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

NCT Number: NCT02392624

Document Dates: Protocol Version 2: 09-May-16

Protocol Version 1: 17-Dec-14

PROTOCOL

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
VERSION NUMBER:	2
EUDRACT NUMBER:	Not applicable
IND NUMBER:	101,612
TEST PRODUCT:	Omalizumab (RO5489789)
MEDICAL MONITOR:	[redacted] M.D., *M.S.*
SPONSOR:	Genentech, Inc.
DATE FINAL:	Version 1: 17 December 2014
DATE AMENDED:	Version 2: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Clinical Science Leader	09-May-2016 18:24:04

PROTOCOL AMENDMENT, VERSION 2:
RATIONALE

Changes to the protocol, along with a rationale for each change, are summarized below:

- The Medical Monitor has been changed to [redacted], M.D., M.S., and contact information has been updated (cover pages and Section 5.4.3).
- Text has been added to clarify that, in order to be eligible for treatment during the open-label period, patients cannot have any missing electronic diary (eDiary) entries in the 7 days prior to baseline. It was also clarified that if a patient fails screening due to missed eDiary entries during this period, the patient will be permitted to rescreen once (Section 3.1).
- In order to be eligible for randomization, the patient must achieve an Urticaria Activity Score over 7 days (UAS7) ≤ 6 in the final 2 weeks of the open-label treatment period, which has been clarified to be the 2 consecutive weeks immediately prior to randomization (instead of Weeks 23 and 24 specifically). These 2 weeks are still scheduled to occur during Weeks 23 and 24, but slight variation has been allowed to accommodate for patient scheduling. Furthermore, it has been clarified that randomization is not permitted after Day 190 from baseline (Sections 3.1 and 4.2; Appendices 1 and 2).
- All pharmacokinetic and pharmacodynamic (PD) assessments have been removed, with the exception of the PD assessment of total serum immunoglobulin E (IgE) level measured at screening (pre-dose), as all other assessments are no longer considered necessary for the study based on further review of the data (Sections 3.1, 3.4.4, 4.2, 4.5.4, and 6.6; Appendices 1, 2, and 3).
- It has been clarified that H1 antihistamine treatment permitted in this study must be non-sedating (Section 4.1.1). In addition, text has been added to state that, if more than one H1 antihistamine is used during the study, the combined total dose cannot exceed four times the approved dose of H1 antihistamines. Furthermore, the dosages of H1 antihistamines, H2 blockers, and leukotriene receptor antagonists should remain stable throughout the study (Section 4.4.1).
- The independent Data Monitoring Committee and the independent Data Coordinating Center have been removed, as an independent panel to adjudicate anaphylaxis events is no longer being used for the study. Instead, a single external adjudicator will be used. In addition, text has been added to clarify that, in order to minimize bias, study site personnel responsible for reconstituting and/or administering study drugs will not be permitted to conduct any safety or efficacy evaluations during or after the randomization period (Week 24 to Week 60), even if the patient has been transitioned back to open-label treatment (Sections 4.2, 4.6.3, and 5.1).
- The stipulation that patients who receive any excluded therapy after randomization will be discontinued from study treatment has been removed. This deletion has been made in order to minimize potential biases that could occur from removing patients from the study after randomization (Section 4.4.2).

- The window for the screening period has been extended from 14 to 20 days long instead of 12 to 18 days long. Additionally, it has been clarified that the Day −14 visit should be conducted 20 to 14 days prior to baseline (instead of 18 to 12 days prior to baseline) (Appendix 1).

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

PROTOCOL AMENDMENT, VERSION 2:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

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

SECTION 3.1: DESCRIPTION OF STUDY

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 ≥ 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 ≥ 8 during the 7 days prior to baseline.

… Patients will be eligible for randomization if they meet both of the following criteria:

- Achieve UAS7 ≤ 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 (UAS $7 = 0$ vs. UAS7 > 0) and study site. Efficacy~~,~~ *and* safety~~, pharmacokinetic (PK), and pharmacodynamic (PD)~~ 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.

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 (*~~the~~ Week 24 visit*)*, which will include ~~a blood draw for~~

~~PK/PD measurement, and~~ assessments for adverse events and PROs (see Appendix 1). Patients will not be required to complete the eDiary during this 12-week period.

After completion of the randomization period (end of Week 48), all patients will enter a 12-week follow-up period to allow for ~~further characterization of the pharmacokinetics and pharmacodynamics of omalizumab and~~ collection of additional efficacy and safety data. Patients will continue to visit the study site at 4-week intervals. ...

FIGURE 2: Study Schema

Figure 2 has been revised to reflect changes to the protocol.

SECTION 3.4.4: ~~Pharmacokinetic/~~Pharmacodynamic Outcome Measures~~**

~~Serum total omalizumab, and total~~*Total* ~~and free~~ *serum* IgE ~~concentrations~~*level* will be measured at *screening (pre-dose).*~~:~~

- ~~Baseline (pre-dose), Week 24 (pre-dose), Week 48, and Week 60 or early termination~~
- ~~The time of discontinuation from blinded treatment (i.e., start of open-label treatment post-randomization [pre-dose]), among patients who make the post-randomization transition to open-label omalizumab~~
- ~~The end of follow-up (i.e., 12 weeks after stopping the initial 24-week course of open-label omalizumab), among patients not responding to the initial 24-week course of open-label omalizumab~~

SECTION 4.1.1: Inclusion Criteria

- Diagnosis of CIU refractory to H1 antihistamines at baseline, as defined by all of the following:
  - Patients must have been on *a non-sedating* H1 antihistamine treatment *specified in Section* 4.4.1 (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.
- *For women who are not postmenopausal (≥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.*

SECTION 4.1.2: Exclusion Criteria

- *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.*

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

SECTION 4.2: METHOD OF TREATMENT ASSIGNMENT AND BLINDING

At the Week 24 visit, patients who completed the 24-week open-label treatment period and have met the criteria for response (UAS7 ≤6 ~~for both Weeks 23 and 24~~ *in the 2 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~~, the independent Data Monitoring Committee [iDMC] members, and the independent Data Coordinating Center [iDCC] personnel~~) will be blinded to treatment assignment. Only the IxRS provider~~,~~ *and* the Sponsor's unblinding statistician~~, and the iDCC statistician~~ will have access to the unblinding code during the study.

… To minimize the risk of potential bias, study site personnel who are responsible for reconstituting and/or administering study drugs will not be permitted to conduct any safety or efficacy evaluations *during or after the randomization period (Week 24 to Week 60), even if the patient has been transitioned back to open-label omalizumab*. Additionally, personnel administering study drug should apply bandages over injections sites to help maintain blinding. ~~To minimize risk of potential bias arising from access to laboratory results that could potentially unblind treatment assignments (e.g., free IgE levels and serum omalizumab concentrations), the Sponsor and sites will be restricted from accessing such laboratory results.~~

SECTION 4.4.1: <u>Permitted Therapy</u>

The long-acting H1 antihistamines, H2 blockers, and LTRAs allowed during the study are as follows. ~~Note that the~~ H1 antihistamines may be used at up to four times the approved dose listed below*; however, if more than one H1 antihistamine is used, the*

combined total dose cannot exceed four times an approved dose of H1 antihistamines. For example, a patient receiving loratadine 20 mg QD would be permitted to also receive cetirizine at up to 20 mg QD. The dosages of H1 antihistamines, H2 blockers, and LTRAs should remain stable throughout the duration of 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~~*study* (*Day –14 to Week 60*~~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.

SECTION 4.4.2: Prohibited Therapy

Patients who receive any excluded therapy during screening should be considered a screen failure. ~~Patients who receive any excluded therapy after randomization will be discontinued from study treatment; if a patient has received at least one dose of omalizumab following enrollment, the patient should enter the 12-week follow up period (see Appendix 2).~~

SECTION 4.5.5: Laboratory Assessments

Instruction manuals and supply kits will be provided for all central laboratory assessments. Please refer to the laboratory manual for additional details on central laboratory assessments and sample handling. The assessments listed below will be performed at a central laboratory or at Genentech:

- ~~PK assessments: serum total omalizumab~~
- PD assessment~~s~~: total serum IgE ~~and free serum IgE~~ level~~s~~ *at screening (pre-dose)*

SECTION 4.6.3: Study and Site Discontinuation

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

- ~~In addition, the Sponsor may decide to discontinue the study based on the iDMC recommendation.~~

SECTION 5.1: SAFETY PLAN

~~An iDMC will review blinded and unblinded safety data provided by an iDCC every 6 months for the duration of the study.~~

SECTION 5.4.3: Medical Contact

Genentech Medical Monitor:

[redacted], M.D.*, M.S.*

Genentech, Inc.

Telephone No.: [redacted]

SECTION 6.6: ~~PHARMACOKINETIC AND~~ PHARMACODYNAMIC ANALYS*I*~~E~~S

~~Serum total omalizumab, and t~~*T*otal ~~and free~~ *serum* IgE ~~concentration~~ *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). ~~Additional PK and PD analyses may be conducted as appropriate.~~

SECTION 7.1: DATA QUALITY ASSURANCE

Paper PRO questionnaires will be faxed*, scanned,* or couriered from the site to the data entry center. Scanned paper PROs will be transferred via a secure email system.

APPENDIX 1: Schedule of Assessments

Appendix 1 has been revised to reflect the changes to the protocol.

APPENDIX 2: Schedule of Assessments for Double-Blind Randomization Period and Follow-Up Period

Appendix 2 has been revised to reflect the changes to the protocol.

APPENDIX 3: Schedule of Assessments for Patients Who Transition to Open-Label Omalizumab After Randomization

Appendix 3 has been revised to reflect the changes to the protocol.

SAMPLE INFORMED CONSENT FORM

The sample Informed Consent Form has been revised to reflect the changes to the protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

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
VERSION NUMBER:	2
EUDRACT NUMBER:	Not applicable
IND NUMBER:	101,612
TEST PRODUCT:	Omalizumab (RO5489789)
MEDICAL MONITOR:	[redacted] M.D., *M.S.*
SPONSOR:	Genentech, Inc.

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by the CRO.

PROTOCOL SYNOPSIS

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
VERSION NUMBER:	2
EUDRACT NUMBER:	Not applicable
IND NUMBER:	101,612
TEST PRODUCT:	Omalizumab (RO5489789)
PHASE:	IV
INDICATION:	Chronic idiopathic urticaria
SPONSOR:	Genentech, Inc.

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) ≥ 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 ≥ 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 ≥ 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 UAS7 ≤ 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 (UAS $7 = 0$ vs. 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 UAS7 ≥ 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 UAS7 ≥ 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 ≥ 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 ≥ 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) ≥ 16 and itch component of UAS7 (range 0–21) ≥ 8 during 7 days prior to baseline
- IC-UAS ≥ 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 ≥ 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 (≥ 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 ≥ 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 ≥ 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

Pharmacodynamic Outcome Measure

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.

Pharmacodynamic Analysis

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 • 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.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartase transaminase
BID	twice per day
BUN	blood urea nitrogen
C-GIC	Clinician Global Impression of Change (scale)
CIU	chronic idiopathic urticaria
CRO	contract research organization
CSU	chronic spontaneous urticaria
DLQI	Dermatology Life Quality Index
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
eDiary	electronic diary (also referred to as the UPDD)
FcεRI	high-affinity IgE receptor
FDA	U.S. Food and Drug Administration
FSH	follicle-stimulating hormone
GAD-7	General Anxiety Disorder 7-Item (scale)
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
IC-UAS	in-clinic Urticaria Activity Score
ICH	International Conference on Harmonisation
IgE	immunoglobulin E
IgG	immunoglobulin G
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
ISI	Insomnia Severity Index
IVIG	intravenous immunoglobulin G
IxRS	interactive voice and web response system
LDH	lactate dehydrogenase
LPLV	last patient, last visit
LTRA	leukotriene receptor antagonist
MID	minimally important difference
mITT	modified intent-to-treat (principle)
P-GIC	Patient Global Impression of Change (scale)

Abbreviation	Definition
PD	pharmacodynamic
PRO	patient-reported outcome
Q4W	every 4 weeks
QD	once per day
QID	four times per day
RBC	red blood cell
RCR	Roche Clinical Repository
SAP	Statistical Analysis Plan
SC	subcutaneous
SWFI	Sterile Water for Injection
U-AIM	Urticaria Activity and Impact Measure
UAS	Urticaria Activity Score
UAS7	Urticaria Activity Score over 7 days
UCT	Urticaria Control Test
ULN	upper limit of normal
UPDD	Urticaria Patient Daily Diary
USPI	U.S. Package Insert
WBC	white blood cell
WPAI	Work Productivity and Activity Index

1. BACKGROUND

1.1 CHRONIC IDIOPATHIC URTICARIA

Chronic idiopathic urticaria (CIU; also referred to as chronic spontaneous urticaria [CSU]) is defined as the spontaneous occurrence of daily, or almost daily, hives and itching for at least 6 weeks without an obvious cause (Greaves 2003). The majority of patients with CIU achieve symptomatic control with conventional H1 antihistamine therapy. In some patients, CIU can be a debilitating condition because of a lack of clinical response as well as the unpredictable course of the disease, both of which can have a profound negative influence on the patient's quality of life (Tilles 2005).

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

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

1.2 OMALIZUMAB

Omalizumab (Xolair®) is a humanized anti-IgE recombinant monoclonal antibody approved to treat allergic asthma by inhibiting the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface-bound IgE on the FcεRI-expressing cells limits the degree of release of mediators in the allergic response. Omalizumab has been studied for safety and efficacy in over 5000 adult and adolescent (≥ 12 years of age) patients with moderate to severe asthma, and more recently, in patients with CIU. Omalizumab was approved by the U.S. Food and Drug Administration (FDA) for CIU in March 2014. More than 60,000 patients have been treated with omalizumab worldwide.

There are two hypotheses for the mechanism of action of omalizumab in patients with CIU. One hypothesis is that the density of IgE receptors at the surface of mast cells and basophils is proportional to the plasma IgE level. Lowering free IgE to near undetectable

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

Omalizumab is indicated for the treatment of adults and adolescents (12 years of age and above) with CIU who remain symptomatic despite H1 antihistamine treatment. The FDA-approved dose for patients with CIU is 150 or 300 mg administered by subcutaneous (SC) injection every 4 weeks (Q4W).

1.2.1 Clinical Experience with Omalizumab in Patients with CIU

The Phase III clinical program for omalizumab consisted of three studies:

- **Study Q4881g** (ASTERIA I; Saini et al. 2014) and **Study Q4882g** (ASTERIA II; Maurer et al. 2013) evaluated patients with CIU who were refractory to H1 antihistamines at approved doses.
- **Study Q4883g** (GLACIAL; Kaplan et al. 2013) evaluated patients with CIU who were refractory to H1 antihistamines at up to four times approved doses, H2 blockers, and/or leukotriene receptor antagonists (LTRAs).

Studies Q4881g and Q4882g were both global, Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy and safety of omalizumab, administered SC Q4W as add-on therapy for the treatment of adolescent and adult patients (12–75 years of age) with CIU refractory to conventional H1 antihistamines, as demonstrated by: the presence of itch and hives for ≥8 consecutive weeks at any time prior to enrollment, Urticaria Activity Score (UAS) over 7 days (UAS7) confirming uncontrolled symptoms prior to randomization, and a CIU diagnosis for ≥6 months. The studies evaluated the comparative efficacy between three doses of omalizumab (75 mg, 150 mg, and 300 mg) and placebo as well as the time to onset of clinical effect for patients with CIU who remained symptomatic despite treatment with approved doses of H1 antihistamine therapy. The 150-mg dose, which was not studied in the Phase II study (Q4577g; Saini et al. 2011), was included as an intermediate between the 75- and 300-mg dose in order to better define the dose response. The inclusion of the 75-mg dose served to characterize the lower end of the dose response after multiple doses, since only a single dose was tested in Study Q4577g.

Studies Q4481g and Q4882g differed in duration of treatment (24 weeks compared to 12 weeks for Studies Q4881g and Q4882g, respectively). The primary efficacy outcome measure was change from baseline in weekly itch score (a component of the UAS7) at Week 12. In total, 319 patients were randomized from 53 centers globally, and 323 patients were randomized from 55 centers globally in Studies Q4881g and Q4882g, respectively.

Study Q4883g was a global Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of omalizumab 300 mg administered SC Q4W as an add-on therapy for the treatment of adolescent and adult patients (12–75 years of age) who have been diagnosed with CIU who remain symptomatic despite H1 antihistamine treatment doses up to four times above the approved dose, H2 blockers, and/or LTRAs. The duration of treatment for Study Q4883g was 24 weeks. The primary safety outcome measure was the incidence and severity of adverse events and serious adverse events. Efficacy, a secondary objective, was measured in a similar manner as Studies Q4881g and Q4882g. In total, 336 patients were randomized from 65 centers globally.

1.2.2 Summary of Omalizumab Clinical Efficacy in Patients with CIU

Consistent treatment effects were observed in all omalizumab-treated groups across all three pivotal studies (Q4881g, Q4882g, and Q4883g), similar to that noted in the Phase II dose-ranging study (Q4577g) (Saini et al. 2011; Kaplan et al. 2013; Maurer et al. 2013; Saini et al. 2014).

Both the 150-mg and 300-mg groups met the primary efficacy endpoint of change from baseline to Week 12 in weekly itch score in all three pivotal studies (in Study Q4883g, only the 300-mg dose was studied), supporting the use of omalizumab for the treatment of adults and adolescents (12 years of age and above) with CIU who remain symptomatic despite H1 antihistamine treatment. For the 300-mg group, the mean change from baseline in weekly itch score at Week 12 showed statistically significant improvements compared with placebo (–9.4 vs. –3.6, –9.8 vs. –5.1, and –8.6 vs. –4.0 for Studies Q4881g, Q4882g, and Q4883g, respectively). The 75-mg group met the primary endpoint in Study Q4881g only.

