

**Official Title:** XTEND-CIU (Xolair Treatment Efficacy of Longer Duration in Chronic Idiopathic Urticaria): A Phase IV, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Omalizumab through 48 Weeks in Patients With Chronic Idiopathic Urticaria

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## DATA ANALYSIS PLAN

TITLE: XTEND-CIU (XOLAIR TREATMENT EFFICACY OF LONGER DURATION IN CHRONIC IDIOPATHIC URTICARIA): A PHASE IV, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OMALIZUMAB THROUGH 48 WEEKS IN PATIENTS WITH CHRONIC IDIOPATHIC URTICARIA

PROTOCOL NUMBER: ML29510

STUDY DRUG: Omalizumab (RO5489789)

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## 1. BACKGROUND

The three pivotal studies (Q4881g, Q4882g, and Q4883g) examined the safety and efficacy of omalizumab administered over 12 to 24 weeks. Currently, there is limited clinical trial experience on the long-term treatment beyond 24 weeks (or approximately 6 months) in patients with CIU. The U.S. Package Insert (USPI) for omalizumab notes that the appropriate duration of therapy for CIU has not been evaluated and advises health practitioners to periodically reassess the need for continued therapy.

This study will assess the safety and potential benefits of continuing omalizumab beyond 24 weeks of dosing (through 48 weeks of dosing, or approximately 1 year). Through the primary outcome, as well as the secondary and exploratory outcomes, this study should assist healthcare providers in weighing the relative benefits of omalizumab continuation beyond 24 weeks by elucidating the extent to which omalizumab might be expected to maintain control of CIU and related symptoms.

In Studies Q4881g (ASTERIA I) and Q4883g (GLACIAL), all patients discontinued omalizumab after 24 weeks and, in Study Q4882g (ASTERIA II), all patients discontinued omalizumab after 12 weeks. Moreover, patients were unblinded at discontinuation (i.e., patients knew they were discontinuing omalizumab). In Studies Q4881g and Q4883g, the mean weekly itch score and UAS7 after omalizumab discontinuation increased to reach values similar to that of the placebo arms ([Kaplan et al. 2013](#); [Maurer et al. 2013](#); [Saini et al. 2014](#)). This study will evaluate whether continuation of omalizumab beyond 24 weeks might be expected to maintain control of CIU and related symptoms in the context of being blinded to omalizumab continuation versus discontinuation.

For full details on the study background, please refer to the study protocol.

This Data Analysis Plan (DAP) describes the statistical methods to be used for study ML29510 and focuses on the analysis of both the open-label and double-blind periods. Tables and listings for these analyses have been highlighted in Module 2 (mockups document). This final version of the DAP has been developed using version 2 of the study protocol dated 09 May 2016.

## **2. STUDY DESIGN**

### **2.1 PROTOCOL SYNOPSIS**

Appendices A, B and C describe the study, including assessments and objectives.

### **2.2 OUTCOME MEASURES**

#### **2.2.1 Primary Efficacy Outcome Measures**

The primary efficacy outcome measure is the percentage of patients who experience clinical worsening in CIU as assessed by UAS7 (see APPENDIX E). The specific threshold for clinical worsening in CIU symptoms will be  $\text{UAS7} \geq 12$ , maintained for at least 2 consecutive weeks, from randomization (Week 24) to Week 48.

#### **2.2.2 Secondary Efficacy Outcome Measures**

The secondary efficacy outcome measures for this study are as follows:

- Time to clinical worsening in CIU, defined based on the same criteria as the primary endpoint (maintaining  $\text{UAS7} \geq 12$  for at least 2 consecutive weeks), from randomization (Week 24) to Week 48
- Percentage of patients who experience clinical worsening in CIU assessed by UAS7, where the threshold for clinical worsening is  $\text{UAS7} > 6$  for at least 2 consecutive weeks, from randomization (Week 24) to Week 48
- UAS7 (24- vs. 48-week value) among patients who have responded to omalizumab treatment at 24 weeks and completed a further 24 weeks of omalizumab (48 weeks total), which will be assessed by the change from randomization (Week 24) to Week 48 in UAS7
- Retreatment efficacy, defined by change in UAS7 from time of retreatment to 12 weeks after retreatment, among patients randomized to the placebo arm who are retreated with open-label omalizumab after randomization and receive at least 12 weeks of omalizumab therapy as retreatment

#### **2.2.3 Other Efficacy Outcome Measures**

The exploratory outcome measures for this study are as follows:

- The proportion of patients experiencing clinical worsening in CIU (defined as maintaining  $\text{UAS7} \geq 12$  for at least 2 consecutive weeks) between Weeks 48 and 60 among patients randomized to continue omalizumab (i.e., during the 12 weeks after discontinuing a 48-week course of omalizumab)

- The proportion of patients experiencing clinical worsening in CIU (defined as maintaining  $\text{UAS7} \geq 12$  for at least 2 consecutive weeks) between Weeks 24 and 36 among patients randomized to placebo
- Change from randomization (Week 24) to Week 48 in weekly itch score
- Change from randomization (Week 24) to Week 48 in UAS7
- The proportion of patients experiencing an MID worsening defined by an increase of  $\geq 3$  points between randomization (Week 24) and Week 48 in health-related quality-of-life as measured by the DLQI total score
- Proportion of angioedema days, evaluated through patient self-reports via eDiary, from Week 24 to Week 48
- UCT response and correlation with UAS7 during the open-label phase
  - Change in UCT from baseline to Week 24
  - Correlation between UCT and UAS7 from baseline to Week 24
- U-AIM response and correlation with UAS7 during the open-label phase
  - Change in U-AIM from baseline to Week 24
  - Correlation between U-AIM and UAS7 from baseline to Week 24

## 2.2.4 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence and severity of adverse events and serious adverse events
- Changes in vital signs
- Clinical laboratory evaluations

## 2.3. DETERMINATION OF SAMPLE SIZE

Assuming a 60% rate of clinical worsening in CIU assessed by UAS7 in the placebo group (including 10% dropout imputed as worsening CIU) and a rate of 30% in the omalizumab continuation group (including 10% dropout imputed as clinical worsening CIU) in the period up to 24 weeks post-randomization, a total of 117 patients will need to be randomized at a 3:2 ratio (3 omalizumab continuation group patients for every 2 placebo patients) to ensure 90% power to detect a difference in clinical worsening CIU rates as a primary analysis comparison at the 0.05 alpha level (2-sided test). In addition, as it is estimated that 15% of patients will either drop out during the open-label treatment period or not meet the adherence criteria, and that 66.5% of those who do not drop out or fail adherence criteria will be responders, this study will need to enroll at least 207 ( $117 / [0.665 \cdot 0.85]$ ) patients to

ensure adequate randomization numbers for the primary analysis. This sample size will also ensure at least 80% power for each of the secondary analyses.

## **2.4 ANALYSIS TIMING**

An initial analysis summarized data collected during the open-label period and occurred after all patients had completed the phase – either by proceeding to the randomization phase or completing the open-label phase.

Regular safety reviews will be conducted by Data Management and the sponsor, as described in Section 3.2.1.

## **3. STUDY CONDUCT**

### **3.1 RANDOMIZATION ISSUES**

At the Week 24 visit, patients who completed the 24-week open-label treatment period and have met the criteria for response ( $UAS7 \leq 6$  in the two consecutive weeks immediately prior to randomization) and also met the omalizumab compliance criteria (5 out of 6 planned doses, including a dosage at Week 20) will be randomized to 300 mg omalizumab or placebo at an approximately 3:2 ratio using an interactive voice and web response system (IxRS). Patients, all study personnel, the designated evaluating physician(s), and the Sponsor and its agents (with the exception of the IxRS service provider, the remote unblinded monitoring staff, the unblinding statistician, and the unblinded pharmacists at the sites) will be blinded to treatment assignment. Only the IxRS provider and the Sponsor's unblinding statistician will have access to the unblinding code during the study.

### **3.2 DATA MONITORING**

#### **3.2.1 SAFETY REVIEW TIMING**

As described in the Data Management Plan (DMP), ongoing safety reviews are performed by Data Management and the sponsor throughout the study.

## **4. STATISTICAL METHODS**

### **4.1 ANALYSIS POPULATIONS**

#### **4.1.3 Enrolled Population**

Enrolled subjects consist of those who enroll in the open-label portion of trial, regardless of whether they progress to the randomized portion.



## **4.1.2 Randomized Population**

Randomized subjects are those who proceed to the randomized portion of the trial. A subject is considered to be randomized if response to the question, “Was the subject randomized?” is “yes” and a date of randomization is present.

For a preliminary analysis of the open-label portion, patients will be summarized as ‘randomized’ or ‘non-randomized’. Non-randomized patients will include (a) those who completed the open-label phase and responded “no” to “Was the subject randomized?” or (b) those who did not complete the phase and were early discontinuations.

### **4.1.1 Modified Intent-to-Treat Population**

Efficacy analyses will be based on the modified intent-to-treat (mITT) principle. All patients meeting criteria for randomization, who are also randomized and receive at least one dosage of blinded study drug, as well as one post-baseline efficacy assessment, will be included in analyses. Analysis groups will be defined according to the patients’ randomly assigned treatments regardless of the actual treatment received.

For selected tables, such as efficacy, mITT tables will also contain the breakdown of randomized patients who have or have not been transitioned during the open-label period. These categories will be presented in addition to the “All Omalizumab” and “All Placebo” groups.

### **4.1.5 Per-protocol population**

A sensitivity analysis will be conducted on Per-protocol patients, defined as those who completed the double-blind period of the trial (up to week 48, inclusively) without major protocol deviations. These were defined and signed-off prior to database lock and unblinding. Protocol deviations will include (but are not limited to) patients enrolled while in violation of inclusion or exclusion criteria or study drug violations.

A review of the protocol deviations by the sponsor Medical Director and Biostatistician prior to database lock and study unblinding revealed that only 4 patients (from mITT) would be excluded from PP; most deviations were deemed to be unimportant. The steps describing how these deviations were selected are summarized below.

- 1. Subject must have been randomized

- 2. The Protocol Deviation (PD) must have occurred within 1 month before randomization or after (after 30-days before randomization) for all PDs
- 3. The PD must have occurred before reaching the Primary Endpoint. The Primary Endpoint date for a subject was defined as the earliest date of any one of three events: (1) Study Completion, (2) Transition to Open-Label, or (3) Subject Withdrawal.
- 4. The PD must have been previously Deemed Important.

