rMOS12);
label SLPA2 = "Sleep Adequacy";

```

```

* Somnolence;

```

```

SLPS3 = mean(of rMOS6, rMOS9, rMOS11);
label SLPS3 = "Somnolence Scale";

```

```

* Sleep Problems Index I;

```

```

SLP6 = mean(of MOS4, rMOS5, rMOS7, rMOS8, rMOS9, MOS12);
label SLP6 = "Sleep Problems Index I";

```

```

* Sleep Problems Index II;

```

```

SLP9 = mean(of MOS1, rMOS3, MOS4, rMOS5, rMOS6, rMOS7, rMOS8, rMOS9, MOS12);
label SLP9 = "Sleep Problems Index II";

```

```

* Sleep Quantity (raw score)";
SLPQRAW=MOS2;
label SLPQRAW = "Sleep Quantity (raw score)";

* Optimal Sleep;
if MOS2>=0 then do;
if (MOS2 = 7 or MOS2 = 8) then SLP0P1=1; else
if (MOS2 < 7 or MOS2 > 8) then SLP0P1=0;
end;
label SLP0P1 = "Optimal Sleep Scale";

run;
*****;

TITLE1 "Descriptive statistics on MOS SLEEP scales"; run;

proc means maxdec=2 data=temp;
var SLPD4 SLPSNR1 SLPS0B1 SLPA2 SLPS3 SLP6 SLP9 slpqraw slpop1;
run;

TITLE1 "Alpha reliability for MOS SLEEP scales"; RUN;

TITLE2 "SLPD4 Sleep Disturbance";
proc corr alpha nomiss;
var MOS1 rMOS3 rMOS7 rMOS8;
run;

TITLE2 "SLPA2 Sleep Adequacy";
proc corr alpha nomiss;
var rMOS4 rMOS12;
run;

TITLE2 "SLPS3 Somnolence";
proc corr alpha nomiss;
var rMOS6 rMOS9 rMOS11;
run;

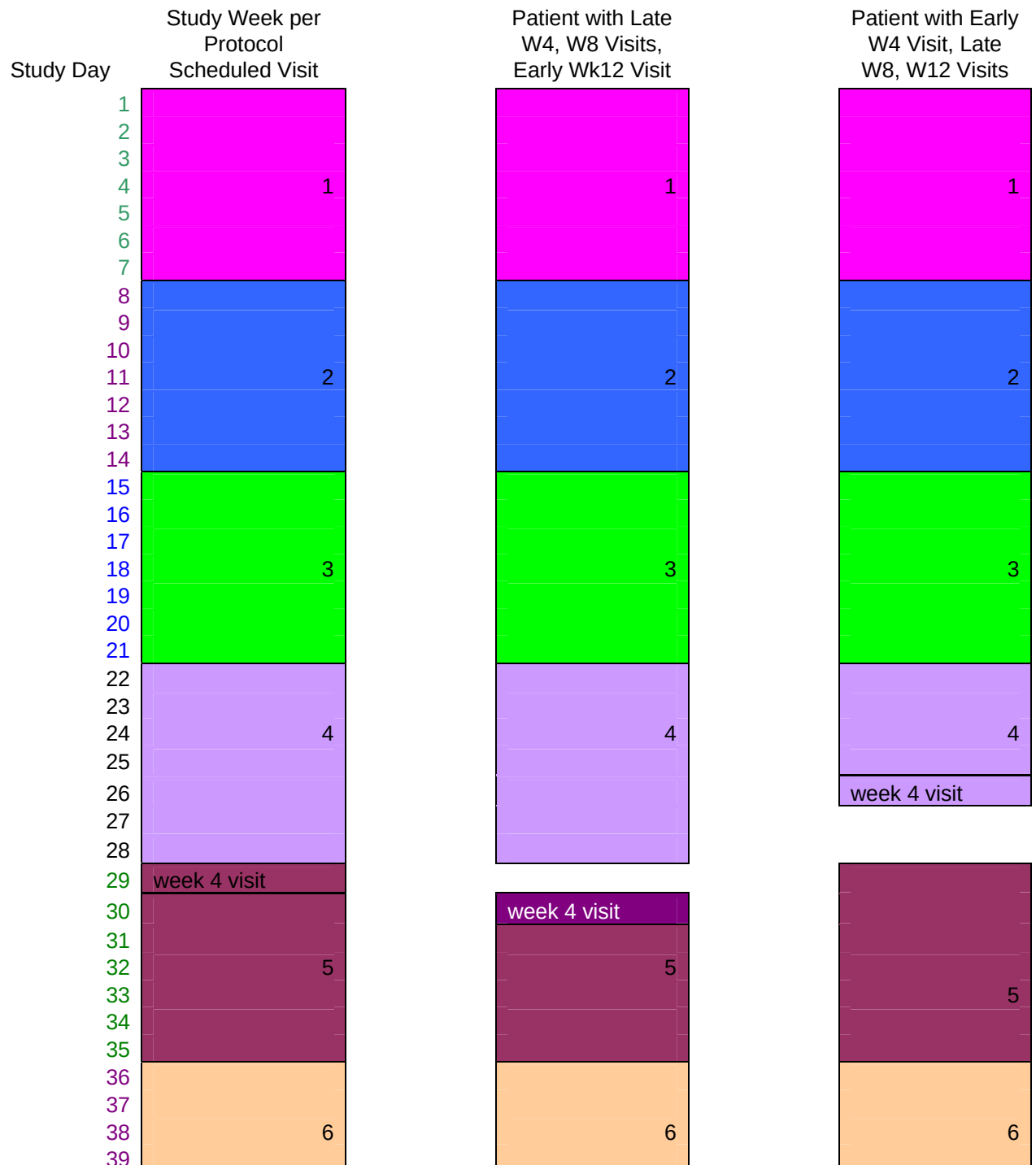
TITLE2 "SLP6 Sleep Problems Index I";
proc corr alpha nomiss;
var MOS4 rMOS5 rMOS7 rMOS8 rMOS9 MOS12;
run;