Studies Q4881g and Q4882g showed consistent evidence of a dose response with the 300-mg dose demonstrating greater therapeutic benefit relative to 150 mg for the primary endpoint (formal statistical comparisons were not performed between omalizumab groups).

At the 300-mg dose, the proportion of patients achieving a therapeutic response at Week 12 (secondary efficacy endpoint) was as follows: 52%, 66%, and 52% with UAS7 $\leq$ 6; and 36%, 44%, and 24% with UAS7 = 0 for Studies Q4881g, Q4882g, and Q4883g, respectively. In addition, the proportion of patients at the 300-mg dose

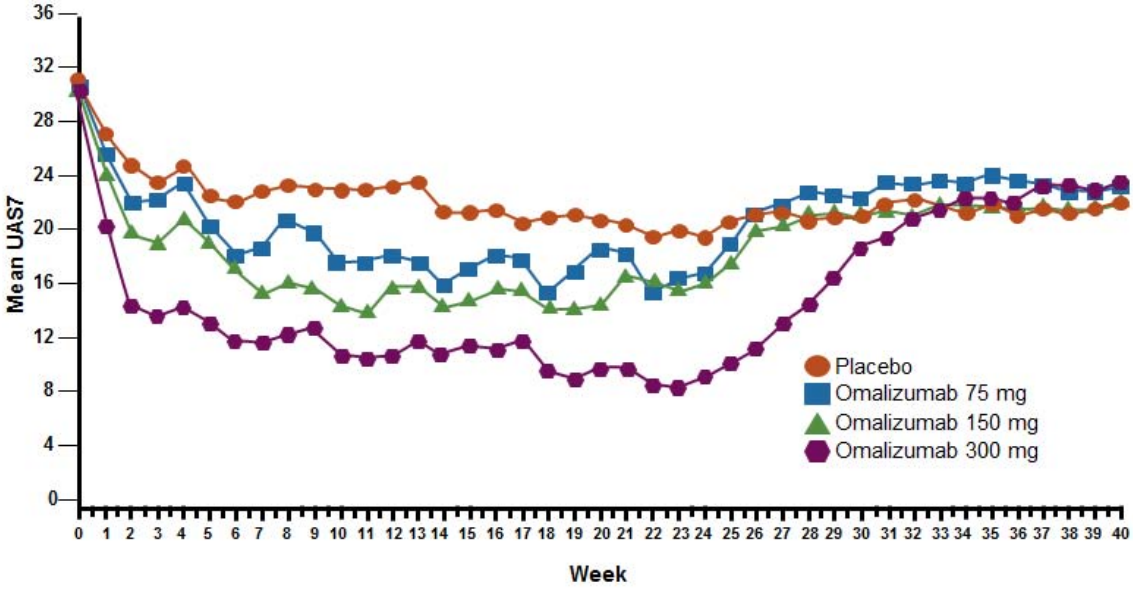
achieving UAS7 ≤6 at both Weeks 23 and 24 was 67.6% and 65.5% for Studies Q4881g and Q4883g, respectively.

As noted in Studies Q4881g and Q4883g, the decreases in mean weekly itch score and UAS7 with omalizumab treatment at Week 12 were maintained for up to 24 weeks of treatment suggesting there was no tolerance or tachyphylaxis to prolonged omalizumab dosing.

After cessation of treatment, mean weekly itch score and UAS7 increased to reach values similar to the placebo group mean values, but did not return to baseline values for the duration of the 16-week follow-up period in any of the omalizumab treatment groups in all three pivotal studies. The mean weekly itch score and UAS7 in the 300-mg group appeared to take longer to reach a similar level to that in the placebo group than was the case for lower omalizumab doses. This suggests a longer lasting effect of the 300-mg dose.

Figure 1 shows UAS7 scores over time in Study Q4881g (ASTERIA I), where the duration of potential omalizumab therapy was 24 weeks (Saini et al. 2014; Genentech data on file). Study Q4883g (GLACIAL) showed a similar pattern of return to placebo group mean after the 24-week omalizumab treatment period (Kaplan et al. 2013).

Figure 1 Change from Baseline in Mean UAS7: Study Q4881g (ASTERIA I; Placebo versus 24 Weeks Omalizumab)



UAS7 = Urticaria Activity Score over 7 days.

1.2.3 Summary of Omalizumab Clinical Safety in Patients with CIU

The overall safety profile of omalizumab in patients with CIU, across all four studies comprising the clinical development program (Q4577g, Q4881g, Q4882g, and Q4883g), revealed no unexpected safety signals or concerns different than the known safety profile of omalizumab in patients with allergic asthma (Saini et al. 2011; Kaplan et al. 2013; Maurer et al. 2013; Saini et al. 2014).

Few serious adverse events were reported (<2% of patients reported serious adverse events during the 12-week treatment period and <4% during the 24-week treatment period) and no deaths were observed in any of the studies. The most frequent adverse events demonstrating imbalances were common conditions such as nasopharyngitis, headache, and sinusitis. The safety profile was similar between 12 weeks and 24 weeks. In general, the majority of adverse events were mild or moderate in intensity. Overall, omalizumab was well tolerated with few adverse events leading to study discontinuation (<2%) or withdrawal of treatment (<4%) during the study period. A treatment comparison of the main safety endpoints over the entire study period for all three Phase III studies pooled showed no major differences in the safety profile between the 150- and 300-mg groups. Treatment differences indicating greater risk in omalizumab-treated patients were small and associated with a higher level of uncertainty. Those differences that were observed were expected given the known safety profile of omalizumab in allergic asthma. Specifically, a dose-dependent increase in suspected adverse events was observed for injection site reactions, which has been previously described (Xolair U.S. Package Insert 2014). Such reactions were infrequent, occurring in <3% of patients among those treated at the higher 300-mg dose, and none were considered severe. Although an imbalance in hypersensitivity events for the 300-mg dose group was observed over the entire study, this imbalance was not observed during either the 12- or 24-week treatment period. For the majority of patients suffering from moderate to severe CIU, the benefit of treatment with omalizumab would likely outweigh these risks.

See the Omalizumab Investigator's Brochure for additional details on clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

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.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

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

2.2 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

2.3 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

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a Phase IV, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of 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 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 UAS ≥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 ≥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 ≥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 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 UAS7 ≤ 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 (UAS $7 = 0$ vs. 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 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 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.

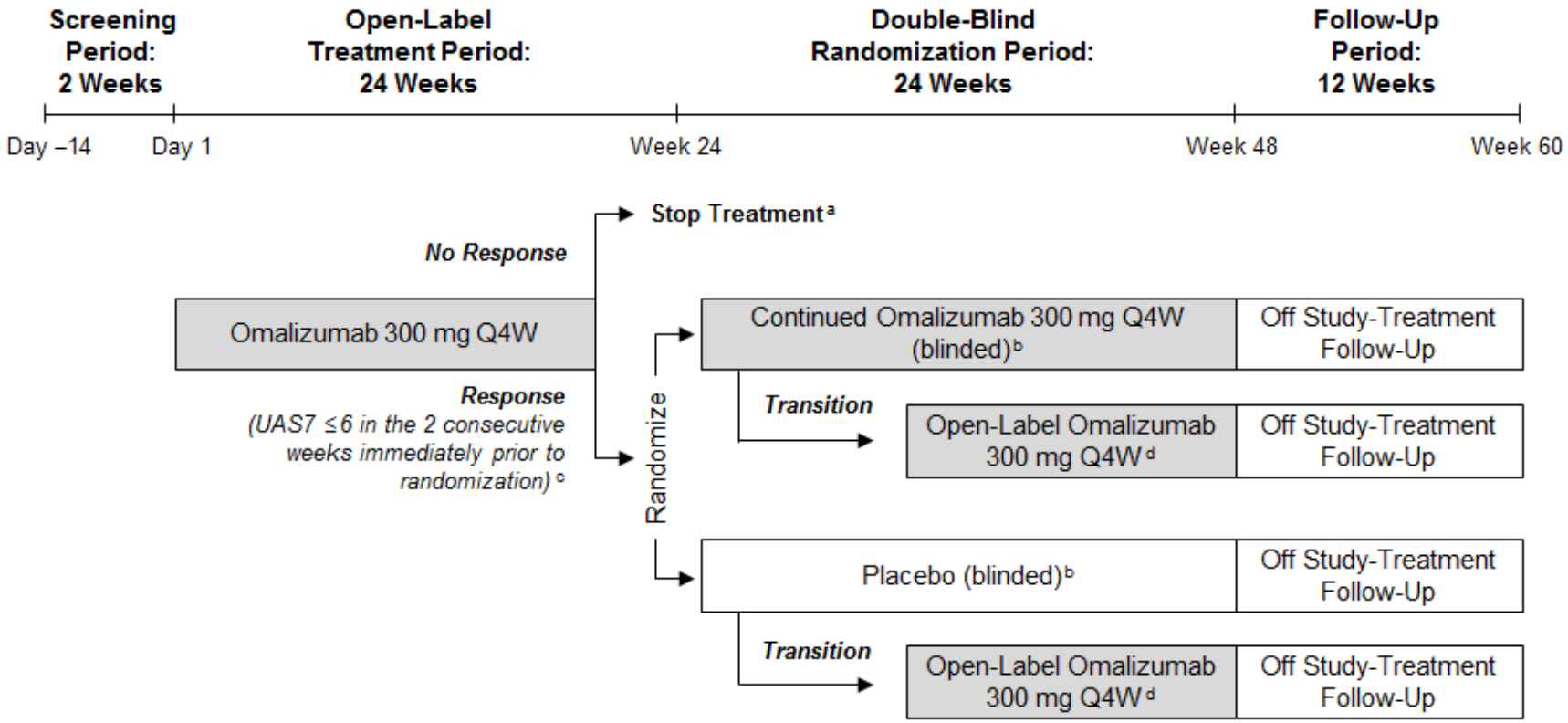
The primary endpoint for this study is the percentage of patients who experience clinical worsening in CIU defined as UAS7 $\geq$12 for at least 2 consecutive weeks.

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.

Figure 2 Study Schema



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

[a] 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 assessments for adverse events and PROs (see Appendix 1). Patients will not be required to complete the eDiary during this 12-week period.

[b] At Week 24, patients will be randomized 3:2 (omalizumab:placebo).

[c] *The final two weeks of the open-label treatment period are scheduled to occur during Weeks 23 and 24 but may vary somewhat depending on patient scheduling. Randomization will not be permitted after Day 190 from baseline.*

Figure 2 Study Schema (cont.)

[d] 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.

3.2 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.

3.3 RATIONALE FOR STUDY DESIGN

The pivotal studies demonstrated efficacy and safety of omalizumab through 24 weeks of treatment. Efficacy and safety beyond 24 weeks of treatment was not examined, as will be addressed in this study. Because of the previously demonstrated efficacy through 24 weeks, this study will begin with an initial 24-week open-label treatment period before any possibility of randomization to placebo.

The primary outcome of this study is clinical worsening in CIU as assessed by UAS7. The specific threshold for clinical worsening in CIU symptoms is UAS7 $\geq$12, maintained for at least 2 consecutive weeks. The threshold of UAS7 $\geq$12 (lower than the inclusion criteria of UAS7 $\geq$16) was chosen to allow patients to restart omalizumab at a lower threshold than that required to initiate omalizumab for the first time. Based on advisor input, this is believed to mirror general clinical practice for reinitiating therapies after withdrawal. Moreover, a requirement for patients to return to their baseline prior to reinitiating therapy is believed to be unreasonable, especially in the context of prior control established by omalizumab. The specific threshold of UAS7 $\geq$12 was chosen because of the precedent established in the CIU Phase II study in which this was used as an inclusion criterion (Saini et al. 2011). Additionally, all patients who are randomized will have a UAS7 $\leq$6 at time of randomization; therefore, a UAS7 $\geq$12 would confirm that the UAS7 score has at least doubled since randomization, representing an intuitive clinical threshold for reinitiating omalizumab. The secondary outcome of this study will also assess time to clinical worsening as well as the level of control of CIU symptoms assessed by whether or not patients maintain UAS7 $\leq$6 during the randomization period (Week 24 to Week 48). Separately, patients who have demonstrated a UAS7 $\geq$12 (maintained for at least 2 consecutive weeks), who are also clinically assessed as having worsening CIU warranting a transition to open-label omalizumab, will be offered such a transition to ensure that patients do not remain symptomatic for an undue period of time.

The inclusion and exclusion criteria for this study allow for up to four times the approved doses of H1 antihistamines, as well as H2 blockers and/or LTRAs. These inclusion/exclusion criteria reflect the reality that such medications are often used at these doses before advancing therapy to omalizumab, as discussed in practice parameters and guidelines (Bernstein et al. 2014; Zuberbier et al. 2014).

This study examines several secondary and exploratory endpoints, including PRO measures. The PRO instruments used in this study include those used in the pivotal trial data (e.g., Dermatology Life Quality Index [DLQI]) as well as new PROs, such as anxiety

symptoms and work productivity that may be related to CIU and response to therapy. In addition, this study will examine the validity of intermittently assessed PROs, such as the Urticaria Control Test (UCT) and Urticaria Activity and Impact Measure (U-AIM), compared with the twice daily eDiary device, in providing a clinical evaluation of patients with CIU.

3.3.1 Omalizumab Dose and Schedule

The FDA-approved dose for patients with CIU is 150 or 300 mg SC Q4W. In this CIU Phase IV study, only the 300-mg dose will be examined. The 300-mg dose was the only dosage to meet both the primary outcome as well as all secondary outcomes in both pivotal efficacy studies (Q4881g and Q4882g). Additionally, as shown in Figure 1, the average efficacy observed was numerically better with the 300-mg dose than for other doses. Also, relapse to mean placebo values after cessation of the 300-mg dose of omalizumab took longer, on average, than after other doses of omalizumab.

3.4 OUTCOME MEASURES

3.4.1 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.

3.4.2 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 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

3.4.3 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

3.4.4 Pharmacodynamic Outcome Measure

Total serum IgE *level* will be measured at *screening (pre-dose).*

3.4.5 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 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
- 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
- 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

4. MATERIALS AND METHODS

4.1 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.

4.1.1 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 ≥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) ≥16 and itch component of UAS7 (range 0–21) ≥ 8 during 7 days prior to baseline
  - IC-UAS ≥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* 4.4.1 (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 ≥ 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 (≥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.*

4.1.2 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
- 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.*

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

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 2 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.

A pharmacist or other qualified individual designated by the study site will prepare and administer the study drug as outlined in Section 4.3.2 and Appendix 4. While blinded treatment kits will be used during the randomization phase of the study (Week 24 to Week 48), and because of potential differences in the viscosity of the omalizumab and placebo preparations, unblinding of the study site personnel responsible for reconstituting and/or administering study drug is possible. To minimize the risk of potential bias, study site personnel who are responsible for reconstituting and/or administering study drugs will not be permitted to conduct any safety or efficacy evaluations *during or after the randomization period (Week 24 to Week 60), even if the patient has been transitioned back to open-label omalizumab*. Additionally, personnel

administering study drug should apply bandages over injections sites to help maintain blinding.

4.3 STUDY TREATMENT

4.3.1 Formulation

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.

Placebo

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

4.3.2 Dosage, Administration, and Storage

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. For details regarding study drug preparation and administration, and the study drug dosing schedule, please refer to Appendix 4 and Appendix 5, respectively.

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

The reconstituted vial is to be used for single-dose administration only. Study drug will be administered SC to patients in the deltoid region of the right or left arm. Alternatively, the injections can be administered in the thigh if medically significant reasons preclude administration in the deltoid region.

Prior to randomization, during the initial open-label treatment period, study drug will be administered open-label as known omalizumab. After randomization, subjects will be assigned to either active or placebo medication. As described in Section 3.1, certain patients meeting prespecified criteria may, at the discretion of the investigator, be transitioned to open-label omalizumab.

Study drug must be stored in refrigerated conditions (2°C–8°C; 36°F–46°F) in a limited access area and/or a locked refrigerator. Study drug should be stored according to the storage instructions on the box immediately upon receipt but no later than 24 hours after receipt.

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

Patients should be closely observed after administration of open-label omalizumab and blinded study drug for signs and symptoms of anaphylaxis. This observation should be for a period of time that is judged to be appropriate by the investigator. In addition, the study staff should be prepared to manage anaphylaxis. Patients should also be informed of the signs and symptoms of anaphylaxis and be instructed to seek immediate care should symptoms occur.

Guidelines for treatment interruption or discontinuation are provided in Section 5.1.3.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. See Section 5.3.5.11 for guidance on adverse events associated with an overdose.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (omalizumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

4.3.4 Post-Trial Access to Omalizumab

The Sponsor (Genentech) may offer continued access to the study drug after study completion, in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

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

The long-acting H1 antihistamines, H2 blockers, and LTRAs allowed during the study are as follows. H1 antihistamines may be used at up to four times the approved dose listed below*; however, if more than one H1 antihistamine is used, the combined total dose cannot exceed four times an approved dose of H1 antihistamines. For example, a patient receiving loratadine 20 mg QD would be permitted to also receive cetirizine at up to 20 mg QD. The dosages of H1 antihistamines, H2 blockers, and LTRAs should remain stable throughout the duration of the study.*

- H1 antihistamines
  - Cetirizine 5 or 10 mg once per day (QD)
  - Levocetirizine dihydrochloride 2.5 or 5 mg QD
  - Fexofenadine 60 mg twice per day (BID), or 180 mg QD
  - Loratadine 10 mg QD
  - Desloratadine 5 mg QD
- H2 blockers
  - Cimetidine 800 mg BID, or 400 mg four times per day (QID)
  - Famotidine 40 mg QD, or 20 mg QD or BID
  - Nizatidine 150 mg QD
  - Ranitadine 150 mg BID
- LTRAs
  - Montelukast 10 mg QD

- Zafirlukast 20 mg BID

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 *study* (*Day –14 to Week 60*). Diphenhydramine (25 mg) may also be used on an as-needed basis (maximum three times/day) during the screening, treatment, and follow-up periods.