As the number of mITT and PP patients are similar, only the Primary efficacy table will be reproduced for the PP population.

#### **4.1.4 Safety Evaluable Population**

Safety analyses will be performed for all patients treated with study drug, defined as omalizumab in the open-label treatment period (baseline to week 24).

Any patient receiving at least one dose of study medication will be included in safety analyses.

For safety data collected prior to randomization, these will be presented by randomization status. After randomization, his or her data will be presented by treatment group (omalizumab/placebo). Randomized patients are those who began the double-blind period and their safety data will also be presented and indicated accordingly.

## **4.2 ANALYSIS OF STUDY CONDUCT**

The disposition of patients for each study period will be summarized by treatment group with respect to the number of patients randomized, treated (with open-label omalizumab or treatment from blinded portion), and completing each study 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. 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.

The open-label period is from baseline (of omalizumab first dose) until immediately prior to randomization visit at week 24—irrespective of whether or not the patient was randomized. At week 24 and onward to week 48, this constitutes the double-blind period which patients

may either complete or discontinue and transition out. The final phase is the follow-up phase and these visits are denoted within the visit dataset with the visit name of Follow-up, up to week 60 or early termination (ET).

Prior to database lock, the list of protocol deviations was provided and reviewed by the sponsor Biostatistician and Medical Director. While there were many deviations (>900), few were considered to be important: many were out-of-window and administrative deviations, for example, and of those, a minority occurred in the randomization period. There were no major issues regarding informed consent violations or study drug or randomization irregularities. Study execution was found to be satisfactory.

### **4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY**

Treatment groups entering the double-blind randomization period of the study will be assessed with respect to demographic (e.g., age, sex, race/ethnicity) and baseline characteristics (e.g., body weight, body mass index, total IgE levels, UAS7, medical history) using descriptive statistics. Data for randomized patients will also be presented against non-randomized patients on baseline characteristics.

Medical / surgical history will be defined as conditions occurring prior to first dose date of omalizumab treatment (during open-label period). These will be coded using MedDRA version 20.0. These will be displayed by treatment group for the double-blind period, as well as by randomization status for the open-label period.

### **4.4 EFFICACY ANALYSES**

All efficacy analyses in the the double-blind phase of the study will based on the mITT population with data from all sites pooled. For missing data related to continuous-outcome analyses, Last Observation Carried Forward (LOCF) will be used and the last observation prior or on the date of transition to open-label omalizumab will be carried forward for analyses during the double-blind phase of the study. Further details are provided below.

Analyses comparing rates of clinical worsening CIU after randomization, including the primary analysis, will include the counts and proportions of the response among all patients as well as in the treatment groups being compared. The 95% confidence intervals will be presented for each within-group proportion and for the difference in proportions between treatment groups if applicable; or using the t-distribution for CIs around the mean. The 2-sided chi-square p-value will be presented to compare the treatment group proportions.

Analyses comparing changes in UAS7 or any other continuous outcome measures will include the means, standard deviations, and 95% confidence intervals for all patients, for each treatment group, and for the difference between groups accompanied by p-values whenever applicable.

For all efficacy analyses, statistical significance will be declared if the p-value for the comparison is less than 0.05. For continuous-outcome analyses, testing will be carried out comparing change from week 24 to week 48; interim visits will be presented, as well as change from week 24 with confidence intervals as appropriate. LOCF will be used for any endpoints missing after week 24 with the last observation before or on the date of transition to open-label omalizumab carried forward to week 48 (only applicable to analyses during double-blind period). Summary of interim visits will also use LOCF with similar pre-transitional observation-carried-forward methods applied.

For the final analysis, results during the double-blind period will be the focus. Summary statistics will focus on change from week 24 (randomization visit) to week 48 (end of double-blind period) or last observation prior to transition.

During the open-label period, “change from baseline” will refer to the baseline visit (Day 1). If the data were collected at baseline and screening visits, the baseline visit will be used. If data are only collected at screening, these will be used for presentation (e.g, demographics). For the final analysis, results will include the “follow-up non-responder” visit for patients who were not randomized; change from baseline will be presented for these patients as well. Similar definitions will be used for the double-blind period, where baseline refers to the randomization visit at week 24.

Summary of the follow-up period will focus on change from week 48 (or end of double-blind period) to week 60 (end of study). All results presented will be descriptive and will employ LOCF whenever necessary to account for missing data related to continuous outcomes. Early termination visits will be displayed with the final observation visit (Week 60) as “Week 60/ET” for summary outputs.

#### **4.4.1 Primary Efficacy Endpoint**

The primary efficacy endpoint examines the worsening of CIU over a sustained period of two weeks during the double-blind period. This is calculated as the percentage of patients who experience a clinical worsening of CIU as defined by UAS7 score  $\geq 12$  for at least 2

consecutive weeks post-randomization between Weeks 24 and 48. The analysis of the primary endpoint will consist of comparisons made using a simple chi-square test which will include the p-value for the comparison between treatment groups as well as the 95% confidence interval for the difference. Subjects who discontinue prematurely and do not have UAS7 scores for 2 consecutive weeks before discontinuing within the randomized period will be considered as having experienced a clinical worsening.

#### **4.4.2 Secondary Efficacy Endpoints**

The analyses for the secondary efficacy endpoints for this study are as follows:

- Time to clinical worsening in CIU, defined based on the same criteria as the primary endpoint (UAS7  $\geq 12$  for at least 2 consecutive weeks), from randomization (Week 24) to Week 48 will consist of treatment comparisons using the log-rank p-value and 95% confidence interval for the difference in the survival estimates from a corresponding Kaplan-Meier survival analysis. Patients who discontinue or transition to open-label omalizumab prior to providing scores for 2 consecutive weeks will be censored at the date of discontinuation or transition, respectively.
- Percentage of patients who experience a clinical worsening of CIU as defined by UAS7 score  $> 6$  for at least 2 consecutive weeks post-randomization between Weeks 24 and 48. The analysis of this secondary endpoint will consist of comparisons made using a Chi-square test which will include the p-value for the comparison between treatment groups during the randomized period as well as the 95% confidence interval for the difference.
- UAS7 (24- vs. 48-week value) among patients who have responded to omalizumab treatment at 24 weeks and completed a further 24 weeks of omalizumab (48 weeks total) will be assessed by the change from randomization (Week 24) to Week 48 in UAS7 among patients randomly assigned to continue omalizumab and analyzed in the context of a one-sided hypothesis test at significance level 0.05. The null hypothesis for this test will be that the mean of the Week 48 – Week 24 UAS7 score  $\geq 5$  and the alternative hypothesis will be that the mean of the Week 48 – Week 24 UAS7 score  $< 5$ . The p-value from this test will be used to determine the value of continued treatment in this study.
- Retreatment efficacy, defined by change in UAS7 from time of retreatment to 12 weeks after retreatment, among patients randomized to the placebo arm who are retreated with open-label omalizumab after randomization and receive at least 12 weeks of omalizumab therapy as retreatment, will be analyzed in the context of a 2-sided, one-sample t-test at the 0.05 significance level. The null hypothesis for this test will be that the mean of the change in UAS7 from the time of retreatment to 12 weeks after retreatment is zero with the alternative hypothesis being that this

change is non-zero. The p-value from this test will be used to evaluate the value of retreating after experiencing clinical worsening among these patients.

#### **4.4.3 Other Efficacy Endpoints**

Prior to database lock and the sign-off of this DAP, it was deemed necessary to override the pre-specification of a number of the non-diary-based exploratory-outcome analyses that were originally planned and pre-specified in the protocol for the double-blind phase (and follow-up phase) due to lack of prior data and clinical impact of their results. For the purposes of pre-specification, the only non-diary PRO that will be analyzed during the double-blind phase and included in this DAP will be the DLQI. Further, no non-diary PROs will be analyzed during the follow-up phase as part of the pre-specified analyses. With respect to the double-blind phase, all other non-diary-based PROs will be left as post-hoc analyses to be handled as part of future exploratory data generation after the study has concluded. Analyses of the PROs in the follow-up phase will also be handled as part of the post-hoc exploratory data analysis program. It was further deemed clinically necessary to modify the analysis of the DLQI endpoint for analysis during the double-blind phase in order to mimic the method used for UAS7 worsening as stated in the primary analysis. More specifically, for this DAP and only for the double-blind phase of the study, the DLQI will be pre-specified as an analysis of the proportion of patients worsening by  $\geq 3$  points (a worsening by at least an MID amount) and will result in a comparison between the 2 treatment arms of omalizumab-continuation vs placebo as assessed by a chi-square test p-value. For further clarity, this “worsening by the MID” proportional analysis for DLQI will be achieved if a patient experiences an increase in their DLQI score from the beginning to the end of the double-blind phase (ie if their change from Week 24 to the end of the phase is equal to or exceeds 3 points). Similar to the primary analysis, any discontinuation or transition to open-label omalizumab prior to this increase will constitute a worsening for this exploratory-outcome analysis.

#### **4.4.4 Sensitivity Analyses**

Sensitivity analyses will be performed to account for different sources of uncertainty and possible bias. A Per-protocol population will be used for this sensitivity analysis. This will be performed for the primary analysis only.

#### **4.4.5 Subgroup Analyses**

No subgroup analyses are planned.

## **4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES**

Protocol Amendment 2 stipulated that PD and PK parameters would not be collected for all patients. No tabulations will be produced; data received will be displayed in listing format.

## **4.6 SAFETY ANALYSES**

Safety analyses will be performed for all patients treated with study drug, starting at the open-label period. Safety will be assessed by adverse events, vital signs, and clinical laboratory evaluations. Safety analyses will be summarized for all study phases as well by open-label, randomization and follow-up periods.

For the final analyses, AEs will be listed for all periods as well as separately for open-label, double-blind and follow-up periods. To ascertain which period the AE occurred the start date must fall on or after the beginning of the period and prior to the first visit of the subsequent period (if applicable).

### **4.6.1 Concomitant Medications**

Medications will be coded using WHODrug DDE + HD version 1Q2017 (March 2017), and summarized by ATC4 class as well as medication name.

Medications are collected from 7 days prior to screening up to the study completion/discontinuation visit.