TITLE2 "SLP9 Sleep Problems Index II";
proc corr alpha nomiss;
var MOS1 rMOS3 MOS4 rMOS5 rMOS6 rMOS7 rMOS8 rMOS9 MOS12;
run;

```

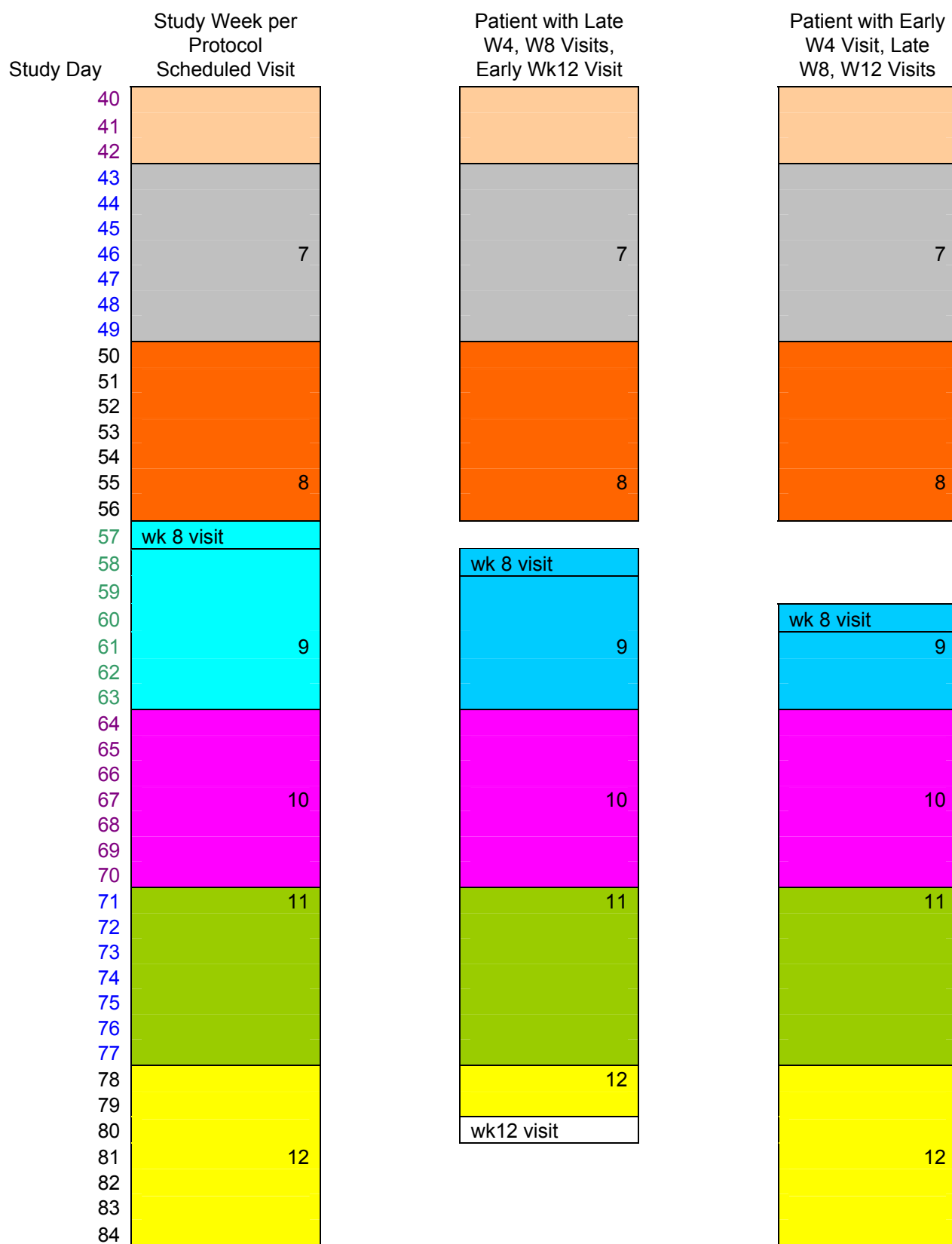
Appendix 7

Patient Visits versus Weekly Score Definitions



Appendix 7

Patient Visits versus Weekly Score Definitions (cont'd)



Appendix 7
Patient Visits versus Weekly Score Definitions (cont'd)

Study Day	Study Week per Protocol Scheduled Visit	Patient with Late W4, W8 Visits, Early Wk12 Visit	Patient with Early W4 Visit, Late W8, W12 Visits
85	wk12 visit		
86			
87			
88	13	13	
89			
90			wk12 visit
91			13
92			
93			
94	14	14	14
95			
96			
97			
98			