4.4.2 Prohibited Therapy

The following medications and treatments will be restricted as specified below:

- Routine (daily or every other day during 5 or more consecutive days) doses of the following medications within 30 days prior to Day –14 and during the study period (baseline to Week 60): systemic corticosteroids, hydroxychloroquine, methotrexate, mycophenolate, cyclosporine, or cyclophosphamide. Additionally, during the study period (baseline to Week 60), prohibited routine usage also includes usage for greater than 10 total days during any 30-day period.
  - Note: inhaled asthma controllers, including inhaled corticosteroids, are permitted during the study.
- Routine (daily or every other day during 5 or more consecutive days) doses of doxepin within 14 days prior to Day –14 and during the study period (baseline to Week 60)
- Omalizumab within 1 year prior to screening and during the study period (baseline to Week 60), except as provided by this study
- Either IVIG or plasmapheresis within 30 days prior to Day –14 and during the study period (baseline to Week 60)

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

4.5 STUDY ASSESSMENTS

Please see Appendix 1, Appendix 2, and Appendix 3 for the schedule of assessments performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent from the patient or a legally authorized representative, and patient assent, if applicable, for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log

to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

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. In addition, the following specific medications used by the patient within 1 year prior to the screening visit will be collected: systemic corticosteroids, cutaneous (topical) corticosteroids, hydroxychloroquine, methotrexate, cyclosporine, and cyclophosphamide.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Vital Signs

Vital signs include measurements of pulse, and systolic and diastolic blood pressure while the patient is in a seated position.

4.5.4 Physical Examinations

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.

During the study, changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.5 Laboratory Assessments

All blood draws should be performed prior to study drug administration.

The following laboratory tests will be performed at the study site's local laboratory:

- Stool ova and parasite evaluation: This test should be conducted in patients who have risk factors for parasitic disease (e.g., living in an endemic area, travel to an endemic area within the last 6 months, chronic GI symptoms, or chronic immunosuppression) AND an eosinophil count >2 times the ULN. This test should be conducted anytime during the screening period after the Day -14 results are available for applicable patients.
- Urine pregnancy test: 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.

Instruction manuals and supply kits will be provided for all central laboratory assessments. Please refer to the laboratory manual for additional details on central laboratory assessments and sample handling. The assessments listed below will be performed at a central laboratory or at Genentech:

- Hematology: hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, white blood cell (WBC) count, percent and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells)
- Serum chemistries: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, alanine transaminase (ALT), aspartase transaminase (AST), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), creatine phosphokinase, and uric acid
- Serum pregnancy test: If a local urine pregnancy test shows a positive result, then the result must be confirmed by a serum pregnancy test (performed by central laboratory).
- Urinalysis: dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- PD assessment: total serum IgE level *at screening (pre-dose)*
- Blood RNA for exploratory research (see Section 4.5.6)
- Blood samples for biomarker and biochemical analyses for exploratory research (see Section 4.5.6)

4.5.6 Exploratory Blood RNA and Blood Biomarker Samples

Blood samples for biomarkers and biochemical analyses will be collected from all patients at selected visits and stored for exploratory research and markers of drug response.

Optional blood RNA samples will be collected from those patients who specifically consent to this optional collection. These samples will be stored for future exploratory research.

4.5.7 Patient eDiary

The patient eDiary (see Appendix 6), also referred to as the Urticaria Patient Daily Diary (UPDD), consists of questions (with specific recall periods) about the following: itch severity (12 hours, twice daily), number of hives (12 hours, twice daily), largest hive size (12 hours, twice daily), sleep interference (24 hours), daily activity interference (24 hours), diphenhydramine use (24 hours), and the occurrence of angioedema (24 hours). In addition, management of angioedema occurrences (24 hours) and calls to

a doctor, nurse, or nurse practitioner because of CIU (24 hours) will be recorded. The eDiary will be given to each patient at the Day −14 visit.

Patients will be instructed to complete the eDiary twice a day for the entire duration of the study, beginning at Day −14. Patients should be encouraged to make every effort to stay current with their eDiary entries, even when travelling or in a location where data reception connectivity will not allow daily transfer of eDiary entries to the central server. When data reception connectivity is not available, data entries will be stored locally on the eDiary device and transferred at the time that such connectivity becomes available.

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

4.5.8 Patient-Reported Outcomes

The following PRO instruments will be administered as specified in Appendix 1, Appendix 2, and Appendix 3:

- Dermatology Life Quality Index (DLQI)

  The DLQI (see Appendix 7) is a 10-item dermatology-specific health-related quality of life measure (Finlay and Khan 1994). Patients rate their dermatology symptoms and the impact of their skin condition on various aspects of their health-related quality of life. An overall score will be calculated as well as separate scores for the following domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The minimally important difference (MID) of overall DLQI score for patients with CIU is estimated at 2.24–3.10 (Shikiar et al. 2005).

- Urticaria Control Test (UCT)

  The UCT (see Appendix 8) 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 questionnaire has a 4-week recall period. Low scores indicate poorly controlled urticaria. The developers recommended a value of 12 for controlled disease (i.e., all patients exhibiting UCT values of ≤11 are considered to have poorly controlled disease).

- Urticaria Activity and Impact Measure (U-AIM)

  The U-AIM (see Appendix 9) is a 9-item instrument designed to assess the patient's urticaria activity and impact during the past 7 days (Genentech data on file). The questionnaire asks about the severity of the CIU symptoms (itch, hives, and angioedema) and how much these symptoms bothered the patient. It also inquires about how much CIU symptoms interfered with the patient's daily activities and sleep. It concludes by asking the patient to rate the extent to which their urticaria was under control.

- Insomnia Severity Index (ISI)

  The ISI (see Appendix 10) is a 7-item questionnaire measuring self-perceptions of insomnia symptoms and the impact of these symptoms on patient health and daily life (Morin 1993). It encompasses sleep onset, sleep maintenance, awakening, sleep pattern satisfaction, interference with daily functioning, noticeability of sleep problem to others, and distress caused by sleep problem. The total score ranges from 0–28 points (higher scores indicate greater insomnia severity). The developers provided the following guidance to the score interpretation; however, this guidance needs further empirical validation: 0–7 = no clinically significant insomnia, 8–14 = sub-threshold insomnia, 15–21 = clinical insomnia (moderate severity), and 22–28 = clinical insomnia (severe). The recommended MID for ISI score is 6 (Bastien 2001; Yang et al. 2009).

- Generalized Anxiety Disorder 7-Item (GAD-7) scale

  The GAD-7 scale (see Appendix 11) is a 7-item questionnaire with good reliability as well as criterion, construct, factorial, and procedural validity. The total score ranges from 0–21, with higher scores indicating greater anxiety. Cut points of 5, 10, and 15 might be interpreted as representing mild, moderate, and severe levels of anxiety, respectively (Spitzer et al. 2006).

- Work Productivity and Activity Index (WPAI)

  The WPAI (see Appendix 12) is a 6-item questionnaire that measures four domains of health-related quality of life associated with reduced productivity: absenteeism, presenteeism, work productivity loss, and activity impairment. The absenteeism is assessed as a percentage of total work time that a patient missed due to a health problem. The presenteeism is evaluated as the extent to which a health problem affected patient's productivity while working. The total productivity loss is the product of absenteeism and presenteeism combined. The impact on activities of daily living represents to what extent a health problem affected the patient's activities of daily living outside of work. The scores are generated as percentages for each of the abovementioned domains, with higher scores indicating more productivity problems associated with the health state (Reilly et al. 1993).

- Patient Global Impression of Change (P-GIC) scale

The P-GIC (see Appendix 13) is a one-item scale asking patients to rate the change in their CIU they experienced since the beginning of the study (Genentech data on file). The questionnaire is intended to understand how patients subjectively perceive the change in their CIU.

Adverse event reports will not be derived from PRO data by the Sponsor. However, any PRO responses suggestive of a possible adverse event that are identified during site review of the PRO data should be reported as outlined in Section 5.3.5.

4.5.9 Clinician-Reported Outcomes

- In-Clinic Measured Urticaria Activity Score (IC-UAS)

  The IC-UAS (see Appendix 14) is a paper-based, in-clinic measured UAS based on the patient's condition during the 12 hours prior to the visit. This score will be recorded every 4 weeks as outlined in the schedule of assessments (see Appendix 1, Appendix 2, and Appendix 3). The IC-UAS should be completed by a healthcare professional based on an interview of the patient.

  The IC-UAS is a composite score with numeric severity intensity ratings (0 = none to 3 = intense/severe) for the number of wheals (hives) and the severity of the itch. The maximum IC-UAS value is 6.

- Clinician Global Impression of Change (C-GIC) scale

  The C-GIC (see Appendix 15) is a one-item scale asking clinicians to rate the change in the patient's CIU since the beginning of the study (Genentech data on file). The questionnaire is intended to understand how clinicians subjectively perceive the change in the patient's CIU.

4.5.10 Samples for Roche Clinical Repository

Genentech is a member of the Roche group and participates in the collection and/or submission of biological samples to the Roche Clinical Repository (RCR). Collection and submission of biological samples to the RCR is contingent upon the review and approval of the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site is not granted the necessary approval for RCR sampling, this section of the protocol will not be applicable at that site.

4.5.10.1 Overview of the Roche Clinical Repository

The RCR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression

- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.10.2 Sample Collection

The following samples will be collected and stored in the RCR for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers related to omalizumab or CIU:

- Blood for biomarker and biochemical analyses (required for patients consenting to participate in this study)
- Blood for RNA extraction (optional)
- Remaining blood samples from study-related procedures (optional)

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

4.5.10.3 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is “double-coded” by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A “linking key” between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

4.5.10.4 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate in the study ML29510. Patients may also withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional blood RNA samples and remaining blood samples from study-related procedures for storage in the RCR. Patients who decline to participate in the collection of these optional samples will not provide a separate signature. A separate, specific signature is not required for submission of blood for biomarker and biochemical analyses to the RCR.

The investigator should document whether or not the patient has given consent to participate in optional blood RNA samples and remaining blood samples from study-related procedures for storage in the RCR by completing the appropriate section of the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.10.5 Withdrawal from the Roche Clinical Repository

Patients have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date

of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study ML29510 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study ML29510.

4.5.10.6 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

4.6.3 Study and Site Discontinuation

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

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.

- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Omalizumab (Xolair) is currently registered in over 90 countries and is indicated for adults and children (6 years of age and above in the E.U.) with moderate to severe persistent allergic asthma whose symptoms are inadequately controlled with inhaled corticosteroids.

As of 30 June 2014, Xolair is currently registered in over 40 countries, including the U.S., for adults and adolescents (12 years of age and above) with chronic spontaneous (idiopathic) urticaria refractory to standard of care. Consult local prescribing information for more information.

The adverse event profile of omalizumab observed during the allergic asthma clinical development program was very similar to placebo with the most commonly reported adverse reactions were injection site reactions, including injection site pain, swelling, erythema, pruritus, and headaches.

Of the adverse events of special interest, anaphylactic reactions were observed but were rare and typically occurring within 2 hours of the first injection.

Although a numerical imbalance in malignancy was observed in the omalizumab treatment group compared with the control group, the short exposure duration is not consistent with the biology of solid organ pathogenesis; additionally, the diversity in the type of cancers observed and the clinical features of the individual cases render a causal relationship unlikely.

The overall adverse event profile in the pooled Phase III CSU studies was consistent with the known safety profile of omalizumab in patients with allergic asthma, with the exception of adverse events that were specifically related to the respective indications.

The overall incidence of adverse events across the omalizumab treatment groups was broadly similar to that seen with placebo. In general, omalizumab at the proposed doses of 150 mg and 300 mg was well tolerated in the treatment of patients with severe, refractory CSU/CIU, including in patients with multiple concomitant medications. Both doses appeared to be well tolerated, with no evidence of dose-related adverse events. Injection site reactions are a known side effect of omalizumab treatment, and those observed in CSU/CIU patients were consistent with those observed in allergic asthma. There were no subsets of patients identified who had increased risks of serious adverse events or adverse events of special interest.

During the conduct of the study, a treatment assignment may be unblinded only in the event of a life-threatening medical emergency that requires immediate unblinding/unmasking. In such cases, unblinding will be implemented following standard procedures, and only following agreement by both the investigator and Medical Monitor that unblinding is necessary.

The Sponsor Safety Reporting Department (independent from the study team) will break the treatment code for all unexpected serious adverse events that are considered by the investigator to be related to study drug for the purpose of regulatory reporting. The study team will remain blinded to study treatment.

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 will be closely monitored and represent selected adverse events for this study.

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

5.1.1 Anaphylaxis

Anaphylaxis has been reported to occur after administration of omalizumab in premarketing clinical trials and in postmarketing spontaneous reports. Signs and symptoms in these reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been life-threatening. In premarketing clinical trials in patients with asthma, anaphylaxis was reported in 3 of 3507 (0.1%) patients.

In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to omalizumab use was estimated to be at least 0.2% of patients based on an estimated

exposure of about 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as early as after the first dose of omalizumab, but also has occurred beyond 1 year after beginning regularly scheduled treatment.

The analysis of all cases of anaphylaxis submitted to Novartis show that, the majority of anaphylactic-type reactions have been reported to occur after the first dose with numbers decreasing with subsequent doses. As expected for an anaphylactic-type reaction (Type I), events were reported to occur predominantly within the first 2 hours post-dosing with few reports occurring as far as >36 hours post-dose.

Warning

Because of the risk of anaphylaxis, patients should be closely observed for an appropriate period of time after omalizumab administration, and healthcare providers administering omalizumab should be prepared to manage anaphylaxis that can be life-threatening. Patients should also be informed of the signs and symptoms of anaphylaxis and instructed to seek immediate medical care should symptoms occur.

Please refer to the Omalizumab Investigator's Brochure for additional information.

5.1.2 Clinical Trial Experience with Omalizumab in Patients with CIU

The safety of omalizumab for the treatment of CIU was assessed in three placebo-controlled, multiple-dose clinical trials of 12 weeks (CIU Trial 2) and 24 weeks in duration (CIU Trials 1 and 3). The data described in Table 2 below reflect omalizumab exposure for 733 patients enrolled and receiving at least one dose of omalizumab in the three clinical trials, including 684 patients exposed for 12 weeks and 427 exposed for 24 weeks.

Table 2 Adverse Reactions Occurring in ≥2% in Omalizumab-Treated Patients and More Frequently than in Patients Treated with Placebo (Day 1 to Week 12) in CIU Trials

	CIU Trials 1, 2, and 3 Pooled		
Adverse Reactions [a]	Omalizumab 150 mg (n=175)	Omalizumab 300 mg (n=412)	Placebo (n=242)
Gastrointestinal disorders			
Nausea	2 (1.1%)	11 (2.7%)	6 (2.5%)
Infections and infestations			
Nasopharyngitis	16 (9.1%)	27 (6.6%)	17 (7.0%)
Sinusitis	2 (1.1%)	20 (4.9%)	5 (2.1%)
Upper respiratory tract infection	2 (1.1%)	14 (3.4%)	5 (2.1%)
Viral upper respiratory tract infection	4 (2.3%)	2 (0.5%)	(0.0%)
Musculoskeletal and connective tissue disorders			
Arthralgia	5 (2.9%)	12 (2.9%)	1 (0.4%)
Nervous system disorders			
Headache	21 (12.0%)	25 (6.1%)	7 (2.9%)
Respiratory, thoracic, and mediastinal disorders			
Cough	2 (1.1%)	9 (2.2%)	3 (1.2%)

CIU = chronic idiopathic urticaria.

[a] by MedDRA (15.1) System Organ Class and Preferred Term.

Malignancies

A small numerical imbalance (0.5% vs. 0.2%) in malignant neoplasms was observed in clinical studies of adults and adolescents (≥12 years of age) with asthma and other allergic disorders. The observed malignancies in omalizumab-treated patients were a variety of types, with breast, non-melanoma skin, prostate, melanoma, and parotid occurring more than once, and five other types occurring once each. The majority of patients were observed for less than 1 year.

A subsequent observational study, A Epidemiologic Study of Xolair (Omalizumab): Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma (EXCELS), was done as a post-marketing commitment to the FDA. This study's pre-specified primary outcomes measures were all malignancy, all malignancies excluding non-melanoma skin carcinoma, and overall serious adverse events. This study enrolled 5007 omalizumab-treated and 2829 non-omalizumab-treated patients ≥12 years old with moderate to severe persistent asthma and followed them for up to 5 years, with mean follow-up of 3.7 years. Patients were not randomized or blinded and were assigned to omalizumab or non-omalizumab cohorts based on clinical decisions related to initiation and continuation of omalizumab. In EXCELS, the

incidence rates of primary malignancies (per 1000 patient years) were similar among omalizumab-treated (12.3) and non-omalizumab-treated patients (13.0). However, study limitations preclude definitively ruling out a malignancy risk with omalizumab. Study limitations include: the observational study design, the bias introduced by allowing enrollment of patients previously exposed to omalizumab (88%), enrollment of patients (56%) while a history of cancer or a premalignant condition were study exclusion criteria, and the high study discontinuation rate (44%).