For the open-label period, prior medications are defined as those initiated and terminated prior to first dose of study medication (i.e. omalizumab during the open-label period); concomitant medications are defined as those with onset on or after first dose of study medication or ongoing at first dose of study medication (i.e. omalizumab for the open-label period).

For the double-blind period the following definitions will be used: medications will be included if they have a start date prior to the earlier of the date of last dose of double-blind treatment + 4 weeks and the date of first dose of transition to open-label treatment.

### **4.6.2 Exposure of Study Medication**

Time on study medication will be calculated with respect to the open-label period as well as the double-blind period. Patients who transition from placebo to open-label omalizumab will also be presented with respect to time on omalizumab. For each period, the number and

frequency of doses taken and doses missed will be displayed, as well as the reason for a missed dose.

#### **4.6.3 Adverse Events**

Adverse events (AEs) will be collected from the time of the first study-specific procedure through the last observation visit (i.e., date of last contact). 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, or worsening of an existing condition, on or after the first dose of study drug. Treatment-emergent adverse events will be summarized for the entire study as well as by phase. Display of events will be by randomization status, occurrence of event or randomization group, depending on the period in which they occurred.

Coding of AEs is performed using version 20.0 of the MedDRA. An adverse event is considered part of the open-label period if the start date is on or after the date of first study treatment, and prior to the earlier of the last open-label treatment + 4 weeks or the first post-randomization treatment. AEs with onset within the open-label period will be summarized by randomization status: randomized vs not randomized.

Adverse events for the double-blind period are defined as adverse events with a start date on or after the date of first dose of double-blind treatment, and prior to the earlier of the date of last dose of double-blind treatment + 4 weeks and the date of first dose of transition to open-label treatment. To account for variable follow-up for the double-blind and follow-up periods, AEs will be presented by “Rate of AE(s) per patient-year”. Patient years is the denominator in the rates of AEs, calculated via the earlier of the two end dates described above and the start date; this is annualized. Due to transitioning patients, the double-blind period will summarize AEs in terms of the medication the patient was taking at the time the event began. If there is a gap between the end of the double-blind period for a patient and the beginning of the transition period, any events and exposure time inbetween will be attributed to the double-blind period proper.

Adverse events for the follow-up period will also be displayed. These are defined as having starting in the follow-up period if the date of onset occurred on or after the date of the first follow-up visit up to the last observation visit. The date of last observation visit used will be the date of last contact.



#### **4.6.4 Laboratory Data**

Clinical laboratory data (e.g., serum chemistry and hematology evaluations) will be summarized by descriptive statistics for each group. Liver enzymes will be explored in combination with other parameters (see Hy's law, Section 4.6.5).

For laboratory endpoints in which data are expressed as a category such as <x, the value of x will be used for the calculation of summary statistics.

#### **4.6.5 Vital Signs**

Vital signs will be summarized by descriptive statistics for each treatment group or randomization status, relative to the period of the study.

#### **4.6.6 Safety Endpoints of Special Interest**

Adverse events of special interest for this study include the following:

- Suspected anaphylaxis due to omalizumab, as defined by Sampson's criteria
- Suspected transmission of an infectious agent by the study drug, as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law.

#### **4.7 HANDLING OF DROPOUTS, MISSING/INCOMPLETE DATA, OR OUTLIERS**

For the purposes of comparing clinical worsening CIU rates, any patient who discontinues from the study before the end of the applicable observation period will be considered to have experienced clinical worsening, as defined by the primary endpoint. For analyses related to continuous endpoints, any patient who discontinues from the study may have their endpoints imputed (as described above) whenever appropriate. eDiary data (e.g, UAS7, weekly hives score, weekly itch score) will use LOCF for monthly summaries, as it is collected weekly.

APPENDIX E discusses the calculation of UAS7 scores, including the handling of missing data.

## **4.8 INTERIM ANALYSES AND/OR SAFETY REVIEWS**

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.

Events described in Section 5.1.1 through Section 5.1.3 of the protocol will be closely monitored and represent selected adverse events for this study, namely: anaphylaxis, malignancies, cardiovascular and cerebrovascular events in patients with asthma, acute asthma symptoms, angioedema, serum sickness, and parasitic infections.

A preliminary analysis of the open-label period will be performed after all patients have completed the open-label phase and were either randomized to the double-blinded phase or discontinued. For this analysis, baseline characteristics will refer to the baseline visit of the open-label period, corresponding to Day 1 up to and including Week 24 assessments.

## **4.9 CHANGES TO STATISTICAL METHODS FROM PROTOCOL**

Prior to database lock and the sign-off of this DAP, it was deemed necessary to override the pre-specification of a number of the non-diary-based exploratory-outcome analyses that were originally planned and pre-specified in the protocol for the double-blind phase (and follow-up phase) due to lack of prior data and clinical impact of their results. For the purposes of pre-specification, the only non-diary PRO that will be analyzed during the double-blind phase and included in this DAP will be the DLQI. No other non-diary PROs will be analyzed during the double-blind phase. Further, no non-diary PROs will be analyzed during the follow-up phase for the purposes of this DAP.

## **APPENDIX A**

### **Protocol Synopsis**

#### **Objectives**

##### **Primary Objective**

The primary objective for this study is to evaluate the level of control of chronic idiopathic urticaria (CIU) symptoms through 48 weeks, among patients continuing omalizumab as compared to those receiving placebo after an initial 24 weeks of omalizumab treatment.

##### **Secondary Objectives**

The secondary objectives for this study are as follows:

- To evaluate the response to retreatment with omalizumab in patients with CIU who have responded to omalizumab, but experienced recurrence or clinical worsening of disease after withdrawal of therapy
- To evaluate whether patients who have achieved response to omalizumab after 24 weeks of therapy demonstrate similar levels of response after 48 weeks of therapy
- To evaluate the safety of omalizumab therapy through 48 weeks in patients with CIU

##### **Exploratory Objectives**

The exploratory objectives for this study are as follows:

- To compare the level of control of CIU symptoms, over 12 weeks after withdrawal of omalizumab, subsequent to completing 48 weeks versus 24 weeks of omalizumab therapy, among patients with CIU who have responded to omalizumab therapy
- To obtain additional data on patient-reported outcome (PRO) response to omalizumab

#### **Study Design**

##### **Description of Study**

This is a Phase IV, multicenter, randomized, double-blind, placebo controlled study to evaluate the efficacy and safety of subcutaneous (SC) omalizumab through 48 weeks as an add-on therapy for the treatment of refractory CIU in adolescent and adult patients (12–75 years of age) who remain symptomatic despite standard H1 antihistamine treatment (including doses up to four times above the approved dose), H2 blockers, and/or leukotriene receptor antagonists (LTRAs). The study will enroll approximately 207 patients at approximately 40 study sites in the U.S.

The study will consist of the following study periods with a total duration of 62 weeks (see Figure 2):

- Screening Period: Day –14 to Baseline (Week –2 to Baseline)
- Open-Label Treatment Period: Day 1 to Day 168 (Baseline to Week 24)
- Double-Blind Randomization Period: Day 169 to Day 336 (Week 24 to Week 48)
- Follow-Up Period: Day 337 to Day 420 (Week 48 to end of Week 60)

The screening period will consist of visits at Day –14 and Day –7. Day 1 (baseline) will mark the commencement of the 24-week open-label treatment period. Patients must meet all of the following criteria prior to receiving treatment in the open-label treatment period:

- Non-electronic diary-based Urticaria Activity Score (UAS)  $\geq 4$  established in the clinic (i.e., in-clinic UAS [IC-UAS]) 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 H1 antihistamine treatment (up to four times the approved dose) for CIU at Day –14 and for at least the 3 consecutive days immediately prior to Day –14 (see Section 4.4.1 for a list of H1 antihistamines available for use in this study)
- Willing and able to complete a symptom electronic diary (eDiary), also referred to as the Urticaria Patient Daily Diary (UPDD), twice daily throughout the screening period to establish the patient's UAS7

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 treatment during the open-label treatment period, patients must have:

- No missing eDiary entries during the 7 days prior to baseline (Note: If a patient fails screening due to missed eDiary entries during this 7-day period, the patient is permitted to rescreen once.);
- A UAS7 symptom score of  $\geq 16$  during the 7 days prior to baseline (equivalent to moderate to severe CIU symptoms for at least 4 out of 7 days in a week); and
- A weekly itch score (a component of the UAS7) of  $\geq 8$  during the 7 days prior to baseline.

Only in exceptional circumstances, when information concerning eligibility is outstanding (e.g., pending laboratory data), will a screening period longer than 2 weeks be permitted. Patients may be re-screened upon approval from the Medical Monitor. Circumstances that may permit re-screening include, but are not limited to, an IC-UAS or laboratory test results that do not meet eligibility requirements.

On Day 1, eligible patients will begin open-label omalizumab 300 mg SC every 4 weeks (Q4W) and will continue on treatment during the 24-week open-label treatment period. During this period, patients will continue reporting twice daily their UAS-related symptoms through the eDiary, necessary for the weekly calculation of UAS7 (which is based on the last 7 days of symptoms). At the end of the open-label treatment period, patients who have responded to omalizumab will be randomized in a double-blinded fashion to either continue omalizumab or to transition to placebo for a further 24 weeks. Patients will be eligible for randomization if they meet both of the following criteria:

- Achieve  $\text{UAS7} \leq 6$  in the final 2 weeks of the open-label treatment period, which are the 2 consecutive weeks immediately prior to randomization. (These final 2 weeks are scheduled to occur during Week 23 and Week 24 but may vary somewhat depending on patient scheduling.)  
AND
- Comply with omalizumab dosing for at least 5 out of the 6 planned doses, including a dosage at Week 20, during the initial 24-week open-label treatment period (i.e., patients may only be randomized if they have missed at most one dosage of omalizumab during the initial open-label treatment period AND did not miss their Week 20 dosage)

Patients who meet the criteria for randomization will be randomized at a ratio of 3:2 (omalizumab:placebo). Randomization to treatment groups will be stratified by UAS7 at the point of randomization ( $\text{UAS7} = 0$  vs.  $\text{UAS7} > 0$ ) and study site. Efficacy and safety data will be collected. Subsequent to randomization, patients will continue to be evaluated twice daily using the eDiary for weekly calculation of UAS7, which includes a weekly itch score.