Cardiovascular and Cerebrovascular Events from Clinical Studies in Patients with Asthma

In the observational EXCELS study, a higher incidence rate of overall cardiovascular and cerebrovascular serious adverse events was observed in omalizumab-treated patients (13.4) compared to non-omalizumab-treated patients (8.1). Increases in rates were observed for transient ischemic attack (0.7 vs. 0.1), myocardial infarction (2.1 vs. 0.8), pulmonary hypertension (0.5 vs. 0), pulmonary embolism/venous thrombosis (3.2 vs. 1.5), and unstable angina (2.2 vs. 1.4), while the rates observed for ischemic stroke and cardiovascular death were similar among both study cohorts.

In the observational EXCELS study, patients were not randomized or blinded and were assigned to omalizumab or non-omalizumab cohorts based on clinical decisions related to initiation and continuation of omalizumab. Omalizumab and non-omalizumab cohorts were balanced for smoking history and age. However, baseline cardiovascular risk factors were higher in the omalizumab-treated cohort than the non-omalizumab-treated cohort (Food and Drug Administration 2014). More omalizumab-treated patients were diagnosed with severe asthma (50%) compared to the non-omalizumab-treated patients (23%).

Interpretation of the EXCELS study results related to cardiovascular and cerebrovascular events has been limited by the observational study design, the inclusion of patients previously exposed to omalizumab (88%), baseline imbalances in cardiovascular risk factors between the treatment groups, an inability to adjust for unmeasured risk factors, and the high study discontinuation rate.

A separate pooled analysis of 25 randomized double-blind, placebo-controlled clinical trials of 8 to 52 weeks in duration included 3342 omalizumab-treated patients and 2895 placebo-treated patients. The primary outcomes of interest included cardiovascular death, myocardial infarction, arrhythmias, heart failure, stroke, transient ischemic attack, pulmonary hypertension, pulmonary embolism, and unstable angina. Across all the studies, a total of 8 events occurred in the omalizumab-treated patients compared with 15 in the placebo patients, and no notable differences were observed in the rates of specific cardiovascular events (Food and Drug Administration 2014). However, the results of the pooled analysis were based on a low number of events, slightly younger patients, and shorter duration of follow-up than the observational EXCELS study;

therefore, the results are insufficient to confirm or reject the findings noted in the observational EXCELS study.

5.1.3 Management of Specific Adverse Events

Guidelines for management of specific adverse events are outlined in Table 3.

Table 3 Guidelines for Management of Specific Adverse Events

Event	Action to Be Taken
Anaphylaxis	• Administer omalizumab only in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. • Observe patients closely for an appropriate period of time after administration of omalizumab. • Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs or symptoms occur.
Acute asthma symptoms	• Omalizumab has not been shown to alleviate asthma exacerbations acutely. • Do not use omalizumab to treat acute bronchospasm or status asthmaticus.
Angioedema	• Patients with CIU can have angioedema as part of their symptoms. – When angioedema poses a risk to the airway, the emergent use of systemic corticosteroids is indicated. – Patients who need to be treated with systemic corticosteroids will be discontinued from study treatment and followed for safety for the remainder of the study. – Patients will be provided emergency contact information and advised to contact a physician during the entire study, in case of angioedema.
Serum sickness	• In post-approval use, some patients have experienced a constellation of signs and symptoms including arthritis/arthralgia, rash, fever, and lymphadenopathy with an onset 1 to 5 days after the first or subsequent injections of omalizumab. – These signs and symptoms have recurred after additional doses in some patients. – Although circulating immune complexes or a skin biopsy consistent with a Type III reaction were not seen with these cases, these signs and symptoms are similar to those seen in patients with serum sickness. – Physicians should stop omalizumab if a patient develops this constellation of signs and symptoms.
Parasitic infections	• Monitor patients at high risk of geohelminth infection while on omalizumab therapy. Insufficient data are available to determine the length of monitoring required for geohelminth infections after stopping omalizumab treatment.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
  - This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.1 for reporting instructions).

5.2.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.1 for reporting instructions). Adverse events of special interest for this study include the following:

- Suspected anaphylaxis due to omalizumab, as defined by Sampson's criteria (Sampson et al. 2006; see Appendix 16)
- 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 (see Section 5.3.5.6).

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4, Section 5.5, and Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.1 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 112 days (approximately 5 drug half-lives) after the last administration of study drug or study discontinuation/termination, whichever is later. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

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

5.3.3 Assessment of Severity of Adverse Events

Table 4 provides guidance for assessing adverse event severity.

Table 4 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating “yes” or “no” accordingly. The following guidance should be taken into consideration (see also Table 5):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 5 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.1 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from “non-serious” to “serious,” providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment
  - Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 $\times$ ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.1).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.1). This includes death attributed to progression of CIU.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

If the death is attributed to progression of CIU, "chronic idiopathic urticaria progression" should be recorded on the Adverse Event eCRF.

5.3.5.8 Preexisting Medical Conditions

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

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

5.3.5.9 Lack of Efficacy or Worsening of Chronic Idiopathic Urticaria

Medical occurrences or symptoms of deterioration that are anticipated as part of CIU should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of CIU on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “accelerated chronic idiopathic urticaria”).

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available

5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.1).

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately using the contact information provided in Section 5.4.1.1; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.1 for further details)
- Non-serious adverse events of special interest (see Section 5.4.1 for further details)
- Pregnancies (see Section 5.4.2 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

5.4.1.1 Events That Occur prior to Study Drug Initiation

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. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided below.

Genentech Drug Safety Department

Fax No.:	650-225-4630
Alternate Fax No:	650-225-4682
Email:	us_drug.safety@gene.com

5.4.1.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported until 112 days (approximately 5 drug half-lives) after the last administration of study drug or study discontinuation/termination, whichever is later. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided in Section 5.4.1.1. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.2 Reporting Requirements for Pregnancies

5.4.2.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 112 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should

continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided in Section 5.4.1.1. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.2.2 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.1). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

5.4.3 Medical Contact

Genentech Medical Monitor:

[redacted], M.D., *M.S.*

Genentech, Inc.

Telephone No.: [redacted]

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.2.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 112 days [approximately 5 drug half-lives] after the last administration of study drug or study discontinuation/termination, whichever is later), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided in Section 5.4.1.1.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the U.S. prescribing information for omalizumab, found in the USPI.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 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 • 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.

6.2 SUMMARIES OF CONDUCT OF STUDY

The disposition of patients for each study period will be summarized by treatment group with respect to the number of patients randomized, treated, and completing each 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.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Treatment groups entering the double-blind randomization period of the study will be assessed for comparability with respect to demographic (e.g., age, sex, race/ethnicity) and baseline characteristics (e.g., body weight, total IgE levels, UAS7).

6.4 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.

6.4.1 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.

6.4.2 Primary Efficacy Endpoint

The primary efficacy endpoint for this study is the percentage of patients who experience a clinical worsening of CIU as defined by UAS7 $\geq$ 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.

6.4.3 Secondary Efficacy Endpoints

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.
- Percentage of patients who experience a clinical worsening of CIU as defined by UAS7 $>$ 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 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.
- 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 and analyzed in the context of a non-inferiority hypothesis test with non-inferiority margin 5. The p-value from the non-inferiority 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 using a 2-sided,

one sample t-test. The p-value from this test will be used to evaluate the superiority of retreating after experiencing clinical worsening among these patients.

6.5 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.

6.6 PHARMACODYNAMIC ANALYSIS

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).

6.7 EXPLORATORY ANALYSES

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

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. Central laboratory data or other electronic data will be sent directly to the CRO, using the CRO's standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

Patient eDiary data will be collected through use of an electronic device provided by a vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The eDiary device data will be available for view access only via secure access to a web server. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor and study sites will have view access only to the web server. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Paper PRO questionnaires will be faxed*, scanned,* or couriered from the site to the data entry center. Scanned paper PROs will be transferred via a secure email system.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the CRO and should be handled in accordance with instructions from the CRO.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Once the study is complete, the eDiary data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all patient data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

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

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

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, PRO completed forms, eDiary data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the E.U. or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Home Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

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

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient

to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

Each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

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

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

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Genentech, a member of the Roche group, and will be managed by Genentech and a CRO. The CRO will provide clinical operations management, data management, and medical monitoring. An IxRS will be used to assign patient numbers, monitor enrollment and patient status, and to manage study treatment requests and shipments.

Patient data will be recorded via an EDC system using eCRFs (see Section 7.2).
A blinded external adjudication committee will review potential events of anaphylaxis.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect

proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2:297–307.

Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol 2014;133:1270–7.

Fiebiger E, Maurer D, Holub H, et al. Serum IgG autoantibodies directed against the alpha chain of Fc epsilon RI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? J Clin Invest 1995;96:2606–12.

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210–16.

Food and Drug Administration. FDA Drug Safety Communication: FDA approves label changes for asthma drug Xolair (omalizumab), including describing slightly higher risk of heart and brain adverse events. 26 September 2014 [cited 24 October 2014]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm414911.htm.

Grattan CE, Francis DM, Hide M, et al. Detection of circulating histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. Clin Exp Allergy 1991;21:695–704.

Greaves MW. Chronic idiopathic urticaria. Curr Opin Allergy Clin Immunol 2003;3:363–8.

Hide M, Francis DM, Grattan CE, et al. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N Engl J Med 1993;328:1599–604.

Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. J Allergy Clin Immunol 2013;132:101–9.

Kozel MM, Sabroe RA. Chronic urticaria: aetiology, management and current and future treatment options. Drugs 2004;64:2515–36.

Maurer M, Rosén K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med. 2013;368:924–35.

Morin CM. Insomnia: Psychological Assessment and Management. New York, NY: Guilford Press; 1993.

Niimi N, Francis DM, Kermani F, et al. Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. J Invest Dermatol 1996;106:1001–6.

Reilly MC, Zbrozek AS, Dukes E. The validity and reproducibility of a work productivity and activity impairment measure. PharmacoEconomics 1993;4:353–65.

Saini SS, Bindslev-Jensen C, Maurer M. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. J Invest Dermatol 2014 Jul 21. doi: 10.1038/jid.2014.306. [Epub ahead of print]

Saini S, Rosen KE, Hsieh HJ. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. J Allergy Clin Immunol 2011;128:567–73.

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391–7.

Shikiar R, Harding G, Leahy M, et al. Minimal Important Difference (MID) of the Dermatology Life Quality Index (DLQI): results from patients with chronic idiopathic urticaria. Health Qual Life Outcomes 2005;3:36.

Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092–7.

Tilles SA. Approach to therapy in chronic urticaria: when benadryl is not enough. Allergy Asthma Proc 2005;26:9–12.

Tong LJ, Balakrishnan G, Kochan JP, et al. Assessment of autoimmunity in patients with chronic urticaria. J Allergy Clin Immunol 1997;99:461–5.

Weller K, Groffik A, Church MK, et al. Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. J Allergy Clin Immunol. 2014;133:1365–72.

XOLAIR® (omalizumab) U.S. Package Insert, Genentech USA, Inc. and Novartis Pharmaceuticals Corporation. 2014 Mar [cited 2014 Apr 15]. Available from http://www.gene.com/download/pdf/xolair_prescribing.pdf.

Yang M, Morin CM, Schaefer K, et al. Interpreting score differences in the Insomnia Severity Index: using health-related outcomes to define the minimally important difference. Curr Med Res Opin. 2009;25:2487–94

Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy 2014;69:868–87.

Zweiman B, Valenzano M, Atkins PC. Modulation of serum histamine releasing activity in chronic idiopathic urticaria. Immunopharmacology 1998;39:225–34.

Appendix 1
Schedule of Assessments for Screening and Open-Label Treatment Period

	Screening [a]		Open-Label Treatment Period (Baseline to Week 24)							Follow-Up Visit for Non-Responders [c]	ET [d]
End of Study Week			Baseline	4	8	12	16	20	24 [b]		
Day (Window)	−14 (*−6*/ +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 [e]	x										
Vital signs (blood pressure and pulse) [f]	x		x	x	x	x	x	x	x		x
Physical examination [g]	x										
Weight/height	x										x
Pregnancy test [h]	x		x	x	x	x	x	x	x		
Concomitant medication usage	x	x	x	x	x	x	x	x	x	x	x
Adverse events [i]		x	x	x	x	x	x	x	x	x	x
Open-label omalizumab administration			x	x	x	x	x	x			
Study drug/placebo administration [b]									x [b]		
Site to contact IxRS	x		x	x	x	x	x	x	x	x	x
PROs											
Patient eDiary [j]	x	x	x	x	x	x	x	x	x		x
DLQI [k]			x			x			x	x	x
UCT [k]	x		x			x			x	x	x

APPENDIX 1 (cont'd)
Schedule of Assessments for Screening and Open-Label Treatment Period

	Screening [a]		Open-Label Treatment Period (Baseline to Week 24)							Follow-Up Visit for Non-Responders [c]	ET [d]
End of Study Week			Baseline	4	8	12	16	20	24 [b]		
Day (Window)	−14 (−6/ +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		
U-AIM [k]	x		x			x			x	x	x
ISI [k]			x			x			x	x	x
GAD-7 [k]			x			x			x	x	x
WPAI [k]			x			x			x	x	x
P-GIC scale [k]									x		
IC-UAS [k]	x	x	x						x	x	x
C-GIC scale [k]									x		
Laboratory tests [l]											
Hematology [m]	x								x		x
Stool ova and parasite evaluation [n]		x									
Chemistry [o]	x										
Urinalysis [p]	x										
Thyroperoxidase antibody	x										
CU index	x										
PD sample (total serum IgE)	x										
Blood samples for storage	x								x		x
Blood RNA (optional) [q]	x								x		x

APPENDIX 1 (cont'd)
Schedule of Assessments for Screening and Open-Label Treatment Period

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; 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.

[a] The screening period should be *14* to *20* days long. Day –14 and Day –7 are provided for reference. The Day –14 visit should be conducted *20* to *14* 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.

[b] 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*; 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 (see Appendix 2). *The final two weeks of the open-label treatment period are scheduled to occur during Weeks 23 and 24 but may vary somewhat depending on patient scheduling. Randomization will not be permitted after Day 190 from baseline.*

[c] 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 assessments for adverse events and PROs. Patients will not be required to complete the eDiary during this 12-week period.

[d] 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."

[e] 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.

[f] 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.

[g] 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.

[h] 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.

APPENDIX 1 (cont'd)
Schedule of Assessments for Screening and Open-Label Treatment Period

[i] 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 (see Section 5.6). 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.

[j] 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.

[k] 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.

[l] Samples for laboratory tests will be taken pre-dose on dosing days.

[m] 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).

[n] 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.

[o] 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.

[p] 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).

[q] 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 2
Schedule of Assessments for Double-Blind Randomization Period and Follow-Up Period

	Double-Blind Randomization Period [a] (Week 24 to Week 48)							Follow-Up Period [b] (Week 48 to Week 60)			ET
End of Study Week	24 [c]	28	32	36	40	44	48 [d,e]	52 [e]	56 [e]	60 [e]	
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) [f]	x	x	x	x	x	x	x			x	x
Weight/height										x	x
Pregnancy test [g]	x	x	x	x	x	x					
Concomitant medication usage	x	x	x	x	x	x	x	x	x	x	x
Adverse events [h]	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 [i]	x	x	x	x	x	x	x	x	x	x	x
DLQI [j]	x			x			x			x	x
UCT [j]	x			x			x			x	x
U-AIM [j]	x			x			x			x	x
ISI [j]	x			x			x			x	x
GAD-7 [j]	x			x			x			x	x
WPAI [j]	x			x			x			x	x
P-GIC scale [j]	x						x				
IC-UAS [j]	x			x			x			x	x
C-GIC scale [j]	x						x				

APPENDIX 2 (cont'd)
Schedule of Assessments for Double-Blind Randomization Period and Follow-Up Period

	Double-Blind Randomization Period [a] (Week 24 to Week 48)							Follow-Up Period [b] (Week 48 to Week 60)			ET
End of Study Week	24 [c]	28	32	36	40	44	48 [d,e]	52 [e]	56 [e]	60 [e]	
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 [k]											
Hematology [l]	x						x			x	x
Blood samples for storage	x						x			x	x
Blood RNA (optional) [m]	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; 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.

[a] 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 according to Appendix 3.

[b] The 12-week follow-up period applies only to patients who have completed the first 48 weeks of the study.

[c] 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 (see Appendix 1) and do not need to be repeated for the double-blind randomization period. *The final two weeks of the open-label treatment period are scheduled to occur during Weeks 23 and 24 but may vary somewhat depending on patient scheduling. Randomization will not be permitted after Day 190 from baseline.*

[d] The Week 48 visit is the end of the double-blind randomization period and the beginning of the follow-up period.

[e] 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.

[f] 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.

APPENDIX 2 (cont'd)
Schedule of Assessments for Double-Blind Randomization Period and Follow-Up Period

[g] 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.

[h] 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 (see Section 5.6). 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.

[i] 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.

[j] 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.

[k] Samples for laboratory tests will be taken pre-dose on dosing days.

[l] 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).

[m] 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 3
Schedule of Assessments for Patients Who Transition to Open-Label Omalizumab after Randomization

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

APPENDIX 3 (cont'd)
Schedule of Assessments for Patients Who Transition to Open-Label Omalizumab After Randomization

	First Day of Transition	Post-Randomization Open-Label Treatment Period [a]		Follow-Up Period [b]			ET
		Every 4 Weeks Until 48 Weeks of Total Treatment	Week 48 [c]	Week 52 [c]	Week 56 [c]	Week 60 [c]	
Visit Window (days)		±3	±3	±3	±3	±3	±3
IC-UAS [h]	x		x			x	x
C-GIC scale [h]	x		x				
Laboratory tests [i]							
Hematology [j]	x		x				x
Blood samples for storage	x		x			x	x
Blood RNA (optional) [k]	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; 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.

[a] 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.

[b] The 12-week follow-up period applies only to patients who have completed the first 48 weeks of the study.

[c] 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.

[d] 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.

[e] 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.

[f] 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 (see Section 5.6). 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.

[g] 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.

[h] 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.

[i] Samples for laboratory tests will be taken pre-dose on dosing days.

[j] Hematology to include hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent, and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells).

[k] 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 4
Study Drug Preparation and Administration

An unblinded pharmacist or other qualified designated individual will prepare the study drug (omalizumab or placebo) injection as outlined below.

RECONSTITUTION

The supplied study drug must be reconstituted with Sterile Water for Injection (SWFI), USP, using the following instructions:

1. Before reconstitution, determine the number of vials that will need to be reconstituted (each vial delivers 150 mg of study drug).
2. Draw 1.4 mL SWFI, USP, into a 3-mL syringe equipped with a 1-inch, 18-gauge needle.
3. Place the vial upright on a flat surface and, using standard aseptic technique, insert the needle and inject the SWFI, USP, directly onto the product.
4. Keeping the vial upright, gently swirl the upright vial for approximately 1 minute to evenly wet the powder. Do not shake.
5. Gently swirl the vial for 5 to 10 seconds approximately every 5 minutes in order to dissolve any remaining solids. **The lyophilized product takes 15 to 20 minutes to dissolve.** If it takes longer than 20 minutes to dissolve completely, gently swirl the vial for 5 to 10 seconds approximately every 5 minutes until there are no visible gel-like particles in the solution. Do not use if the contents of the vial do not dissolve completely in 40 minutes.
6. After reconstitution, the study drug solution is somewhat viscous and will appear clear or slightly opalescent. It is acceptable if there are a few small bubbles or foam around the edge of the vial; there should be no visible gel-like particles in the reconstituted solution. Do not use if foreign particles are present.
7. Invert the vial for 15 seconds to allow the solution to drain toward the stopper.
8. **Use the study drug solution within 8 hours following reconstitution when stored in the vial at 2 to 8°C (36 to 46°F), or within 4 hours of reconstitution when stored at room temperature.** Reconstituted study drug vials should be protected from sunlight.
9. Using a new 3-mL syringe equipped with a 1-inch, 18-gauge needle, insert the needle into the inverted vial. Position the needle tip at the very bottom of the solution in the vial stopper when drawing the solution into the syringe. The reconstituted product is somewhat viscous; in order to obtain the full 1.2-mL dose, **all of the product must be withdrawn** from the vial before expelling any air or excess solution from the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel to remove all of the solution from the inverted vial.
10. Replace the 18-gauge needle with a 25-gauge needle for subcutaneous (SC) injection.

11. Expel air, large bubbles, and any excess solution in order to obtain the required 1.2-mL dose. A thin layer of small bubbles may remain at the top of the solution in the syringe.

ADMINISTRATION

Administer study drug by SC injection. The injection may take 5–10 seconds to administer because the solution is slightly viscous. Do not administer more than 150 mg (contents of one vial) per injection site.

Cap the syringe. Label the syringe with the patient number, kit number details, and protocol number (ML29510). The syringe is now ready for use.

Appendix 5
Study Drug Dosing and Scheduling Table

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

Dose (mg)	Number of Injections	Total Volume Injected (mL) [a]
300	2 injections: 1.2 mL omalizumab + 1.2 mL omalizumab	2.4
Placebo	2 injections: 1.2 mL placebo + 1.2 mL placebo	2.4

[a] 1.2 mL maximum delivered volume per vial.

Appendix 6
Patient Electronic Diary (eDiary)

Note: The patient eDiary is also referred to as the Urticaria Patient Daily Diary (UPDD).

GENERAL INSTRUCTIONS

Please answer each question to the best of your ability.

There are no right or wrong answers.

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

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

INSTRUCTIONS FOR COUNTING THE NUMBER OF HIVES AND MEASURING THE SIZE OF THE LARGEST HIVE

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

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

APPENDIX 6 (cont'd)
Patient Electronic Diary (eDiary)

Today's Date

		-				-				

Day **Month** **Year**

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

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

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

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

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

APPENDIX 6 (cont'd)
Patient Electronic Diary (eDiary)

Today's Date

		-				-				

Day **Month** **Year**

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

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

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

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

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

APPENDIX 6 (cont'd)
Patient Electronic Diary (eDiary)

Today's Date

		-				-				
Day			**Month**				**Year**			

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

(Please circle only one response.)

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

   0 No interference

   1 Mild, little interference with sleep

   2 Moderate, awoke occasionally, some interference with sleep

   3 Substantial, woke up often, severe interference with sleep

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

   0 No interference

   1 Mild, little interference with daily activities

   2 Moderate, some interference with daily activities

   3 Substantial, severe interference with daily activities

APPENDIX 6 (cont'd)
Patient Electronic Diary (eDiary)

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

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

   0 = 0 pills

   1 = 1 pill

   2 = 2 pills

   3 = 3 pills

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

   0 = No (**GO TO Question 7**) 1 = Yes

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

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

   1 Took some prescription or non-prescription medication

   2 Called my doctor, nurse, or nurse practitioner

   3 Went to see my doctor, nurse, or nurse practitioner

   4 Went to the emergency room at the hospital

   5 Was hospitalized

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

   0 = No 1 = Yes

Appendix 7
Dermatology Life Quality Index (DLQI)

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

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

Please check you have answered EVERY question. Thank you.

Appendix 8
Urticaria Control Test (UCT)

Patient name: _____ Date: (dd mmm yyyy): ___ ____ _____

Date of birth (dd mmm yyyy): ___ ____ _____

Instructions: You have urticaria. The following questions should help us understand your current health situation. Please read through each question carefully and choose an answer from the five options that *best fits* your situation. Please limit yourself to *the last four weeks*. *Please don't think about the questions for a long time*, and do remember to answer *all questions* and to provide *only one answer to each question.*

1. How much have you suffered from the **physical symptoms of the urticaria (itch, hives (welts) and/or swelling)** in the last four weeks?

   O very much O much O somewhat O a little O not at all

2. How much was your **quality of life** affected by the urticaria in the last 4 weeks?

   O very much O much O somewhat O a little O not at all

3. How often was the **treatment** for your urticaria in the last 4 weeks **not enough** to control your urticaria symptoms?

   O very often O often O sometimes O seldom O not at all

4. **Overall**, how well have you had your urticaria **under control** in the last 4 weeks?

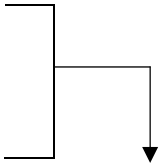
   O not at all O a little O somewhat O well O very well

Appendix 9
Urticaria Activity and Impact Measure (U-AIM)

This questionnaire asks you about your **urticaria** and how it may have affected your life **in the past 7 days**. Please answer each question to the best of your ability. There are no right or wrong answers. For each question, mark an ☒ in the one box that best describes your experience.

1. Thinking about your urticaria in the past 7 days, on average, **how severe was your itch**?

   ☐ 0 None (skip to question 2)
   ☐ 1 Mild
   ☐ 2 Moderate
   ☐ 3 Severe

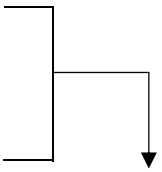
   

   1a. In the past 7 days, how much of the time did your **itch bother** you?

   ☐ 0 None of the time
   ☐ 1 A little of the time
   ☐ 2 Some of the time
   ☐ 3 Most of the time
   ☐ 4 All of the time

2. Thinking about your urticaria in the past 7 days, on average, **how many hives** did you have per day? Count *each hive separately* even if you had more than one hive grouped together with other hives.

   ☐ 0 None (skip to question 3)
   ☐ 1 Between 1 and 6 hives
   ☐ 2 Between 7 and 12 hives
   ☐ 3 Greater than 12 hives

   2a. In the past 7 days, how much of the time did your **hives bother** you?

   ☐ 0 None of the time
   ☐ 1 A little of the time
   ☐ 2 Some of the time
   ☐ 3 Most of the time
   ☐ 4 All of the time

3. In the past 7 days, how many days did you have any **rapid swelling** on your face, (especially your eyelids or lips), inside your mouth (including your throat or tongue), or elsewhere on your body? This rapid swelling, also called **angioedema**, is at a deeper level under your skin than hives.

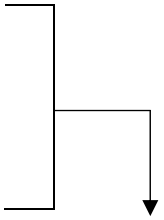
☐ 0 Did not experience angioedema (skip to question 4)

☐ 1 1 – 2 days

☐ 2 3 – 4 days

☐ 3 5 – 6 days

☐ 4 7 days



3a. In the past 7 days, how much of the time did this **rapid swelling (angioedema) bother** you?

☐ 0 None of the time

☐ 1 A little of the time

☐ 2 Some of the time

☐ 3 Most of the time

☐ 4 All of the time

4. In the past 7 days, how much of the time did urticaria symptoms **interfere with your daily activities**? This could include work, school, sports, hobbies, and activities with friends and family.

☐ 0 None of the time

☐ 1 A little of the time

☐ 2 Some of the time

☐ 3 Most of the time

☐ 4 All of the time

5. In the past 7 days, how much of the time did urticaria symptoms **interfere with your sleep**?

☐ 0 None of the time

☐ 1 A little of the time

☐ 2 Some of the time

☐ 3 Most of the time

☐ 4 All of the time

APPENDIX 9 (cont'd)
Urticaria Activity and Impact Measure (U-AIM)

6. How would you rate your **urticaria control** in the past 7 days?

☐ 0 Completely controlled

☐ 1 Well controlled

☐ 2 Somewhat controlled

☐ 3 Poorly controlled

☐ 4 Not controlled at all

Please check that you answered *every* question. Thank you for your answers!

Appendix 10
Insomnia Severity Index (ISI)

Subject ID: _____ Date: _____

For each question below, please circle the number corresponding most accurately to your sleep patterns in the last **two weeks.**

For the first three questions, please rate the **SEVERITY** of your sleep difficulties.

1. Difficulty falling asleep:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

2. Difficulty staying asleep:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

3. Problem waking up too early in the morning:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

4. How **SATISFIED/DISSATISFIED** are you with your current sleep pattern?

Very Satisfied	Satisfied	Neutral	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. To what extent do you consider your sleep problem to **INTERFERE** with your daily functioning (e.g., daytime fatigue, ability to function at work/daily chores, concentration, memory, mood).

Not at all Interfering	A Little Interfering	Somewhat Interfering	Much Interfering	Very Much Interfering
0	1	2	3	4

6. How **NOTICEABLE** to others do you think your sleeping problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little Noticeable	Somewhat Noticeable	Much Noticeable	Very Much Noticeable
0	1	2	3	4

7. How **WORRIED/DISTRESSED** are you about your current sleep problem?

Not at all	A Little	Somewhat	Much	Very Much
0	1	2	3	4

APPENDIX 10 (cont'd)
Insomnia Severity Index (ISI)

Guidelines for Scoring/Interpretation:

Add scores for all seven items = _____

Total score ranges from 0–28

0–7 = No clinically significant insomnia

8–14 = Subthreshold insomnia

15–21 = Clinical insomnia (moderate severity)

22–28 = Clinical insomnia (severe)

Appendix 11
Generalized Anxiety Disorder 7 Item (GAD-7) Scale

GAD-7				
Over the <u>last 2 weeks</u>, how often have you been bothered by the following problems? *(Use "✓" to indicate your answer)*	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

(For office coding: Total Score T____ = ____ + ____ + ____)

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

Appendix 12
Work Productivity and Activity Impairment Questionnaire: Chronic Urticaria V2.0 (WPAI:CU)

The following questions ask about the effect of your chronic urticaria on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ No ____ Yes

   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your chronic urticaria? *Include hours you missed on sick days, times you went in late, left early, etc., because of your chronic urticaria. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____ HOURS

4. During the past seven days, how many hours did you actually work?

   _____ HOURS (*If "0", skip to question 6.*)

APPENDIX 12 (cont'd)
Work Productivity and Activity Impairment Questionnaire: Chronic Urticaria V2.0 (WPAI:CU)

5. During the past seven days, how much did your chronic urticaria affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If chronic urticaria affected your work only a little, choose a low number. Choose a high number if chronic urticaria affected your work a great deal.

   Consider only how much chronic urticaria affected productivity while you were working.

Chronic urticaria had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Chronic urticaria completely prevented me from working

   CIRCLE A NUMBER

6. During the past seven days, how much did your chronic urticaria affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If chronic urticaria affected your activities only a little, choose a low number. Choose a high number if chronic urticaria affected your activities a great deal.

   Consider only how much chronic urticaria affected your ability to do your regular daily activities, other than work at a job.

Chronic urticaria had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Chronic urticaria completely prevented me from doing my daily activities

   CIRCLE A NUMBER

Appendix 13
Patient Global Impression of Change (P-GIC) Scale

Please rate how your chronic idiopathic urticaria has changed since the beginning of the study:

1. ☐ Very much improved
2. ☐ Much improved
3. ☐ Minimally improved
4. ☐ No change
5. ☐ Minimally worse
6. ☐ Much worse
7. ☐ Very much worse

Appendix 14
In-Clinic Urticaria Activity Score (IC-UAS) (Max 6)

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

Pruritus:

0 = None

1 = Mild – minimal awareness, easily tolerated

2 = Moderate – definite awareness, bothersome but tolerable

3 = Severe – difficult to tolerate

Number of Hives:

0 = none

1 = 1–6

2 = 7–12

3 = >12

Appendix 15
Clinician Global Impression of Change (C-GIC) Scale

Please rate how patient's chronic idiopathic urticaria has changed since the beginning of the study:

1. ☐ Very much improved
2. ☐ Much improved
3. ☐ Minimally improved
4. ☐ No change
5. ☐ Minimally worse
6. ☐ Much worse
7. ☐ Very much worse

Appendix 16
Sampson's Criteria of Anaphylaxis

ANAPHYLAXIS: Sampson definition of anaphylaxis (clinical definition) is the acute onset of illness which involves **SKIN, MUCOSAL TISSUE, or BOTH** (e.g., generalized hives, pruritus or flushing, swollen lips- tongue uvula) **with one OR more of the following:**

- **RESPIRATORY:** Airway compromise (e.g. dyspnea, wheeze, or bronchospasm, stridor and reduced PEF)
- **CIRCULATORY:** Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope)

OR

TWO or MORE of the following that occur rapidly after exposure:

- **SKIN, MUCOSAL TISSUE:** e.g. generalized hives, itch-flush, swollen lips- tongue-uvula
- **RESPIRATORY:** Airway compromise (e.g. dyspnea, wheeze, or bronchospasm, stridor and reduced PEF)
- **CIRCULATORY:** Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope)
- **GASROINTESTINAL:** Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting, nausea, diarrhea)

PROTOCOL

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
VERSION NUMBER:	1
EUDRACT NUMBER:	Not applicable
IND NUMBER:	101,612
TEST PRODUCT:	Omalizumab (RO5489789)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	17-Dec-2014 19:57:48

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL ACCEPTANCE FORM

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
VERSION NUMBER:	1
EUDRACT NUMBER:	Not applicable
IND NUMBER:	101,612
TEST PRODUCT:	Omalizumab (RO5489789)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by the CRO.

PROTOCOL SYNOPSIS

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
VERSION NUMBER:	1
EUDRACT NUMBER:	Not applicable
IND NUMBER:	101,612
TEST PRODUCT:	Omalizumab (RO5489789)
PHASE:	IV
INDICATION:	Chronic idiopathic urticaria
SPONSOR:	Genentech, Inc.

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) ≥ 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, a UAS7 symptom score of ≥ 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 ≥ 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 UAS7 ≤ 6 in the final 2 weeks of the open-label treatment period (Week 23 and Week 24)

  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 (UAS $7 = 0$ vs. UAS7 > 0) and study site. Efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) 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 the Week 24 visit, which will include a blood draw for PK/PD measurement, and 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 UAS7 ≥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 UAS7 ≥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 ≥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 further characterization of the pharmacokinetics and pharmacodynamics of omalizumab and 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 ≥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) ≥16 and itch component of UAS7 (range 0–21) ≥8 during 7 days prior to baseline
  - IC-UAS ≥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 H1 antihistamine treatment (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 ≥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.

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

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

Serum total omalizumab, and total and free immunoglobulin E (IgE) concentrations will be measured at:

- Baseline (pre dose), Week 24 (pre-dose), Week 48, and Week 60 or early termination
- The time of discontinuation from blinded treatment (i.e., start of open-label treatment post-randomization [pre-dose]), among patients who make the post-randomization transition to open-label omalizumab
- The end of follow-up (i.e., 12 weeks after stopping the initial 24-week course of open-label omalizumab), among patients not responding to the initial 24-week course of open-label omalizumab

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

Serum total omalizumab, and total and free IgE concentration versus time data will be tabulated by treatment group and summarized using descriptive statistics (e.g., mean, standard deviation, minimum, and maximum). Additional PK and PD analyses may be conducted as appropriate.