Throughout the study (Day -14 to Week 60), patients must maintain stable doses of their pre-randomization combination therapy with H1 antihistamine treatment, H2 blockers, and/or LTRAs. Patients will be prohibited from using non-study-drug omalizumab during the study (Day -14 to Week 60) (e.g., commercially available omalizumab is not permitted during the study). Patients receiving non-study-drug omalizumab during the study, for any indication, will be discontinued from the study.

Patients who do not meet the criteria for randomization (e.g., because of non-response to omalizumab during the open-label treatment period) should return for a final follow-up visit 12 weeks after Visit 9 (Week 24 visit), which will include assessments for adverse events and PROs (see Appendix 1). Patients will not be required to complete the eDiary during this 12-week period.

Subsequent to randomization, patients may, at the discretion of the investigator, be transitioned from blinded study drug to open-label omalizumab at 300 mg SC Q4W if they experience clinically significant worsening in their CIU (as judged by the investigator); clinical worsening must also be accompanied by  $\text{UAS7} \geq 12$  for at least 2 consecutive weeks. That is, patients may potentially be transitioned to open-label omalizumab if this is deemed by the investigator to be clinically indicated based on clinical worsening CIU and if, after the investigator has made this assessment, patients are confirmed to have experienced  $\text{UAS7} \geq 12$  for at least 2 consecutive weeks as determined by eDiary entries. Patients who are transitioned to open-label omalizumab will not be unblinded with respect to the treatment they had received between randomization and transition to open-label omalizumab. Patients who are transitioned to open-label omalizumab will continue to receive open-label omalizumab as study drug until Week 48, after which omalizumab will be discontinued.

The primary endpoint for this study is the percentage of patients who experience clinical worsening in CIU defined as UAS7  $\geq 12$  for at least 2 consecutive weeks.

After completion of the randomization period (end of Week 48), all patients will enter a 12-week follow-up period to allow for collection of additional efficacy and safety data. Patients will continue to visit the study site at 4-week intervals. The Week 48 and Week 60 visits will take place at the study site. The Week 52 and Week 56 visits will take place by telephone by the study site personnel to include collection of adverse events and concomitant medication information. Patients will continue to be assessed via eDiary during this period. No study treatment will be given during the follow-up period.

The double blindness of randomization to treatment groups should be maintained for the full post-randomization period of the study (until the end of the study).

Schedule of assessments are provided in Appendix 1, Appendix 2, and Appendix 3.

### **Number of Patients**

Approximately 207 patients are planned to be enrolled in this study at approximately 40 study sites in the U.S. Approximately 117 patients will be randomized in this study after accounting for dropout, non-adherence, and non-response during the open-label treatment period.

### **Target Population**

#### Inclusion Criteria

Patients must meet the following criteria for study entry:

- Age 12–75 years
- Diagnosis of CIU refractory to H1 antihistamines at baseline, as defined by all of the following:
  - The presence of itch and hives for  $\geq 8$  consecutive weeks at any time prior to enrollment despite current use of H1 antihistamine treatment (up to four times the approved dose) during this time period
  - UAS7 score (range 0–42)  $\geq 16$  and itch component of UAS7 (range 0–21)  $\geq 8$  during 7 days prior to baseline
  - IC-UAS  $\geq 4$  on at least one of the screening visit days (Day –14, Day –7, or Day 1) (see Section 4.5.9 for details on IC-UAS)
  - Patients must have been on a non-sedating H1 antihistamine treatment specified in Section 4.4 (up to four times the approved dose) 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  $\geq 6$  months. The methods used to confirm duration of CIU diagnosis may include patient report of onset of CIU symptoms, and the duration of CIU diagnosis may be made based on the initial date of these symptoms even if the diagnosis of CIU was made at a later date.
- Willing to give written informed consent, adhere to the visit schedules, and meet study requirements
  - For 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 baseline.
- For women who are not postmenopausal ( $\geq 12$  months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use two adequate methods of contraception, including at least one method with a failure rate of  $<1\%$  per year, during the treatment period and for at least 4 months after the last dose of study drug
  - Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- Barrier methods must always be supplemented with the use of a spermicide.

#### 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
 Any of the following diseases, which 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 (chronic gastrointestinal [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 (ULN)
  - AND
  - Evidence of parasitic colonization or infection on stool evaluation for ova and parasites. Stool ova and parasite evaluation will only be conducted in patients with both risk factors and an eosinophil count more than twice the ULN.
- Atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus, or other skin disease associated with itch
- Previous treatment with omalizumab within 1 year prior to Day –14
- Routine (daily/every other day during 5 or more consecutive days) doses of the following medications within 30 days prior to Day –14: systemic corticosteroids, hydroxychloroquine, methotrexate, mycophenolate, cyclosporine, or cyclophosphamide
- Intravenous 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
- 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
- Contraindications to diphenhydramine
- Pregnant or lactating, or intending to become pregnant during the study
  - Women of childbearing potential must have a negative serum pregnancy test result within 3 days prior to initiation of study drug.

#### **Length of Study**

The total duration of the study is anticipated to be 62 weeks consisting of a 2-week screening period, a 24-week open-label treatment period, a 24-week double-blind randomization period, and a 12-week follow-up period.

## **End of Study**

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur 60 weeks after the last patient is enrolled.

## **Outcome Measures**

### **Primary Efficacy Outcome Measure**

The primary efficacy outcome measure is the percentage of patients who experience clinical worsening in CIU as assessed by UAS7. The specific threshold for clinical worsening in CIU symptoms will be UAS7  $\geq 12$ , maintained for at least 2 consecutive weeks, from randomization (Week 24) to Week 48.

### **Secondary Efficacy Outcome Measures**

The secondary efficacy outcome measures for this study are as follows:

- Time to clinical worsening in CIU, defined based on the same criteria as the primary endpoint (maintaining UAS7  $\geq 12$  for at least 2 consecutive weeks), from randomization (Week 24) to Week 48
- Percentage of patients who experience clinical worsening in CIU assessed by UAS7, where the threshold for clinical worsening is UAS7  $> 6$  for at least 2 consecutive weeks, from randomization (Week 24) to Week 48
- UAS7 (24- vs. 48-week value) among patients who have responded to omalizumab treatment at 24 weeks and completed a further 24 weeks of omalizumab (48 weeks total), which will be assessed by the change from randomization (Week 24) to Week 48 in UAS7
- Retreatment efficacy, defined by change in UAS7 from time of retreatment to 12 weeks after retreatment, among patients randomized to the placebo arm who are retreated with open-label omalizumab after randomization and receive at least 12 weeks of omalizumab therapy as retreatment

### **Safety Outcome Measures**

The safety outcome measures for this study are as follows:

- Incidence and severity of adverse events and serious adverse events
- Changes in vital signs
- Clinical laboratory evaluations

### **Pharmacokinetic/Pharmacodynamic Outcome Measures**

Total serum immunoglobulin E (IgE) level will be measured at screening (pre-dose)

### **Exploratory Outcome Measures**

The exploratory outcome measures for this study are as follows:

- The proportion of patients experiencing clinical worsening in CIU (defined as maintaining UAS7  $\geq 12$  for at least 2 consecutive weeks) between Weeks 48 and 60 among patients randomized to continue omalizumab (i.e., during the 12 weeks after discontinuing a 48-week course of omalizumab)
- The proportion of patients experiencing clinical worsening in CIU (defined as maintaining UAS7  $\geq 12$  for at least 2 consecutive weeks) between Weeks 24 and 36 among patients randomized to placebo
- Change from randomization (Week 24) to Week 48 in weekly itch score
- Change from randomization (Week 24) to Week 48 in UAS7
- Change from randomization (Week 24) to Week 48 in health-related quality-of-life as measured by the Dermatology Life Quality Index (DLQI) total score
- Insomnia Severity Index (ISI); General Anxiety Disorder 7-Item (GAD-7) scale; and Work Productivity and Activity Index (WPAI) will be assessed as:
  - Change from baseline to Week 24
  - Change from randomization to Week 48
  - Change from the end of the randomization period (Week 48) to the end of the study (end of Week 60)

- Proportion of angioedema days, evaluated through patient self-reports via eDiary, from
- Week 24 to Week 48
- Urticaria Control Test (UCT) response and correlation with UAS7
  - Change in UCT from baseline to Week 24
  - Change in UCT from randomization to Week 48
  - Correlation between UCT and UAS7 from baseline to Week 24
- Urticaria Activity and Impact Measure (U-AIM) response and correlation with UAS7
  - Change in U-AIM from baseline to Week 24
  - Change in U-AIM from randomization to Week 48
  - Correlation between U-AIM and UAS7 from baseline to Week 24
- Patient Global Impression of Change (P-GIC) scale and Clinician Global Impression of Change (C-GIC) scale assessed at Week 24 and Week 48

### **Investigational Medicinal Products**

#### **Study Drug**

Omalizumab will be supplied by the Sponsor. Omalizumab is a sterile, white, preservative-free, lyophilized powder, contained in a single-use, 5-mL vial that will be reconstituted with Sterile Water for Injection (SWFI), USP, and administered as a SC 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 additional details, see the pharmacy manual and the Omalizumab Investigator's Brochure.

Patients will receive omalizumab 300 mg or placebo administered SC Q4W at the study site. Missed doses will not be replaced. Each patient will receive two injections of study medication at every treatment visit.

#### **Placebo**

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

### **Non-Investigational Medicinal Products**

See Section 4.4.1 for the long-acting H1 antihistamines, H2 blockers, and LTRAs allowed during the study.

All patients will be allowed to take study-defined H1 antihistamine medications at up to four times the approved dose, H2 blockers, and/or LTRAs during the screening, treatment, and follow-up periods. Patients should remain on a stable H1 antihistamine, H2 blocker, and/or LTRA treatment regimen throughout the randomization period (Week 24 to Week 48).

Diphenhydramine (25 mg) may also be used on an as-needed basis (maximum three times/day) during the screening, treatment, and follow-up periods.

### **Statistical Methods**

#### **Efficacy Analyses**

Efficacy analyses will be based on the modified intent-to-treat (mITT) principle. All patients meeting criteria for randomization, who are also randomized and receive at least one dosage of blinded study drug, will be included in analyses. Analyses groups will be defined according to the patients' assigned treatments regardless of the actual treatment received.

Analyses comparing rates of clinical worsening CIU after randomization, including the primary analysis, will include the counts and proportions of the response among all patients as well as in the treatment groups being compared. The 95% confidence intervals will be presented for each within-group proportion and for the difference in proportions between treatment groups. The 2-sided chi-square p-value will be presented to compare the treatment group proportions.

Analyses comparing changes in UAS7 or any other continuous outcome measure will include the means, standard deviations, and 95% confidence intervals for all patients, for each treatment group, and for the difference between groups accompanied by p-values whenever applicable.



For all efficacy analyses, statistical significance will be declared if the p-value for the comparison is less than 0.05.

#### Missing Data for Efficacy Analyses

For the purposes of comparing clinical worsening CIU rates, any patient who discontinues from the study before the end of the applicable observation period will be considered to have experienced clinical worsening, as defined by the primary endpoint. For analyses related to continuous endpoints, any patient who discontinues from the study may have their endpoints imputed whenever appropriate. Further details related to imputations for missing data will be outlined in the Statistical Analysis Plan (SAP) before the database is locked.

#### **Safety Analyses**

Safety analyses will be performed for all patients treated with study drug. Safety will be assessed by adverse events, vital signs, and clinical laboratory evaluations.

Adverse events will be collected from the time of the first study-specific procedure through the last observation visit. 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, or worsening of an existing condition on or after the first dose of study drug. Treatment-emergent adverse events will be summarized by treatment group. Clinical laboratory data (e.g., serum chemistry and hematology evaluations) and vital signs will be summarized by descriptive statistics for each treatment group.

#### **Pharmacokinetic and Pharmacodynamic Analyses**

Total serum IgE level at screening (pre-dose) versus time data will be tabulated by treatment group and summarized using descriptive statistics (e.g., mean, standard deviation, minimum, and maximum).

#### **Exploratory Analyses**

For details on how each exploratory analysis will be conducted, see the SAP.

#### **Determination of Sample Size**

Assuming a 60% rate of clinical worsening in CIU assessed by UAS7 in the placebo group (including 10% dropout imputed as worsening CIU) and a rate of 30% in the omalizumab continuation group (including 10% dropout imputed as clinical worsening CIU) in the period up to 24 weeks post-randomization, a total of 117 patients will need to be randomized at a 3:2 ratio (3 omalizumab continuation group patients for every 2 placebo patients) to ensure 90% power to detect a difference in clinical worsening CIU rates as a primary analysis comparison at the 0.05 alpha level (2-sided test). In addition, as it is estimated that 15% of patients will either drop out during the open-label treatment period or not meet the adherence criteria, and that 66.5% of those who do not drop out or fail adherence criteria will be responders, this study will need to enroll at least 207 ( $117 / [0.665 \cdot 0.85]$ ) patients to ensure adequate randomization numbers for the primary analysis. This sample size will also ensure at least 80% power for each of the secondary analyses.

**APPENDIX B**  
**Schedule of Assessments**

**Schedule of Assessments for Screening and Open-Label Treatment Period**

	Screening <sup>a</sup>		Open-Label Treatment Period (Baseline to Week 24)							Follow-Up Visit for Non-Responders <sup>c</sup>	ET <sup>d</sup>
End of Study Week			Baseline	4	8	12	16	20	24 <sup>b</sup>		
Day (Window)	-14 (-4/+2)	-7 (±3)	1	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	169 (±3)	Day 253 (±7)	
Visit #	1	2	3	4	5	6	7	8	9		
Signed Informed Consent Form(s)	x										
Inclusion/exclusion criteria	x	x	x								
Demographic data	x										
Medical/surgical history <sup>e</sup>	x										
Vital signs (blood pressure and pulse) <sup>f</sup>	x		x	x	x	x	x	x	x		x
Physical examination <sup>g</sup>	x										
Weight/height	x										x
Pregnancy test <sup>h</sup>	x		x	x	x	x	x	x	x		
Concomitant medication usage	x	x	x	x	x	x	x	x	x	x	x
Adverse events <sup>i</sup>		x	x	x	x	x	x	x	x	x	x
Open-label omalizumab administration			x	x	x	x	x	x			
Study drug/placebo administration <sup>b</sup>									x <sup>b</sup>		
Site to contact IxRS	x		x	x	x	x	x	x	x	x	x
PROs											
Patient eDiary <sup>j</sup>	x	x	x	x	x	x	x	x	x		x
DLQI <sup>k</sup>			x			x			x	x	x

	Screening <sup>a</sup>		Open-Label Treatment Period (Baseline to Week 24)							Follow-Up Visit for Non-Responders <sup>c</sup>	ET <sup>d</sup>
End of Study Week			Baseline	4	8	12	16	20	24 <sup>b</sup>		
Day (Window)	-14 (-4/+2)	-7 (±3)	1	29 (±3)	57 (±3)	85 (±3)	113 (±3)	141 (±3)	169 (±3)	Day 253 (±7)	
Visit #	1	2	3	4	5	6	7	8	9		
UCT <sup>k</sup>	x		x			x			x	x	x
U-AIM <sup>k</sup>	x		x			x			x	x	x
ISI <sup>k</sup>			x			x			x	x	x
GAD-7 <sup>k</sup>			x			x			x	x	x
WPAI <sup>k</sup>			x			x			x	x	x
P-GIC scale <sup>k</sup>									x		
IC-UAS <sup>k</sup>	x	x	x						x	x	x
C-GIC scale <sup>k</sup>									x		
Laboratory tests <sup>l</sup>											
Hematology <sup>m</sup>	x								x		x
Stool ova and parasite evaluation <sup>n</sup>		x									
Chemistry <sup>o</sup>	x										
Urinalysis <sup>p</sup>	x										
Thyroperoxidase antibody	x										
CU index	x										
PK sample (total serum IgE)	x										
Blood samples for storage	x								x		x
Blood RNA (optional) <sup>q</sup>	x								x		x

C-GIC= Clinical Global Impression of Change; CU= chronic urticaria; DLQI= Dermatology Life Quality Index; eDiary= electronic diary; ET= early termination; GAD-7= Generalized Anxiety Disorder Assessment 7-Item Scale; IC-UAS= in-clinic Urticaria Activity Score; IgE= immunoglobulin E; ISI= Insomnia Severity Index; IxRS= interactive voice and web response systems; P-GIC= Patient Global Impression of Change; PD= pharmacodynamic; PK= pharmacokinetic; PRO= patient-reported outcome; U-AIM= Urticaria Activity and Impact Measure; UAS= Urticaria Activity Score; UCT= Urticaria Control Test; WPAI= Work Productivity and Activity Index.

Note: Unless otherwise indicated, all assessments should be performed prior to study drug administration.

- <sup>a</sup> The screening period should be 12 to 18 days long. Day –14 and Day –7 are provided for reference. The Day –14 visit should be conducted 18 to 12 days prior to baseline (Day 1). Complete eDiary 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 IC-UAS score, evaluation of patients' eDiary use, and additional eDiary training if necessary.
- <sup>b</sup> The Week 24 visit is the end of the open-label treatment period and the start of the double-blind randomization period. This visit should be scheduled on Day 169 (not Day 168) in order to collect eDiary data of Day 168. A 3-day window is allowed. Patients who meet criteria for randomization will be randomized and receive their first dose of blinded study drug at this visit; this is the only assessment (noted by gray shading) being performed as part of the double-blind randomization period.
- <sup>c</sup> Patients who do not meet the criteria for randomization (e.g., because of non-response to omalizumab during the open-label treatment period) should return for a final follow-up visit 12 weeks after the Week 24 visit, which will include a blood draw for PK/PD measurement, and assessments for adverse events and PROs. Patients will not be required to complete the eDiary during this 12-week period.
- <sup>d</sup> Patients who discontinue study treatment early (after baseline, but before Week 24 [Day 169]) should return for an early termination visit. These assessments do NOT apply to non-responders who discontinue study treatment before the Day 253 visit. Non-responders who complete the Week 24 visit but discontinue study treatment before Day 253 should instead complete the assessments listed under the column "Follow-Up Visit for Non-Responders."
- <sup>e</sup> Medical history includes clinically significant diseases (including onset of CIU symptoms, date of diagnosis, and therapies received for CIU), surgeries, reproductive status, smoking history, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the screening visit.
- <sup>f</sup> Vital signs include measurements of pulse, and systolic and diastolic blood pressure while the patient is in a seated position. Record abnormalities on the Adverse Event eCRF.
- <sup>g</sup> A complete physical examination performed at screening should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.
- <sup>h</sup> All women of childbearing potential (including those who have had a tubal ligation) will have a 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 and/or open-label omalizumab 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.

- <sup>i</sup> After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 112 days (approximately 5 drug half-lives) after the last dose of study drug or study discontinuation/termination, whichever is later. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that are believed to be related to prior study drug treatment. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.
- <sup>j</sup> Includes UAS7 (itch score, number of hives), largest size of hives, sleep interference score, activity interference question, rescue medication (diphenhydramine) use, angioedema episodes, and number of calls to doctor or nurse. Daily eDiary is to be completed twice a day by the patient. The eDiary will be given to patients on Day –14.
- <sup>k</sup> All PROs, including the DLQI, UCT, U-AIM, ISI, GAD-7, WPAI, P-GIC scale, IC-UAS (itch score + number of hives score), and C-GIC scale must be completed prior to administration of study drug.
- <sup>l</sup> Samples for laboratory tests will be taken pre-dose on dosing days.
- <sup>m</sup> Hematology to include hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent and absolute differential count (e.g., neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells).
- <sup>n</sup> Note that stool ova and parasite examination should be performed on Day –7 in patients with an eosinophil count > 2 times the ULN on Day –14 AND risk factors for parasitic disease. Stool ova and parasite examination will be performed by a local laboratory.
- <sup>o</sup> Serum chemistries to include 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.
- <sup>p</sup> Urinalysis to include dipstick (i.e., pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (e.g., sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).
- <sup>q</sup> Blood RNA to be collected only in patients providing a separate, specific signature on the Informed Consent Form to document the patient's agreement to participate in this optional procedure.