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 • 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.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartase transaminase
BID	twice per day
BUN	blood urea nitrogen
C-GIC	Clinician Global Impression of Change (scale)
CIU	chronic idiopathic urticaria
CRO	contract research organization
CSU	chronic spontaneous urticaria
DLQI	Dermatology Life Quality Index
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
eDiary	electronic diary (also referred to as the UPDD)
FcεRI	high-affinity IgE receptor
FDA	U.S. Food and Drug Administration
FSH	follicle-stimulating hormone
GAD-7	General Anxiety Disorder 7-Item (scale)
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
IC-UAS	in-clinic Urticaria Activity Score
ICH	International Conference on Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IgE	immunoglobulin E
IgG	immunoglobulin G
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
ISI	Insomnia Severity Index
IVIG	intravenous immunoglobulin G
IxRS	interactive voice and web response system
LDH	lactate dehydrogenase
LPLV	last patient, last visit
LTRA	leukotriene receptor antagonist

Abbreviation	Definition
MID	minimally important difference
mITT	modified intent-to-treat (principle)
P-GIC	Patient Global Impression of Change (scale)
PD	pharmacodynamic
PK	pharmacokinetic
PRO	patient-reported outcome
Q4W	every 4 weeks
QD	once per day
QID	four times per day
RBC	red blood cell
RCR	Roche Clinical Repository
SAP	Statistical Analysis Plan
SC	subcutaneous
SWFI	Sterile Water for Injection
U-AIM	Urticaria Activity and Impact Measure
UAS	Urticaria Activity Score
UAS7	Urticaria Activity Score over 7 days
UCT	Urticaria Control Test
ULN	upper limit of normal
UPDD	Urticaria Patient Daily Diary
USPI	U.S. Package Insert
WBC	white blood cell
WPAI	Work Productivity and Activity Index

1. BACKGROUND

1.1 CHRONIC IDIOPATHIC URTICARIA

Chronic idiopathic urticaria (CIU; also referred to as chronic spontaneous urticaria [CSU]) is defined as the spontaneous occurrence of daily, or almost daily, hives and itching for at least 6 weeks without an obvious cause (Greaves 2003). The majority of patients with CIU achieve symptomatic control with conventional H1 antihistamine therapy. In some patients, CIU can be a debilitating condition because of a lack of clinical response as well as the unpredictable course of the disease, both of which can have a profound negative influence on the patient's quality of life (Tilles 2005).

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

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

1.2 OMALIZUMAB

Omalizumab (Xolair®) is a humanized anti-IgE recombinant monoclonal antibody approved to treat allergic asthma by inhibiting the binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. Reduction in surface-bound IgE on the FcεRI-expressing cells limits the degree of release of mediators in the allergic response. Omalizumab has been studied for safety and efficacy in over 5000 adult and adolescent (≥ 12 years of age) patients with moderate to severe asthma, and more recently, in patients with CIU. Omalizumab was approved by the U.S. Food and Drug Administration (FDA) for CIU in March 2014. More than 60,000 patients have been treated with omalizumab worldwide.

There are two hypotheses for the mechanism of action of omalizumab in patients with CIU. One hypothesis is that the density of IgE receptors at the surface of mast cells and basophils is proportional to the plasma IgE level. Lowering free IgE to near undetectable

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

Omalizumab is indicated for the treatment of adults and adolescents (12 years of age and above) with CIU who remain symptomatic despite H1 antihistamine treatment. The FDA-approved dose for patients with CIU is 150 or 300 mg administered by subcutaneous (SC) injection every 4 weeks (Q4W).

1.2.1 Clinical Experience with Omalizumab in Patients with CIU

The Phase III clinical program for omalizumab consisted of three studies:

- **Study Q4881g** (ASTERIA I; Saini et al. 2014) and **Study Q4882g** (ASTERIA II; Maurer et al. 2013) evaluated patients with CIU who were refractory to H1 antihistamines at approved doses.
- **Study Q4883g** (GLACIAL; Kaplan et al. 2013) evaluated patients with CIU who were refractory to H1 antihistamines at up to four times approved doses, H2 blockers, and/or leukotriene receptor antagonists (LTRAs).

Studies Q4881g and Q4882g were both global, Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies to evaluate the efficacy and safety of omalizumab, administered SC Q4W as add-on therapy for the treatment of adolescent and adult patients (12–75 years of age) with CIU refractory to conventional H1 antihistamines, as demonstrated by: the presence of itch and hives for ≥8 consecutive weeks at any time prior to enrollment, Urticaria Activity Score (UAS) over 7 days (UAS7) confirming uncontrolled symptoms prior to randomization, and a CIU diagnosis for ≥6 months. The studies evaluated the comparative efficacy between three doses of omalizumab (75 mg, 150 mg, and 300 mg) and placebo as well as the time to onset of clinical effect for patients with CIU who remained symptomatic despite treatment with approved doses of H1 antihistamine therapy. The 150-mg dose, which was not studied in the Phase II study (Q4577g; Saini et al. 2011), was included as an intermediate between the 75- and 300-mg dose in order to better define the dose response. The inclusion of the 75-mg dose served to characterize the lower end of the dose response after multiple doses, since only a single dose was tested in Study Q4577g.

Studies Q4481g and Q4882g differed in duration of treatment (24 weeks compared to 12 weeks for Studies Q4881g and Q4882g, respectively). The primary efficacy outcome measure was change from baseline in weekly itch score (a component of the UAS7) at Week 12. In total, 319 patients were randomized from 53 centers globally, and 323 patients were randomized from 55 centers globally in Studies Q4881g and Q4882g, respectively.

Study Q4883g was a global Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of omalizumab 300 mg administered SC Q4W as an add-on therapy for the treatment of adolescent and adult patients (12–75 years of age) who have been diagnosed with CIU who remain symptomatic despite H1 antihistamine treatment doses up to four times above the approved dose, H2 blockers, and/or LTRAs. The duration of treatment for Study Q4883g was 24 weeks. The primary safety outcome measure was the incidence and severity of adverse events and serious adverse events. Efficacy, a secondary objective, was measured in a similar manner as Studies Q4881g and Q4882g. In total, 336 patients were randomized from 65 centers globally.

1.2.2 Summary of Omalizumab Clinical Efficacy in Patients with CIU

Consistent treatment effects were observed in all omalizumab-treated groups across all three pivotal studies (Q4881g, Q4882g, and Q4883g), similar to that noted in the Phase II dose-ranging study (Q4577g) (Saini et al. 2011; Kaplan et al. 2013; Maurer et al. 2013; Saini et al. 2014).

Both the 150-mg and 300-mg groups met the primary efficacy endpoint of change from baseline to Week 12 in weekly itch score in all three pivotal studies (in Study Q4883g, only the 300-mg dose was studied), supporting the use of omalizumab for the treatment of adults and adolescents (12 years of age and above) with CIU who remain symptomatic despite H1 antihistamine treatment. For the 300-mg group, the mean change from baseline in weekly itch score at Week 12 showed statistically significant improvements compared with placebo (–9.4 vs. –3.6, –9.8 vs. –5.1, and –8.6 vs. –4.0 for Studies Q4881g, Q4882g, and Q4883g, respectively). The 75-mg group met the primary endpoint in Study Q4881g only.

Studies Q4881g and Q4882g showed consistent evidence of a dose response with the 300-mg dose demonstrating greater therapeutic benefit relative to 150 mg for the primary endpoint (formal statistical comparisons were not performed between omalizumab groups).

At the 300-mg dose, the proportion of patients achieving a therapeutic response at Week 12 (secondary efficacy endpoint) was as follows: 52%, 66%, and 52% with UAS7 $\leq$ 6; and 36%, 44%, and 24% with UAS7 = 0 for Studies Q4881g, Q4882g, and Q4883g, respectively. In addition, the proportion of patients at the 300-mg dose

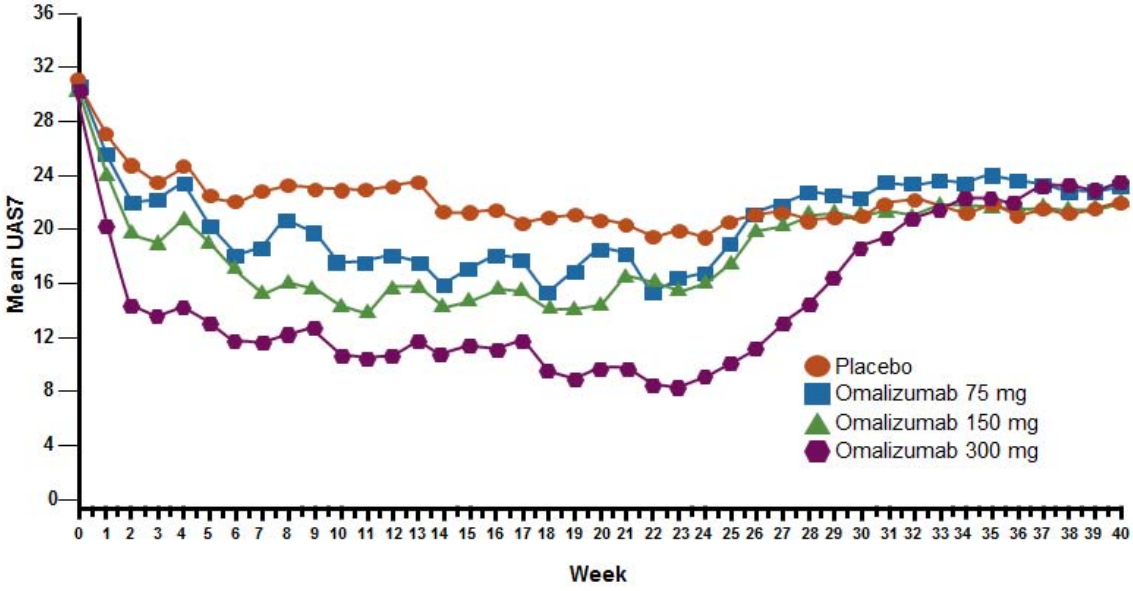
achieving UAS7 ≤6 at both Weeks 23 and 24 was 67.6% and 65.5% for Studies Q4881g and Q4883g, respectively.

As noted in Studies Q4881g and Q4883g, the decreases in mean weekly itch score and UAS7 with omalizumab treatment at Week 12 were maintained for up to 24 weeks of treatment suggesting there was no tolerance or tachyphylaxis to prolonged omalizumab dosing.

After cessation of treatment, mean weekly itch score and UAS7 increased to reach values similar to the placebo group mean values, but did not return to baseline values for the duration of the 16-week follow-up period in any of the omalizumab treatment groups in all three pivotal studies. The mean weekly itch score and UAS7 in the 300-mg group appeared to take longer to reach a similar level to that in the placebo group than was the case for lower omalizumab doses. This suggests a longer lasting effect of the 300-mg dose.

Figure 1 shows UAS7 scores over time in Study Q4881g (ASTERIA I), where the duration of potential omalizumab therapy was 24 weeks (Saini et al. 2014; Genentech data on file). Study Q4883g (GLACIAL) showed a similar pattern of return to placebo group mean after the 24-week omalizumab treatment period (Kaplan et al. 2013).

Figure 1 Change from Baseline in Mean UAS7: Study Q4881g (ASTERIA I; Placebo versus 24 Weeks Omalizumab)



UAS7 = Urticaria Activity Score over 7 days.

1.2.3 Summary of Omalizumab Clinical Safety in Patients with CIU

The overall safety profile of omalizumab in patients with CIU, across all four studies comprising the clinical development program (Q4577g, Q4881g, Q4882g, and Q4883g), revealed no unexpected safety signals or concerns different than the known safety profile of omalizumab in patients with allergic asthma (Saini et al. 2011; Kaplan et al. 2013; Maurer et al. 2013; Saini et al. 2014).

Few serious adverse events were reported (<2% of patients reported serious adverse events during the 12-week treatment period and <4% during the 24-week treatment period) and no deaths were observed in any of the studies. The most frequent adverse events demonstrating imbalances were common conditions such as nasopharyngitis, headache, and sinusitis. The safety profile was similar between 12 weeks and 24 weeks. In general, the majority of adverse events were mild or moderate in intensity. Overall, omalizumab was well tolerated with few adverse events leading to study discontinuation (<2%) or withdrawal of treatment (<4%) during the study period. A treatment comparison of the main safety endpoints over the entire study period for all three Phase III studies pooled showed no major differences in the safety profile between the 150- and 300-mg groups. Treatment differences indicating greater risk in omalizumab-treated patients were small and associated with a higher level of uncertainty. Those differences that were observed were expected given the known safety profile of omalizumab in allergic asthma. Specifically, a dose-dependent increase in suspected adverse events was observed for injection site reactions, which has been previously described (Xolair U.S. Package Insert 2014). Such reactions were infrequent, occurring in <3% of patients among those treated at the higher 300-mg dose, and none were considered severe. Although an imbalance in hypersensitivity events for the 300-mg dose group was observed over the entire study, this imbalance was not observed during either the 12- or 24-week treatment period. For the majority of patients suffering from moderate to severe CIU, the benefit of treatment with omalizumab would likely outweigh these risks.

See the Omalizumab Investigator's Brochure for additional details on clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

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.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

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

2.2 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

2.3 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

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a Phase IV, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of 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 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 UAS ≥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, a UAS7 symptom score of ≥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 ≥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 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 UAS7 ≤ 6 in the final 2 weeks of the open-label treatment period (Week 23 and Week 24)

  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 (UAS $7 = 0$ vs. UAS7 > 0) and study site. Efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) 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 the Week 24 visit, which will include a blood draw for PK/PD measurement, and 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 UAS7 ≥ 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 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.

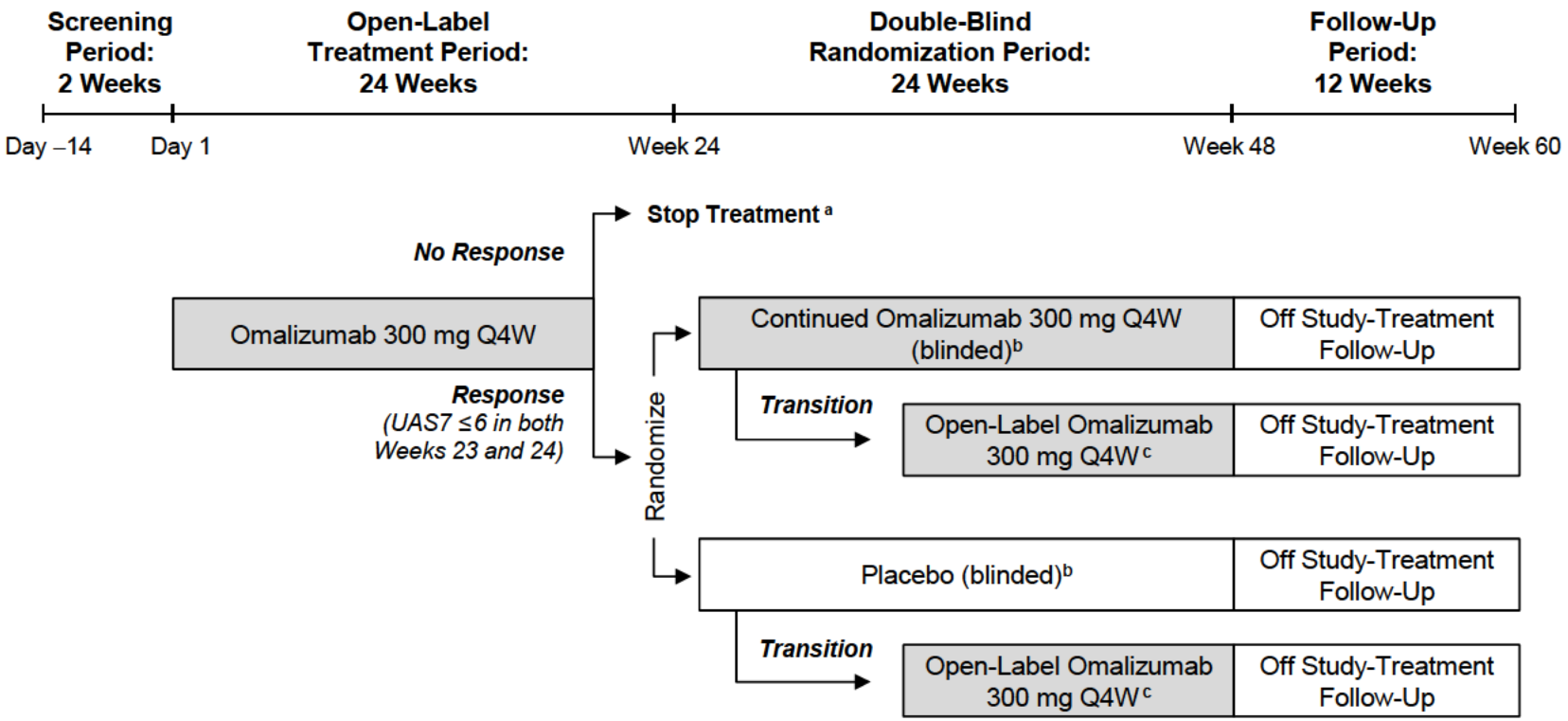
The primary endpoint for this study is the percentage of patients who experience clinical worsening in CIU defined as UAS7 $\geq$12 for at least 2 consecutive weeks.

After completion of the randomization period (end of Week 48), all patients will enter a 12-week follow-up period to allow for further characterization of the pharmacokinetics and pharmacodynamics of omalizumab and 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.

Figure 2 Study Schema



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

[a] 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 (see Appendix 1). Patients will not be required to complete the eDiary during this 12-week period.

[b] At Week 24, patients will be randomized 3:2 (omalizumab:placebo).

[c] 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 ≥ 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.

3.2 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.

3.3 RATIONALE FOR STUDY DESIGN

The pivotal studies demonstrated efficacy and safety of omalizumab through 24 weeks of treatment. Efficacy and safety beyond 24 weeks of treatment was not examined, as will be addressed in this study. Because of the previously demonstrated efficacy through 24 weeks, this study will begin with an initial 24-week open-label treatment period before any possibility of randomization to placebo.

The primary outcome of this study is clinical worsening in CIU as assessed by UAS7. The specific threshold for clinical worsening in CIU symptoms is UAS7 $\geq$12, maintained for at least 2 consecutive weeks. The threshold of UAS7 $\geq$12 (lower than the inclusion criteria of UAS7 $\geq$16) was chosen to allow patients to restart omalizumab at a lower threshold than that required to initiate omalizumab for the first time. Based on advisor input, this is believed to mirror general clinical practice for reinitiating therapies after withdrawal. Moreover, a requirement for patients to return to their baseline prior to reinitiating therapy is believed to be unreasonable, especially in the context of prior control established by omalizumab. The specific threshold of UAS7 $\geq$12 was chosen because of the precedent established in the CIU Phase II study in which this was used as an inclusion criterion (Saini et al. 2011). Additionally, all patients who are randomized will have a UAS7 $\leq$6 at time of randomization; therefore, a UAS7 $\geq$12 would confirm that the UAS7 score has at least doubled since randomization, representing an intuitive clinical threshold for reinitiating omalizumab. The secondary outcome of this study will also assess time to clinical worsening as well as the level of control of CIU symptoms assessed by whether or not patients maintain UAS7 $\leq$6 during the randomization period (Week 24 to Week 48). Separately, patients who have demonstrated a UAS7 $\geq$12 (maintained for at least 2 consecutive weeks), who are also clinically assessed as having worsening CIU warranting a transition to open-label omalizumab, will be offered such a transition to ensure that patients do not remain symptomatic for an undue period of time.

The inclusion and exclusion criteria for this study allow for up to four times the approved doses of H1 antihistamines, as well as H2 blockers and/or LTRAs. These inclusion/exclusion criteria reflect the reality that such medications are often used at these doses before advancing therapy to omalizumab, as discussed in practice parameters and guidelines (Bernstein et al. 2014; Zuberbier et al. 2014).

This study examines several secondary and exploratory endpoints, including PRO measures. The PRO instruments used in this study include those used in the pivotal trial data (e.g., Dermatology Life Quality Index [DLQI]) as well as new PROs, such as anxiety

symptoms and work productivity that may be related to CIU and response to therapy. In addition, this study will examine the validity of intermittently assessed PROs, such as the Urticaria Control Test (UCT) and Urticaria Activity and Impact Measure (U-AIM), compared with the twice daily eDiary device, in providing a clinical evaluation of patients with CIU.

3.3.1 Omalizumab Dose and Schedule

The FDA-approved dose for patients with CIU is 150 or 300 mg SC Q4W. In this CIU Phase IV study, only the 300-mg dose will be examined. The 300-mg dose was the only dosage to meet both the primary outcome as well as all secondary outcomes in both pivotal efficacy studies (Q4881g and Q4882g). Additionally, as shown in Figure 1, the average efficacy observed was numerically better with the 300-mg dose than for other doses. Also, relapse to mean placebo values after cessation of the 300-mg dose of omalizumab took longer, on average, than after other doses of omalizumab.

3.4 OUTCOME MEASURES

3.4.1 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.

3.4.2 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 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

3.4.3 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

3.4.4 Pharmacokinetic/Pharmacodynamic Outcome Measures

Serum total omalizumab, and total and free IgE concentrations will be measured at:

- Baseline (pre-dose), Week 24 (pre-dose), Week 48, and Week 60 or early termination
- The time of discontinuation from blinded treatment (i.e., start of open-label treatment post-randomization [pre-dose]), among patients who make the post-randomization transition to open-label omalizumab
- The end of follow-up (i.e., 12 weeks after stopping the initial 24-week course of open-label omalizumab), among patients not responding to the initial 24-week course of open-label omalizumab

3.4.5 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 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

- 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
- 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

4. MATERIALS AND METHODS

4.1 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.

4.1.1 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 ≥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) ≥16 and itch component of UAS7 (range 0–21) ≥ 8 during 7 days prior to baseline
  - IC-UAS ≥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 H1 antihistamine treatment (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 ≥ 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.

4.1.2 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
- 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
- Nursing women or women of childbearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they meet the following definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone (FSH) levels $>$40 mIU/mL or 6 weeks post-surgical bilateral oophorectomy (with or without hysterectomy) or hysterectomy OR are using one or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception (implantable, patch, oral), and double-barrier methods (any double combination of: intrauterine device, male or female condom with spermicidal gel, diaphragm, sponge, or cervical cap)
- Contraindications to diphenhydramine

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

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 for both Weeks 23 and 24) 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, the unblinded pharmacists at the sites, the independent Data Monitoring Committee [iDMC] members, and the independent Data Coordinating Center [iDCC] personnel) will be blinded to treatment assignment. Only the IxRS provider, the Sponsor's unblinding statistician, and the iDCC statistician will have access to the unblinding code during the study.

A pharmacist or other qualified individual designated by the study site will prepare and administer the study drug as outlined in Section 4.3.2 and Appendix 4. While blinded treatment kits will be used during the randomization phase of the study (Week 24 to Week 48), and because of potential differences in the viscosity of the omalizumab and placebo preparations, unblinding of the study site personnel responsible for reconstituting and/or administering study drug is possible. To minimize the risk of potential bias, study site personnel who are responsible for reconstituting and/or administering study drugs will not be permitted to conduct any safety or efficacy evaluations. Additionally, personnel administering study drug should apply bandages over injections sites to help maintain blinding. To minimize risk of potential bias arising from access to laboratory results that could potentially unblind treatment assignments (e.g., free IgE levels and serum omalizumab concentrations), the Sponsor and sites will be restricted from accessing such laboratory results.

4.3 STUDY TREATMENT

4.3.1 Formulation

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.

Placebo

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

4.3.2 Dosage, Administration, and Storage

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. For details regarding study drug preparation and administration, and the study drug dosing schedule, please refer to Appendix 4 and Appendix 5, respectively.

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

The reconstituted vial is to be used for single-dose administration only. Study drug will be administered SC to patients in the deltoid region of the right or left arm. Alternatively, the injections can be administered in the thigh if medically significant reasons preclude administration in the deltoid region.

Prior to randomization, during the initial open-label treatment period, study drug will be administered open-label as known omalizumab. After randomization, subjects will be assigned to either active or placebo medication. As described in Section 3.1, certain patients meeting prespecified criteria may, at the discretion of the investigator, be transitioned to open-label omalizumab.

Study drug must be stored in refrigerated conditions (2°C–8°C; 36°F–46°F) in a limited access area and/or a locked refrigerator. Study drug should be stored according to the storage instructions on the box immediately upon receipt but no later than 24 hours after receipt.

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

Patients should be closely observed after administration of open-label omalizumab and blinded study drug for signs and symptoms of anaphylaxis. This observation should be for a period of time that is judged to be appropriate by the investigator. In addition, the study staff should be prepared to manage anaphylaxis. Patients should also be informed of the signs and symptoms of anaphylaxis and be instructed to seek immediate care should symptoms occur.

Guidelines for treatment interruption or discontinuation are provided in Section 5.1.3.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. See Section 5.3.5.11 for guidance on adverse events associated with an overdose.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (omalizumab) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

4.3.4 Post-Trial Access to Omalizumab

The Sponsor (Genentech) may offer continued access to the study drug after study completion, in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

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

The long-acting H1 antihistamines, H2 blockers, and LTRAs allowed during the study are as follows. Note that the H1 antihistamines may be used at up to four times the approved dose listed below:

- H1 antihistamines
  - Cetirizine 5 or 10 mg once per day (QD)
  - Levocetirizine dihydrochloride 2.5 or 5 mg QD
  - Fexofenadine 60 mg twice per day (BID), or 180 mg QD
  - Loratadine 10 mg QD
  - Desloratadine 5 mg QD
- H2 blockers
  - Cimetidine 800 mg BID, or 400 mg four times per day (QID)
  - Famotidine 40 mg QD, or 20 mg QD or BID

  - Nizatidine 150 mg QD
  - Ranitadine 150 mg BID
- LTRAs
  - Montelukast 10 mg QD
  - Zafirlukast 20 mg BID

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.

4.4.2 Prohibited Therapy

The following medications and treatments will be restricted as specified below:

- Routine (daily or every other day during 5 or more consecutive days) doses of the following medications within 30 days prior to Day −14 and during the study period (baseline to Week 60): systemic corticosteroids, hydroxychloroquine, methotrexate, mycophenolate, cyclosporine, or cyclophosphamide. Additionally, during the study period (baseline to Week 60), prohibited routine usage also includes usage for greater than 10 total days during any 30-day period.
  - Note: inhaled asthma controllers, including inhaled corticosteroids, are permitted during the study.
- Routine (daily or every other day during 5 or more consecutive days) doses of doxepin within 14 days prior to Day −14 and during the study period (baseline to Week 60)
- Omalizumab within 1 year prior to screening and during the study period (baseline to Week 60), except as provided by this study
- Either IVIG or plasmapheresis within 30 days prior to Day −14 and during the study period (baseline to Week 60)

Patients who receive any excluded therapy during screening should be considered a screen failure. Patients who receive any excluded therapy after randomization will be discontinued from study treatment; if a patient has received at least one dose of omalizumab following enrollment, the patient should enter the 12-week follow-up period (see Appendix 2).

4.5 STUDY ASSESSMENTS

Please see Appendix 1, Appendix 2, and Appendix 3 for the schedule of assessments performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent from the patient or a legally authorized representative, and patient assent, if applicable, for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History and Demographic Data

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. In addition, the following specific medications used by the patient within 1 year prior to the screening visit will be collected: systemic corticosteroids, cutaneous (topical) corticosteroids, hydroxychloroquine, methotrexate, cyclosporine, and cyclophosphamide.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Vital Signs

Vital signs include measurements of pulse, and systolic and diastolic blood pressure while the patient is in a seated position.

4.5.4 Physical Examinations

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.

During the study, changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.5 Laboratory Assessments

All blood draws should be performed prior to study drug administration.

The following laboratory tests will be performed at the study site's local laboratory:

- Stool ova and parasite evaluation: This test should be conducted in patients who have risk factors for parasitic disease (e.g., living in an endemic area, travel to an endemic area within the last 6 months, chronic GI symptoms, or chronic immunosuppression) AND an eosinophil count >2 times the ULN. This test should be conducted anytime during the screening period after the Day -14 results are available for applicable patients.
- Urine pregnancy test: 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.

Instruction manuals and supply kits will be provided for all central laboratory assessments. Please refer to the laboratory manual for additional details on central laboratory assessments and sample handling. The assessments listed below will be performed at a central laboratory or at Genentech:

- Hematology: hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, white blood cell (WBC) count, percent and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells)
- Serum chemistries: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, alanine transaminase (ALT), aspartase transaminase (AST), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), creatine phosphokinase, and uric acid
- Serum pregnancy test: If a local urine pregnancy test shows a positive result, then the result must be confirmed by a serum pregnancy test (performed by central laboratory).
- Urinalysis: dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- PK assessments: serum total omalizumab
- PD assessments: total serum IgE and free serum IgE levels
- Blood RNA for exploratory research (see Section 4.5.6)
- Blood samples for biomarker and biochemical analyses for exploratory research (see Section 4.5.6)

4.5.6 Exploratory Blood RNA and Blood Biomarker Samples

Blood samples for biomarkers and biochemical analyses will be collected from all patients at selected visits and stored for exploratory research and markers of drug response.

Optional blood RNA samples will be collected from those patients who specifically consent to this optional collection. These samples will be stored for future exploratory research.

4.5.7 Patient eDiary

The patient eDiary (see Appendix 6), also referred to as the Urticaria Patient Daily Diary (UPDD), consists of questions (with specific recall periods) about the following: itch severity (12 hours, twice daily), number of hives (12 hours, twice daily), largest hive size (12 hours, twice daily), sleep interference (24 hours), daily activity interference (24 hours), diphenhydramine use (24 hours), and the occurrence of angioedema (24 hours). In addition, management of angioedema occurrences (24 hours) and calls to a doctor, nurse, or nurse practitioner because of CIU (24 hours) will be recorded. The eDiary will be given to each patient at the Day −14 visit.

Patients will be instructed to complete the eDiary twice a day for the entire duration of the study, beginning at Day −14. Patients should be encouraged to make every effort to stay current with their eDiary entries, even when travelling or in a location where data reception connectivity will not allow daily transfer of eDiary entries to the central server. When data reception connectivity is not available, data entries will be stored locally on the eDiary device and transferred at the time that such connectivity becomes available.

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

4.5.8 Patient-Reported Outcomes

The following PRO instruments will be administered as specified in Appendix 1, Appendix 2, and Appendix 3:

- Dermatology Life Quality Index (DLQI)

  The DLQI (see Appendix 7) is a 10-item dermatology-specific health-related quality of life measure (Finlay and Khan 1994). Patients rate their dermatology symptoms and the impact of their skin condition on various aspects of their health-related quality of life. An overall score will be calculated as well as separate scores for the following domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The minimally important difference (MID) of overall DLQI score for patients with CIU is estimated at 2.24–3.10 (Shikiar et al. 2005).

- Urticaria Control Test (UCT)

  The UCT (see Appendix 8) 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 questionnaire has a 4-week recall period. Low scores indicate poorly controlled urticaria. The developers recommended a value of 12 for controlled disease (i.e., all patients exhibiting UCT values of ≤ 11 are considered to have poorly controlled disease).

- Urticaria Activity and Impact Measure (U-AIM)

  The U-AIM (see Appendix 9) is a 9-item instrument designed to assess the patient's urticaria activity and impact during the past 7 days (Genentech data on file). The questionnaire asks about the severity of the CIU symptoms (itch, hives, and angioedema) and how much these symptoms bothered the patient. It also inquires about how much CIU symptoms interfered with the patient's daily activities and sleep. It concludes by asking the patient to rate the extent to which their urticaria was under control.

- Insomnia Severity Index (ISI)

  The ISI (see Appendix 10) is a 7-item questionnaire measuring self-perceptions of insomnia symptoms and the impact of these symptoms on patient health and daily life (Morin 1993). It encompasses sleep onset, sleep maintenance, awakening, sleep pattern satisfaction, interference with daily functioning, noticeability of sleep problem to others, and distress caused by sleep problem. The total score ranges from 0–28 points (higher scores indicate greater insomnia severity). The developers provided the following guidance to the score interpretation; however, this guidance needs further empirical validation: 0–7 = no clinically significant insomnia, 8–14 = sub-threshold insomnia, 15–21 = clinical insomnia (moderate severity), and 22–28 = clinical insomnia (severe). The recommended MID for ISI score is 6 (Bastien 2001; Yang et al. 2009).

- Generalized Anxiety Disorder 7-Item (GAD-7) scale

  The GAD-7 scale (see Appendix 11) is a 7-item questionnaire with good reliability as well as criterion, construct, factorial, and procedural validity. The total score ranges from 0–21, with higher scores indicating greater anxiety. Cut points of 5, 10, and 15 might be interpreted as representing mild, moderate, and severe levels of anxiety, respectively (Spitzer et al. 2006).

- Work Productivity and Activity Index (WPAI)

  The WPAI (see Appendix 12) is a 6-item questionnaire that measures four domains of health-related quality of life associated with reduced productivity: absenteeism, presenteeism, work productivity loss, and activity impairment. The absenteeism is assessed as a percentage of total work time that a patient missed due to a health problem. The presenteeism is evaluated as the extent to which a health problem affected patient's productivity while working. The total productivity loss is the product of absenteeism and presenteeism combined. The impact on activities of daily living represents to what extent a health problem affected the patient's activities of daily living outside of work. The scores are generated as percentages for each of the abovementioned domains, with higher scores indicating more productivity problems associated with the health state (Reilly et al. 1993).

- Patient Global Impression of Change (P-GIC) scale

  The P-GIC (see Appendix 13) is a one-item scale asking patients to rate the change in their CIU they experienced since the beginning of the study (Genentech data on file). The questionnaire is intended to understand how patients subjectively perceive the change in their CIU.

Adverse event reports will not be derived from PRO data by the Sponsor. However, any PRO responses suggestive of a possible adverse event that are identified during site review of the PRO data should be reported as outlined in Section 5.3.5.

4.5.9 Clinician-Reported Outcomes

- In-Clinic Measured Urticaria Activity Score (IC-UAS)

  The IC-UAS (see Appendix 14) is a paper-based, in-clinic measured UAS based on the patient's condition during the 12 hours prior to the visit. This score will be recorded every 4 weeks as outlined in the schedule of assessments (see Appendix 1, Appendix 2, and Appendix 3). The IC-UAS should be completed by a healthcare professional based on an interview of the patient.

  The IC-UAS is a composite score with numeric severity intensity ratings (0 = none to 3 = intense/severe) for the number of wheals (hives) and the severity of the itch. The maximum IC-UAS value is 6.

- Clinician Global Impression of Change (C-GIC) scale

  The C-GIC (see Appendix 15) is a one-item scale asking clinicians to rate the change in the patient's CIU since the beginning of the study (Genentech data on file). The questionnaire is intended to understand how clinicians subjectively perceive the change in the patient's CIU.