### Schedule of Assessments for Double-Blind Randomization Period and Follow-Up Period

	Double-Blind Randomization Period <sup>a</sup> (Week 24 to Week 48)							Follow-Up Period <sup>b</sup> (Week 48 to Week 60)			ET
End of Study Week	24 <sup>c</sup>	28	32	36	40	44	48 <sup>d,e</sup>	52 <sup>e</sup>	56 <sup>e</sup>	60 <sup>e</sup>	
Day (Window)	169 (±3)	197 (±3)	225 (±3)	253 (±3)	281 (±3)	309 (±3)	337 (±3)	365 (±3)	393 (±3)	421 (±3)	
Visit #	9	10	11	12	13	14	15	16	17	18	
Vital signs (blood pressure and pulse) <sup>f</sup>	x	x	x	x	x	x	x			x	x
Weight/height										x	x
Pregnancy test <sup>g</sup>	x	x	x	x	x	x					
Concomitant medication usage	x	x	x	x	x	x	x	x	x	x	x
Adverse events <sup>h</sup>	x	x	x	x	x	x	x	x	x	x	x
Study drug/placebo administration	x	x	x	x	x	x					
Site to contact IxRS	x	x	x	x	x	x				x	x
PROs											
Patient eDiary <sup>i</sup>	x	x	x	x	x	x	x	x	x	x	x
DLQI <sup>j</sup>	x			x			x			x	x
UCT <sup>j</sup>	x			x			x			x	x
U-AIM <sup>j</sup>	x			x			x			x	x
ISI <sup>j</sup>	x			x			x			x	x
GAD-7 <sup>j</sup>	x			x			x			x	x
WPAI <sup>j</sup>	x			x			x			x	x
P-GIC scale <sup>j</sup>	x						x				
IC-UAS <sup>j</sup>	x			x			x			x	x
C-GIC scale <sup>j</sup>	x						x				

	Double-Blind Randomization Period <sup>a</sup> (Week 24 to Week 48)							Follow-Up Period <sup>b</sup> (Week 48 to Week 60)			ET
End of Study Week	24 <sup>c</sup>	28	32	36	40	44	48 <sup>d,e</sup>	52 <sup>e</sup>	56 <sup>e</sup>	60 <sup>e</sup>	
Day (Window)	169 (±3)	197 (±3)	225 (±3)	253 (±3)	281 (±3)	309 (±3)	337 (±3)	365 (±3)	393 (±3)	421 (±3)	
Visit #	9	10	11	12	13	14	15	16	17	18	
Laboratory tests <sup>k</sup>											
Hematology <sup>l</sup>	x						x			x	x
PK sample (serum total omalizumab)	x						x			x	x
PD samples (total serum IgE and free serum IgE)	x						x			x	x
Blood samples for storage	x						x			x	x
Blood RNA (optional) <sup>m</sup>	x						x			x	x

C-GIC= Clinical Global Impression of Change; CU= chronic urticaria; DLQI= Dermatology Life Quality Index; eDiary= electronic diary; ET= early termination; GAD-7= Generalized Anxiety Disorder Assessment 7-Item Scale; IC-UAS= in-clinic Urticaria Activity Score; IgE= immunoglobulin E; ISI= Insomnia Severity Index; IxRS= interactive voice and web response systems; P-GIC= Patient Global Impression of Change; PD= pharmacodynamic; PK= pharmacokinetic; PRO= patient-reported outcome; U-AIM= Urticaria Activity and Impact Measure; UAS= Urticaria Activity Score; UCT= Urticaria Control Test; WPAI= Work Productivity and Activity Index.

Note: Unless otherwise indicated, all assessments should be performed prior to study drug administration.

<sup>a</sup> Patients who meet the criteria for transition to open-label omalizumab after randomization (e.g., because of clinical worsening in CIU and UAS7 ≥ 12 for at least 2 consecutive weeks) should be transitioned and follow the assessments.

<sup>b</sup> The 12-week follow-up period applies only to patients who have completed the first 48 weeks of the study.

<sup>c</sup> The Week 24 visit is the end of the open-label treatment period and the start of the double-blind randomization period. Patients who meet the criteria for randomization will be randomized and receive their first dose of blinded study drug at this visit; this is the only assessment being performed as part of the double-blind randomization period. The assessments noted by gray shading are conducted as part of the Week 24 visit of the open-label treatment period for the double-blind randomization period.

<sup>d</sup> The Week 48 visit is the end of the double-blind randomization period and the beginning of the follow-up period.

<sup>e</sup> The Week 48 and Week 60 visits will take place at the study site. The Week 52 and Week 56 visits will take place by telephone by the study site personnel to include collection of adverse event and concomitant medication information. Patients will continue to be assessed via eDiary during this period. No study treatment will be given during the follow-up period.

- <sup>f</sup> Vital signs include measurements of pulse, and systolic and diastolic blood pressure while the patient is in a seated position. Record abnormalities on the Adverse Event eCRF.
- <sup>g</sup> All women of childbearing potential (including those who have had a tubal ligation) will have a 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 and/or open-label omalizumab 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.
- <sup>h</sup> After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 112 days (approximately 5 drug half-lives) after the last dose of study drug or study discontinuation/termination, whichever is later. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that are believed to be related to prior study drug treatment. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.
- <sup>i</sup> Includes UAS7 (itch score, number of hives), largest size of hives, sleep interference score, activity interference question, rescue medication (diphenhydramine) use, angioedema episodes, and number of calls to doctor or nurse. Daily eDiary is to be completed twice a day by the patient. The eDiary will be given to patients on Day –14.
- <sup>j</sup> All PROs, including the DLQI, UCT, U-AIM, ISI, GAD-7, WPAI, P-GIC scale, IC-UAS (itch score + number of hives score), and C-GIC scale must be completed prior to administration of study drug.
- <sup>k</sup> Samples for laboratory tests will be taken pre-dose on dosing days.
- <sup>l</sup> Hematology to include hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent and absolute differential count (e.g., neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells).
- <sup>m</sup> Blood RNA to be collected only in patients providing a separate, specific signature on the Informed Consent Form to document the patient's agreement to participate in this optional procedure.



**Schedule of Assessments for Patients Who Transition to Open-Label Omalizumab  
after Randomization**

	First Day of Transition	Post-Randomization Open-Label Treatment Period <sup>a</sup>	Follow-Up Period <sup>b</sup>				ET
		Every 4 Weeks Until 48 Weeks of Total Treatment	Week 48 <sup>c</sup>	Week 52 <sup>c</sup>	Week 56 <sup>c</sup>	Week 60 <sup>c</sup>	
Visit Window (days)		± 3	± 3	± 3	± 3	± 3	± 3
Vital signs (blood pressure and pulse) <sup>d</sup>	x	x	x			x	x
Weight/height						x	x
Pregnancy test <sup>e</sup>	x	x					
Concomitant medication usage	x	x	x	x	x	x	x
Adverse events <sup>f</sup>	x	x	x	x	x	x	x
Open-label omalizumab	x	x					
Site to contact IxRS	x	x				x	x
PROs							
Patient eDiary <sup>g</sup>	x	x	x	x	x	x	x
DLQI <sup>h</sup>	x		x			x	x
UCT <sup>h</sup>	x		x			x	x
U-AIM <sup>h</sup>	x		x			x	x
ISI <sup>h</sup>	x		x			x	x
GAD-7 <sup>h</sup>	x		x			x	x
WPAI <sup>h</sup>	x		x			x	x
P-GIC scale <sup>h</sup>	x		x				
IC-UAS <sup>h</sup>	x		x			x	x

	First Day of Transition	Post-Randomization Open-Label Treatment Period <sup>a</sup>	Follow-Up Period <sup>b</sup>				ET
		Every 4 Weeks Until 48 Weeks of Total Treatment	Week 48 <sup>c</sup>	Week 52 <sup>c</sup>	Week 56 <sup>c</sup>	Week 60 <sup>c</sup>	
Visit Window (days)		± 3	± 3	± 3	± 3	± 3	± 3
C-GIC scale <sup>h</sup>	x		x				
Laboratory tests <sup>i</sup>							
Hematology <sup>j</sup>	x		x				x
PK sample (serum total omalizumab)	x		x			x	x
PD samples (total serum IgE and free serum IgE)	x		x			x	x
Blood samples for storage	x		x			x	x
Blood RNA (optional) <sup>k</sup>	x		x			x	x

C-GIC= Clinical Global Impression of Change; DLQI= Dermatology Life Quality Index; eDiary= electronic diary; ET= early termination; GAD-7= Generalized Anxiety Disorder Assessment 7-Item Scale; IC-UAS= in-clinic Urticaria Activity Score; IgE= immunoglobulin E; ISI= Insomnia Severity Index; IxRS= interactive voice and web response systems; P-GIC= Patient Global Impression of Change; PD= pharmacodynamic; PK= pharmacokinetic; PRO= patient-reported outcome; U-AIM= Urticaria Activity and Impact Measure; UAS= Urticaria Activity Score; UCT= Urticaria Control Test; WPAI= Work Productivity and Activity Index.

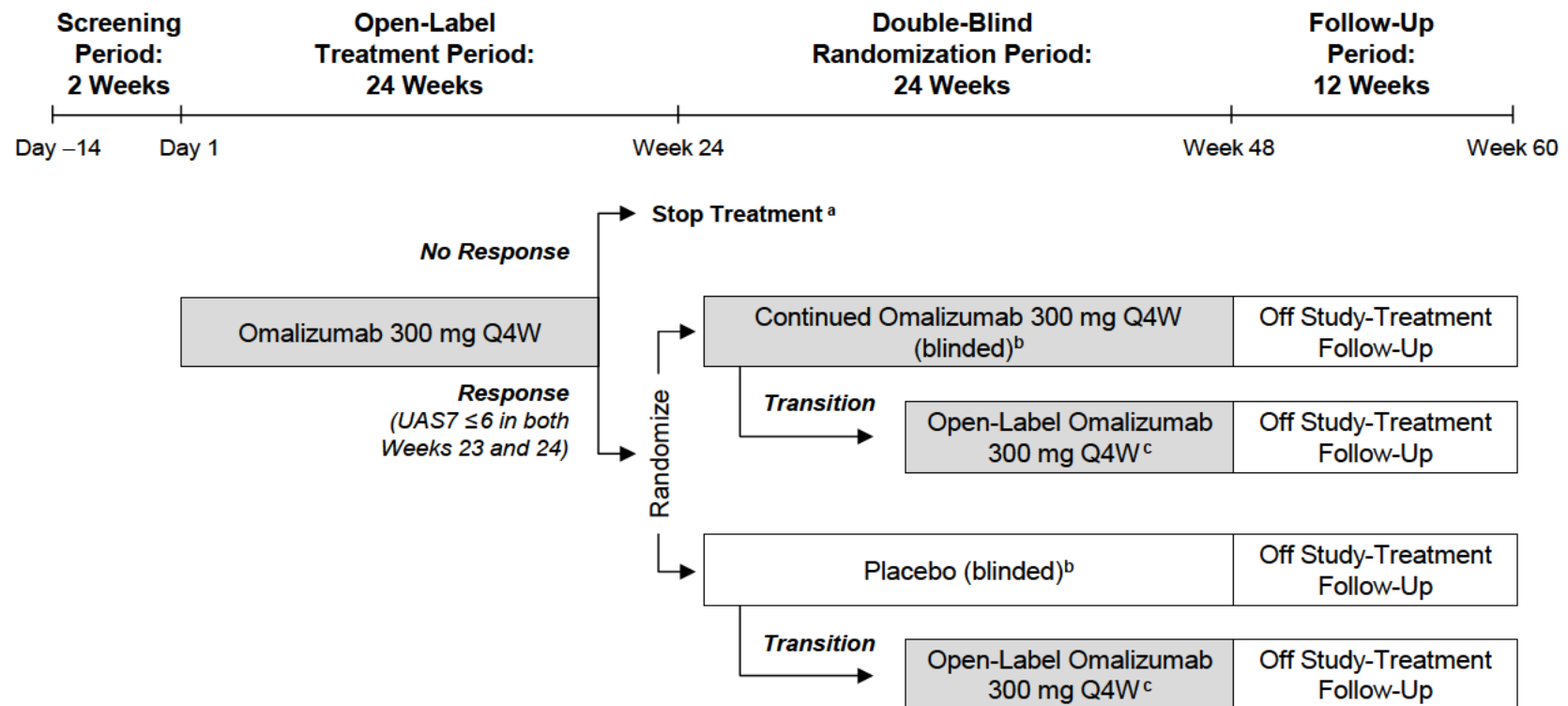
Note: Unless otherwise indicated, all assessments should be performed prior to study drug administration.

- <sup>a</sup> Patients will complete a variable number of study visits during this time period, depending upon when they have transitioned to open-label omalizumab. For example, if a patient transitioned to open-label omalizumab 10 weeks after randomization (Week 34), this patient would complete study visits at day of transition (Week 34), 4 weeks after transition (Week 38), 8 weeks after transition (Week 42), and 12 weeks after transition (Week 46) and subsequently, at Week 48 would enter the follow-up period, during which time omalizumab would be withdrawn.
- <sup>b</sup> The 12-week follow-up period applies only to patients who have completed the first 48 weeks of the study.
- <sup>c</sup> The Week 48 and Week 60 visits will take place at the study site. The Week 52 and Week 56 visits will take place by telephone by the study site personnel to include collection of adverse event and concomitant medication information. Patients will continue to be assessed via eDiary during this period. No study treatment will be given during the follow-up period.

- <sup>d</sup> Vital signs include measurements of pulse, and systolic and diastolic blood pressure while the patient is in a seated position. Record abnormalities on the Adverse Event eCRF.
- <sup>e</sup> All women of childbearing potential (including those who have had a tubal ligation) will have a 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 and/or open-label omalizumab 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.
- <sup>f</sup> After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 112 days (approximately 5 drug half-lives) after the last dose of study drug or study discontinuation/termination, whichever is later. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that are believed to be related to prior study drug treatment. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.
- <sup>g</sup> Includes UAS7 (itch score, number of hives), largest size of hives, sleep interference score, activity interference question, rescue medication (diphenhydramine) use, angioedema episodes, and number of calls to doctor or nurse. Daily eDiary is to be completed twice a day by the patient. The eDiary will be given to patients on Day –14.
- <sup>h</sup> All PROs, including the DLQI, UCT, U-AIM, ISI, GAD-7, WPAI, P-GIC scale, IC-UAS (itch score + number of hives score), and C-GIC scale must be completed prior to administration of study drug.
- <sup>i</sup> Samples for laboratory tests will be taken pre-dose on dosing days.
- <sup>j</sup> Hematology to include hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent, and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells).
- <sup>k</sup> Blood RNA to be collected only in patients providing a separate, specific signature on the Informed Consent Form to document the patient's agreement to participate in this optional procedure.

## APPENDIX C Study Flowchart

Figure 1 Study Schema



Q4W = every 4 weeks; UAS7 = Urticaria Activity Score over 7 days.

- <sup>a</sup> Patients who do not meet the criteria for randomization (e.g., because of non-response to omalizumab during the open-label treatment period) should return for a final follow-up visit 12 weeks after the Week 24 visit, which will include a blood draw for PK/PD measurement, and assessments for adverse events and PROs. Patients will not be required to complete the eDiary during this 12-week period.
- <sup>b</sup> At Week 24, patients will be randomized 3:2 (omalizumab:placebo).
- <sup>c</sup> Patients will be eligible to transition to open-label omalizumab, at the discretion of the investigator, if they experience clinically significant worsening in their CIU (as judged by the investigator) that is also accompanied by  $UAS7 \geq 12$  for at least 2 consecutive weeks. Patients who begin open-label omalizumab subsequent to randomization will receive omalizumab as study drug until Week 48.

## **APPENDIX D**

### **Documentation of Additional Analyses Performed after Database Lock**

To be determined.

## APPENDIX E

### Data Handling Rules

#### 1. Algorithms for calculation of PRO scores

For additional details, see references section for original articles regarding each PRO.

##### a) UAS7

The UAS is a composite score (recorded via eDiary) that reflects daily itch severity and daily number of hives. The daily itch score (range 0–3) comprises the average of the two scores of itch severity (12-hour recall each morning and evening; see Table 1). The daily number of hives score (range 0–3) comprises the average of the two scores (12-hour recall each morning and evening; see Table 1) associated with number of hives. The daily UAS (range 0–6) is the sum of the daily itch score and the daily number of hives score. The UAS7 is the sum of the daily UAS during the last 7 days.

Table 1 Twice Daily Assessment of Disease Activity in Patients with Chronic Idiopathic Urticaria (Urticaria Activity Score)

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

The following algorithm was provided by the Sponsor statistician, [REDACTED]:

### **Calculation of any weekly UAS7 score with Examples**

The UAS7 score is the sum of the daily UAS scores over the past 7 days. The daily UAS score is a composite of the daily hive and daily itch scores and is computed as follows:

Compute the average of the morning and night Hive Scores from the table below (This is the daily hive score). Then compute the average of the morning and night Itch Scores from the table below (This is the daily itch score). Add these 2 averages together (i.e. Add the daily hive and itch score together). That is your daily UAS score. In other words, the daily UAS score is just the sum of the daily itch and daily hive scores, both of which are derived by taking morning and night averages.

Please note that during the trial it was observed that a small number of patients entered duplicate observations: e.g, 2 hive scores for the same time (PM) on the same day; this was a result of device malfunction. To handle this in the analysis, the first or earliest record entered at that time will be retained after having sorted the records by (1) patient, (2) date/time of record and (3) record entry timestamp.

### **Weekly UAS7 Score and daily UAS Missing data handling:**

#### ***Daily itch, hive and UAS score***

When either the morning or evening hive/itch score is missing for either the daily hive or daily itch score calculation, the non-missing hive/itch severity score for that day (morning or evening) will be used as the daily hive/itch severity score, and when both the morning and evening hive/itch scores are missing, the daily hive/itch score will be missing. If either the daily hive or itch score is missing, then the daily UAS score will be missing.

For example, if you have a morning hive score of 1 but a missing night score then your daily hive score will be 1. But if it is missing in morning and night then your daily hive score will be missing and so will your UAS for that day.



### **Weekly UAS7**

In calculating the UAS7 score, you must make sure that you are adding the 7 NON-MISSING daily UAS scores from a given diary week.

When one or more UAS Scores are missing or if a given diary week is <7 days then-

- a) If a patient has at least 4 non-missing daily UAS scores included in the calculation of the Weekly UAS7, the weekly UAS7 is defined as the sum of the available daily UAS in that week, divided by the number of days that have a non-missing daily UAS, multiplied by 7.
- b) If there are less than 4 non-missing daily UAS scores included in the calculation of the weekly score, then the Weekly UAS7 is defined as missing for that week.

### **EXAMPLE 1**

Day 1 Morning:	HivesAM1=2	ItchAM1=3
Day 1 Evening:	HivesPM1=1	ItchPM1=0

Day 2 Morning:	HivesAM2=3	ItchAM2=1
Day 2 Evening:	HivesPM2=2	ItchPM2=1

Day 3 Morning:	HivesAM3=3	ItchAM3=2
Day 3 Evening:	HivesPM3=0	ItchPM3=1

Day 4 Morning:	HivesAM4=0	ItchAM4=3
Day 4 Evening:	HivesPM4=2	ItchPM4=1

Day 5 Morning:	HivesAM5=3	ItchAM5=0
Day 5 Evening:	HivesPM5=1	ItchPM5=0

Day 6 Morning:	HivesAM6=1	ItchAM6=0
Day 6 Evening:	HivesPM6=0	ItchPM6=3

Day 7 Morning:	HivesAM7=2	ItchAM7=1
Day 7 Evening:	HivesPM7=3	ItchPM7=2

#### *General Formula:*

$$\text{Daily\_UAS1} = (\text{HivesAM1} + \text{HivesPM1})/2 + (\text{ItchAM1} + \text{ItchPM1})/2$$

$$\text{Daily\_UAS2} = (\text{HivesAM2} + \text{HivesPM2})/2 + (\text{ItchAM2} + \text{ItchPM2})/2$$

$$\text{Daily\_UAS3} = (\text{HivesAM3} + \text{HivesPM3})/2 + (\text{ItchAM3} + \text{ItchPM3})/2$$

$$\text{Daily\_UAS4} = (\text{HivesAM4} + \text{HivesPM4})/2 + (\text{ItchAM4} + \text{ItchPM4})/2$$

$$\text{Daily\_UAS5} = (\text{HivesAM5} + \text{HivesPM5})/2 + (\text{ItchAM5} + \text{ItchPM5})/2$$

$$\text{Daily\_UAS6} = (\text{HivesAM6} + \text{HivesPM6})/2 + (\text{ItchAM6} + \text{ItchPM6})/2$$

$$\text{Daily\_UAS7} = (\text{HivesAM7} + \text{HivesPM7})/2 + (\text{ItchAM7} + \text{ItchPM7})/2$$

$$\text{UAS7} = \text{DailyUAS1} + \text{DailyUAS2} + \text{DailyUAS3} + \text{DailyUAS4} + \text{DailyUAS5} + \text{DailyUAS6} + \text{DailyUAS7}$$

*Therefore, range of UAS7 is 0-42*

### EXAMPLE 1 Calculation

$$\begin{aligned}\text{Daily\_UAS1} &= (2 + 1)/2 + (3 + 0)/2 = 3 \\ \text{Daily\_UAS2} &= (3 + 2)/2 + (1 + 1)/2 = 3.5 \\ \text{Daily\_UAS3} &= (3 + 0)/2 + (2 + 1)/2 = 3 \\ \text{Daily\_UAS4} &= (0 + 2)/2 + (3 + 1)/2 = 3 \\ \text{Daily\_UAS5} &= (3 + 1)/2 + (0 + 0)/2 = 2 \\ \text{Daily\_UAS6} &= (1 + 0)/2 + (0 + 3)/2 = 2 \\ \text{Daily\_UAS7} &= (2 + 3)/2 + (1 + 2)/2 = 4\end{aligned}$$

$$\text{UAS7} = 3 + 3.5 + 3 + 3 + 2 + 2 + 4 = \mathbf{20.5}$$

### EXAMPLE 2

Day 1 Morning:	HivesAM1= Missing	ItchAM1=3
Day 1 Evening:	HivesPM1=1	ItchPM1=0
Day 2 Morning:	HivesAM2=Missing	ItchAM2=1
Day 2 Evening:	HivesPM2=Missing	ItchPM2=1
Day 3 Morning:	HivesAM3=Missing	ItchAM3=Missing
Day 3 Evening:	HivesPM3=0	ItchPM3=1
Day 4 Morning:	HivesAM4=Missing	ItchAM4=Missing
Day 4 Evening:	HivesPM4=2	ItchPM4=Missing
Day 5 Morning:	HivesAM5=3	ItchAM5=0
Day 5 Evening:	HivesPM5=1	ItchPM5=0
Day 6 Morning:	HivesAM6=1	ItchAM6=0
Day 6 Evening:	HivesPM6=0	ItchPM6=3
Day 7 Morning:	HivesAM7=2	ItchAM7=1
Day 7 Evening:	HivesPM7=3	ItchPM7=2

Daily\_UAS1 = ?

*Can we calculate a valid UAS score here? If so, what is it?*

*\*Answer: Yes we can but the daily hive score here will be 1 so the daily UAS1=1+(3+0)/2 = 2.5*

Daily\_UAS2 = ?

*Can we calculate a valid UAS score here? If so, what is it?*

*\*Answer: No we cannot because the daily hive score will be missing. So the Daily UAS2 = missing.*

Daily\_UAS3 = ?

*Can we calculate a valid UAS score here? If so, what is it?*

*\*Answer: Yes we can. The daily hive score will be 0 and the daily itch 1. So the daily UAS3=1.*

Daily\_UAS4 = ?

*Can we calculate a valid UAS score here? If so, what is it?*

*\*Answer: No we cannot because the daily itch will be missing. So Daily UAS4= missing.*

$$\text{Daily\_UAS5} = (3 + 1)/2 + (0 + 0)/2 = 2$$

$$\text{Daily\_UAS6} = (1 + 0)/2 + (0 + 3)/2 = 2$$

$$\text{Daily\_UAS7} = (2 + 3)/2 + (1 + 2)/2 = 4$$

$$\text{UAS7} = ((2.5 + 1 + 2 + 2 + 4)/5) \times 7 = 16.1$$

---

### **b) Weekly Itch Score**

The weekly itch score is the sum of the daily itch score over the last 7 days. The daily itch score, as described for the UAS7 above, calculated as the average of both 12-hour (AM/PM) itch scores within the same day.

### **c) Weekly Hive Score**

The weekly hive score is the sum of the daily hive score over the last 7 days. The daily hive score, as described for the UAS7 above, calculated as the average of both 12-hour (AM/PM) hives scores within the same day.

## **2. Weekly Angioedema Score**

The weekly angioedema score is the sum of “yes” responses to the following question over the last 7 days: “During the past 24 hours, did you have any rapid swelling on your face...?”

## **3. DLQI**

The first preliminary analysis will focus on the total DLQI score (domains will follow for final analysis) .

The score is calculated by summing the values of each of the 10 questions asked on the questionnaire. Thus, DLQOVR=Set to SUM(DLQI1, DLQI2,...DLQI10). If the “NOT DONE” box is checked on the crf page then set the whole score to missing for the visit.

Note:if DLQI1-DLQI10 value is missing or have value 98 then set their value to 0 before the sum. In other words, we will count missing questions as zeros before summing.

For this study, the likert scales need to start at 3 and descend to zero. Recoding may be necessary, depending on the raw data. So for DLQI1, it should be:

Over the last week, how itchy, sore, painful or stinging has your skin been:

Very much=3

A lot =2

A little=1

Not at all=0

\*\*As long as they are coded like this, the total score will fall in the range [0,30]. I noticed on the annotated crf that Very much=5, A lot=4, etc etc which would be incorrect to use in the summation.

#### **4. U-AIM**

This PRO was not analyzed in the first analysis.

To calculate the "U-AIM: UAS7 Proxy Score":

a) Sum questions 1 and 2 and add them together (at each visit).

a. For question 1 responses:

0 = None;

1= Mild;

2= Moderate;

3= Severe;

. = Missing.

b. For question 2 responses:

0 = None;

1= Between 1 and 6 hives;

2= Between 7 and 12 hives;

3= Greater than 12 hives;

. =Missing.

b) Multiple the sum of both responses by 7.

The resulting proxy score will be between 0 and 42.

If one or both responses are missing, the score cannot be calculated and will be missing.

#### **5. P-GIC and C-GIC**

These 2 PROs are simple frequencies at each timepoint. No further coding is required.

## 6. WPAI

There are 4 variables to derive, 3 related to the work component and an overall activity impairment score. First the Work-Impairment score, Second the overall Activity Score:

### Work-Impairment and overall Activity-Impairment

\*Calculate these at both baseline and endpoint. The analysis should be based on change from BL.

On the WPAI CRF page, question 1 will be called EMPLOY(YES OR NO). Question 2 is called Wrkhrm. Wrkhr will be the sum of questions 2-4. So Wrkhr is the number of hours someone usually works.

Question 5 is called WKPROD(should be between 0 and 10 on CRF). Question 6 is called REAGACT(should be between 0 and 10 on CRF).

So you can now derive the 4 variables of interest and summarize them accordingly.

```
/*#1- The % of work time missed due to ciu*/  
if employ NE 'YES' OR wrkhr<=0 or wrkhrm=. then PWRKMISS=.;  
else PWRKMISS= 100*(wrkhrm/wrkhr);  
  
/*#2-The % work impairment due to ciu*/  
if employ NE 'YES' OR WKPROD=. then PWRKIMP=.;  
else PWRKIMP=100*(WKPROD/10);  
  
/*#3-The % overall work impairment due to ciu*/  
POVWKIMP=PWRKMISS + (100-PWRKMISS)*(WKPROD/10);  
/*#4-The % of activity impairment due to ciu*/  
PACTIMP=100*(REAGACT/10);
```

In the end, the 4 variables to be summarized are PWRKMISS, PWRKIMP, POVWKIMP, and PACTIMP

## 7. In-Clinic Urticaria Activity Score (IC-UAS)(Max 6)

Here just add the 2 components together (Pruritus + Number of Hives). If either component is missing then make the score missing.

## 8. Insomnia Severity Index (ISI)

Add all seven items of the questionnaire to get a total score(range 0-28). In addition to the total score, please create a categorical variable at each visit based on the total score:

0-7=No clinically significant insomnia

>7-14=Subthreshold insomnia

>14-21=Clinical insomnia(moderate severity)

>21-28=Clinical insomnia(severe)

\*This PRO has specific missing data handling instructions. If there are one or two missing questions for a patient at a given visit, their missing values should be imputed with the average score of the remaining items. If there are more than two items with no response, make the total score missing.

## **9. GAD-7**

Add the 7 items together for a total score. In addition, we want to create a categorical variable from the total score:

0-4=Minimal

>4-9=Mild

>9-14=Moderate

>14-21=Severe

\*This PRO has specific missing data handling instructions, and are the same ones used above in the ISI. If there are one or two missing questions for a patient at a given visit, their missing values should be imputed with the average score of the remaining items. If there are more than two items with no response, make the total score missing.

## **10. Urticaria Control Test (UCT)**

The UCT is 4-item instrument, designed as a brief and easy-to-use tool; it may be utilized to assess urticarial control and to screen urticaria patients with poorly controlled disease (Weller et al. 2014).

The UCT consists of 4 questions with 5 responses, with responses scored from 0 to 4. A low score indicates high disease activity or poor disease control.

The UCT total score is the sum of the 4 questions and may range from 0 to 16. If data are missing for a patient, they will have their data excluded for the score.

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Statistical Analysis Plan (SAP) Module 1 Final Sign-Off Sheet

Study title:	XTEND-CIU (XOLAIR TREATMENT EFFICACY OF LONGER DURATION IN CHRONIC IDIOPATHIC URTICARIA): A PHASE IV, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OMALIZUMAB THROUGH 48 WEEKS IN PATIENTS WITH CHRONIC IDIOPATHIC URTICARIA		
Protocol #:	ML29510	DAP Version:	2.0
Authors:	[REDACTED]		
CRO Study Statistician:	[REDACTED]	Signature	26-May-2017 Date
Reviewers:	[REDACTED]		
CRO Peer Review Statistician	[REDACTED]	Signature	26-May-2017 Date
Approvers:	[REDACTED]		
Study Statistician :	[REDACTED]	Signature	May 26, 2017 Date
Associate Director, Biostatistics:	[REDACTED]	Signature	May 26, 2017 Date

\* The Biostatistics approver(s) has ensured that key team members have been involved, contributed and reviewed the content of the List of Planned Outputs as described in the SAP Module guideline.