4.5.10 Samples for Roche Clinical Repository

Genentech is a member of the Roche group and participates in the collection and/or submission of biological samples to the Roche Clinical Repository (RCR). Collection and submission of biological samples to the RCR is contingent upon the review and approval of the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site is not granted the necessary approval for RCR sampling, this section of the protocol will not be applicable at that site.

4.5.10.1 Overview of the Roche Clinical Repository

The RCR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.10.2 Sample Collection

The following samples will be collected and stored in the RCR for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers related to omalizumab or CIU:

- Blood for biomarker and biochemical analyses (required for patients consenting to participate in this study)
- Whole blood for RNA extraction (optional)
- Remaining blood samples from study-related procedures (optional)

For all samples, dates of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

4.5.10.3 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

4.5.10.4 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate in the study ML29510. Patients may also withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional blood RNA samples and remaining blood samples from study-related

procedures for storage in the RCR. Patients who decline to participate in the collection of these optional samples will not provide a separate signature. A separate, specific signature is not required for submission of blood for biomarker and biochemical analyses to the RCR.

The investigator should document whether or not the patient has given consent to participate in optional blood RNA samples and remaining blood samples from study-related procedures for storage in the RCR by completing the appropriate section of the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.10.5 Withdrawal from the Roche Clinical Repository

Patients have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study ML29510 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study ML29510.

4.5.10.6 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

4.6.3 Study and Site Discontinuation

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

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

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Omalizumab (Xolair) is currently registered in over 90 countries and is indicated for adults and children (6 years of age and above in the E.U.) with moderate to severe persistent allergic asthma whose symptoms are inadequately controlled with inhaled corticosteroids.

As of 30 June 2014, Xolair is currently registered in over 40 countries, including the U.S., for adults and adolescents (12 years of age and above) with chronic spontaneous (idiopathic) urticaria refractory to standard of care. Consult local prescribing information for more information.

The adverse event profile of omalizumab observed during the allergic asthma clinical development program was very similar to placebo with the most commonly reported adverse reactions were injection site reactions, including injection site pain, swelling, erythema, pruritus, and headaches.

Of the adverse events of special interest, anaphylactic reactions were observed but were rare and typically occurring within 2 hours of the first injection.

Although a numerical imbalance in malignancy was observed in the omalizumab treatment group compared with the control group, the short exposure duration is not consistent with the biology of solid organ pathogenesis; additionally, the diversity in the type of cancers observed and the clinical features of the individual cases render a causal relationship unlikely.

The overall adverse event profile in the pooled Phase III CSU studies was consistent with the known safety profile of omalizumab in patients with allergic asthma, with the exception of adverse events that were specifically related to the respective indications.

The overall incidence of adverse events across the omalizumab treatment groups was broadly similar to that seen with placebo. In general, omalizumab at the proposed doses of 150 mg and 300 mg was well tolerated in the treatment of patients with severe, refractory CSU/CIU, including in patients with multiple concomitant medications. Both doses appeared to be well tolerated, with no evidence of dose-related adverse events. Injection site reactions are a known side effect of omalizumab treatment, and those observed in CSU/CIU patients were consistent with those observed in allergic asthma. There were no subsets of patients identified who had increased risks of serious adverse events or adverse events of special interest.

During the conduct of the study, a treatment assignment may be unblinded only in the event of a life-threatening medical emergency that requires immediate unblinding/unmasking. In such cases, unblinding will be implemented following standard

procedures, and only following agreement by both the investigator and Medical Monitor that unblinding is necessary.

The Sponsor Safety Reporting Department (independent from the study team) will break the treatment code for all unexpected serious adverse events that are considered by the investigator to be related to study drug for the purpose of regulatory reporting. The study team will remain blinded to study treatment.

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.

An iDMC will review blinded and unblinded safety data provided by an iDCC every 6 months for the duration of the study.

Events described in Section 5.1.1 through Section 5.1.3 will be closely monitored and represent selected adverse events for this study.

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

5.1.1 Anaphylaxis

Anaphylaxis has been reported to occur after administration of omalizumab in premarketing clinical trials and in postmarketing spontaneous reports. Signs and symptoms in these reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been life-threatening. In premarketing clinical trials in patients with asthma, anaphylaxis was reported in 3 of 3507 (0.1%) patients.

In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to omalizumab use was estimated to be at least 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as early as after the first dose of omalizumab, but also has occurred beyond 1 year after beginning regularly scheduled treatment.

The analysis of all cases of anaphylaxis submitted to Novartis show that, the majority of anaphylactic-type reactions have been reported to occur after the first dose with numbers decreasing with subsequent doses. As expected for an anaphylactic-type reaction (Type I), events were reported to occur predominantly within the first 2 hours post-dosing with few reports occurring as far as $>$36 hours post-dose.

Warning

Because of the risk of anaphylaxis, patients should be closely observed for an appropriate period of time after omalizumab administration, and healthcare providers administering omalizumab should be prepared to manage anaphylaxis that can be life-threatening. Patients should also be informed of the signs and symptoms of anaphylaxis and instructed to seek immediate medical care should symptoms occur.

Please refer to the Omalizumab Investigator's Brochure for additional information.

5.1.2 Clinical Trial Experience with Omalizumab in Patients with CIU

The safety of omalizumab for the treatment of CIU was assessed in three placebo-controlled, multiple-dose clinical trials of 12 weeks (CIU Trial 2) and 24 weeks in duration (CIU Trials 1 and 3). The data described in Table 2 below reflect omalizumab exposure for 733 patients enrolled and receiving at least one dose of omalizumab in the three clinical trials, including 684 patients exposed for 12 weeks and 427 exposed for 24 weeks.

Table 2 Adverse Reactions Occurring in ≥2% in Omalizumab-Treated Patients and More Frequently than in Patients Treated with Placebo (Day 1 to Week 12) in CIU Trials

	CIU Trials 1, 2, and 3 Pooled		
Adverse Reactions [a]	Omalizumab 150 mg (n=175)	Omalizumab 300 mg (n=412)	Placebo (n=242)
Gastrointestinal disorders			
Nausea	2 (1.1%)	11 (2.7%)	6 (2.5%)
Infections and infestations			
Nasopharyngitis	16 (9.1%)	27 (6.6%)	17 (7.0%)
Sinusitis	2 (1.1%)	20 (4.9%)	5 (2.1%)
Upper respiratory tract infection	2 (1.1%)	14 (3.4%)	5 (2.1%)
Viral upper respiratory tract infection	4 (2.3%)	2 (0.5%)	(0.0%)
Musculoskeletal and connective tissue disorders			
Arthralgia	5 (2.9%)	12 (2.9%)	1 (0.4%)
Nervous system disorders			
Headache	21 (12.0%)	25 (6.1%)	7 (2.9%)
Respiratory, thoracic, and mediastinal disorders			
Cough	2 (1.1%)	9 (2.2%)	3 (1.2%)

CIU=chronic idiopathic urticaria.

[a] by MedDRA (15.1) System Organ Class and Preferred Term.

Malignancies

A small numerical imbalance (0.5% vs. 0.2%) in malignant neoplasms was observed in clinical studies of adults and adolescents (≥12 years of age) with asthma and other allergic disorders. The observed malignancies in omalizumab-treated patients were a variety of types, with breast, non-melanoma skin, prostate, melanoma, and parotid occurring more than once, and five other types occurring once each. The majority of patients were observed for less than 1 year.

A subsequent observational study, A Epidemiologic Study of Xolair (Omalizumab): Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate to Severe Asthma (EXCELS), was done as a post-marketing commitment to the FDA. This study's pre-specified primary outcomes measures were all malignancy, all malignancies excluding non-melanoma skin carcinoma, and overall serious adverse events. This study enrolled 5007 omalizumab-treated and 2829 non-omalizumab-treated patients ≥12 years old with moderate to severe persistent asthma and followed them for up to 5 years, with mean follow-up of 3.7 years. Patients were not randomized or blinded and were assigned to omalizumab or non-omalizumab cohorts based on clinical decisions related to initiation and continuation of omalizumab. In EXCELS, the incidence rates of primary malignancies (per 1000 patient years) were similar among omalizumab-treated (12.3) and non-omalizumab-treated patients (13.0). However, study limitations preclude definitively ruling out a malignancy risk with omalizumab. Study limitations include: the observational study design, the bias introduced by allowing enrollment of patients previously exposed to omalizumab (88%), enrollment of patients (56%) while a history of cancer or a premalignant condition were study exclusion criteria, and the high study discontinuation rate (44%).

Cardiovascular and Cerebrovascular Events from Clinical Studies in Patients with Asthma

In the observational EXCELS study, a higher incidence rate of overall cardiovascular and cerebrovascular serious adverse events was observed in omalizumab-treated patients (13.4) compared to non-omalizumab-treated patients (8.1). Increases in rates were observed for transient ischemic attack (0.7 vs. 0.1), myocardial infarction (2.1 vs. 0.8), pulmonary hypertension (0.5 vs. 0), pulmonary embolism/venous thrombosis (3.2 vs. 1.5), and unstable angina (2.2 vs. 1.4), while the rates observed for ischemic stroke and cardiovascular death were similar among both study cohorts.

In the observational EXCELS study, patients were not randomized or blinded and were assigned to omalizumab or non-omalizumab cohorts based on clinical decisions related to initiation and continuation of omalizumab. Omalizumab and non-omalizumab cohorts were balanced for smoking history and age. However, baseline cardiovascular risk factors were higher in the omalizumab-treated cohort than the non-omalizumab-treated cohort (Food and Drug Administration 2014). More omalizumab-treated patients were diagnosed with severe asthma (50%) compared to the non-omalizumab-treated patients (23%).

Interpretation of the EXCELS study results related to cardiovascular and cerebrovascular events has been limited by the observational study design, the inclusion of patients previously exposed to omalizumab (88%), baseline imbalances in cardiovascular risk factors between the treatment groups, an inability to adjust for unmeasured risk factors, and the high study discontinuation rate.

A separate pooled analysis of 25 randomized double-blind, placebo-controlled clinical trials of 8 to 52 weeks in duration included 3342 omalizumab-treated patients and 2895 placebo-treated patients. The primary outcomes of interest included cardiovascular death, myocardial infarction, arrhythmias, heart failure, stroke, transient ischemic attack, pulmonary hypertension, pulmonary embolism, and unstable angina. Across all the studies, a total of 8 events occurred in the omalizumab-treated patients compared with 15 in the placebo patients, and no notable differences were observed in the rates of specific cardiovascular events (Food and Drug Administration 2014). However, the results of the pooled analysis were based on a low number of events, slightly younger patients, and shorter duration of follow-up than the observational EXCELS study; therefore, the results are insufficient to confirm or reject the findings noted in the observational EXCELS study.

5.1.3 Management of Specific Adverse Events

Guidelines for management of specific adverse events are outlined in Table 3.

Table 3 Guidelines for Management of Specific Adverse Events

Event	Action to Be Taken
Anaphylaxis	• Administer omalizumab only in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. • Observe patients closely for an appropriate period of time after administration of omalizumab. • Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs or symptoms occur.
Acute asthma symptoms	• Omalizumab has not been shown to alleviate asthma exacerbations acutely. • Do not use omalizumab to treat acute bronchospasm or status asthmaticus.
Angioedema	• Patients with CIU can have angioedema as part of their symptoms. – When angioedema poses a risk to the airway, the emergent use of systemic corticosteroids is indicated. – Patients who need to be treated with systemic corticosteroids will be discontinued from study treatment and followed for safety for the remainder of the study. – Patients will be provided emergency contact information and advised to contact a physician during the entire study, in case of angioedema.
Serum sickness	• In post-approval use, some patients have experienced a constellation of signs and symptoms including arthritis/arthralgia, rash, fever, and lymphadenopathy with an onset 1 to 5 days after the first or subsequent injections of omalizumab. – These signs and symptoms have recurred after additional doses in some patients. – Although circulating immune complexes or a skin biopsy consistent with a Type III reaction were not seen with these cases, these signs and symptoms are similar to those seen in patients with serum sickness. – Physicians should stop omalizumab if a patient develops this constellation of signs and symptoms.
Parasitic infections	• Monitor patients at high risk of geohelminth infection while on omalizumab therapy. Insufficient data are available to determine the length of monitoring required for geohelminth infections after stopping omalizumab treatment.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
  - This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.1 for reporting instructions).

5.2.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.1 for reporting instructions). Adverse events of special interest for this study include the following:

- Suspected anaphylaxis due to omalizumab, as defined by Sampson's criteria (Sampson et al. 2006; see Appendix 16)
- 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 (see Section 5.3.5.6).

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4, Section 5.5, and Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

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

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.1 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 112 days (approximately 5 drug half-lives) after the last administration of study drug or study discontinuation/termination, whichever is later. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

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

5.3.3 Assessment of Severity of Adverse Events

Table 4 provides guidance for assessing adverse event severity.

Table 4 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating “yes” or “no” accordingly. The following guidance should be taken into consideration (see also Table 5):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 5 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.1 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from “non-serious” to “serious,” providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment
  - Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 $\times$ ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.1).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.1). This includes death attributed to progression of CIU.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

If the death is attributed to progression of CIU, "chronic idiopathic urticaria progression" should be recorded on the Adverse Event eCRF.

5.3.5.8 Preexisting Medical Conditions

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

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

5.3.5.9 Lack of Efficacy or Worsening of Chronic Idiopathic Urticaria

Medical occurrences or symptoms of deterioration that are anticipated as part of CIU should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of CIU on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “accelerated chronic idiopathic urticaria”).

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event

The following hospitalization scenarios are not considered to be serious adverse events, but should be reported as adverse events instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available

5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.1).

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately using the contact information provided in Section 5.4.1.1; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.1 for further details)
- Non-serious adverse events of special interest (see Section 5.4.1 for further details)
- Pregnancies (see Section 5.4.2 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Reporting Requirements for Serious Adverse Events and Non-Serious Adverse Events of Special Interest

5.4.1.1 Events That Occur prior to Study Drug Initiation

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. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided below.

Genentech Drug Safety Department

Fax No.:	650-225-4630
Alternate Fax No:	650-225-4682
Email:	us_drug.safety@gene.com

5.4.1.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported until 112 days (approximately 5 drug half-lives) after the last administration of study drug or study discontinuation/termination, whichever is later. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided in Section 5.4.1.1. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.2 Reporting Requirements for Pregnancies

5.4.2.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 112 days after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the patient, discussing the risks of the

pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided in Section 5.4.1.1. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.2.2 Congenital Anomalies/Birth Defects and Abortions

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.1). Any abortion should be reported in the same fashion (as the Sponsor considers abortions to be medically significant).

5.4.3 Medical Contact

Genentech Medical Monitor:

[redacted], M.D.

Genentech, Inc.

Telephone No.: [redacted]

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.2.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 112 days [approximately 5 drug half-lives] after the last administration of study drug or study discontinuation/termination, whichever is later), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided in Section 5.4.1.1.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the U.S. prescribing information for omalizumab, found in the USPI.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 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 • 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.

6.2 SUMMARIES OF CONDUCT OF STUDY

The disposition of patients for each study period will be summarized by treatment group with respect to the number of patients randomized, treated, and completing each 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.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Treatment groups entering the double-blind randomization period of the study will be assessed for comparability with respect to demographic (e.g., age, sex, race/ethnicity) and baseline characteristics (e.g., body weight, total IgE levels, UAS7).

6.4 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.

6.4.1 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.

6.4.2 Primary Efficacy Endpoint

The primary efficacy endpoint for this study is the percentage of patients who experience a clinical worsening of CIU as defined by UAS7 ≥ 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.

6.4.3 Secondary Efficacy Endpoints

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 ≥ 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.
- Percentage of patients who experience a clinical worsening of CIU as defined by UAS7 > 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 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.
- 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 and analyzed in the context of a non-inferiority hypothesis test with non-inferiority margin 5. The p-value from the non-inferiority 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 using a 2-sided, one sample t-test. The p-value from this test will be used to evaluate the superiority of retreating after experiencing clinical worsening among these patients.

6.5 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.

6.6 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Serum total omalizumab, and total and free IgE concentration versus time data will be tabulated by treatment group and summarized using descriptive statistics (e.g., mean, standard deviation, minimum, and maximum). Additional PK and PD analyses may be conducted as appropriate.

6.7 EXPLORATORY ANALYSES

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

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. Central laboratory data or other electronic data will be sent

directly to the CRO, using the CRO's standard procedures to handle and process the electronic transfer of these data.

The Sponsor will perform oversight of the data management of this study, including approval of the CRO's data management plans and specifications. Data will be periodically transferred electronically from the CRO to the Sponsor, and the Sponsor's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO's standard procedures.

Patient eDiary data will be collected through use of an electronic device provided by a vendor. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The eDiary device data will be available for view access only via secure access to a web server. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor and study sites will have view access only to the web server. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Paper PRO questionnaires will be faxed or couriered from the site to the data entry center. Scanned paper PROs will be transferred via a secure email system.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the CRO and should be handled in accordance with instructions from the CRO.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

Once the study is complete, the eDiary data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the

compact disc is required. In addition, the Sponsor will receive all patient data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

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

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

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, PRO completed forms, eDiary data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the E.U. or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Home Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

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

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

Each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible

for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

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

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

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored by Genentech, a member of the Roche group, and will be managed by Genentech and a CRO. The CRO will provide clinical operations management, data management, and medical monitoring. An IxRS will be used to assign patient numbers, monitor enrollment and patient status, and to manage study treatment requests and shipments.

Patient data will be recorded via an EDC system using eCRFs (see Section 7.2).
A blinded external adjudication committee will review potential events of anaphylaxis.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect

proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001;2:297–307.

Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol 2014;133:1270–7.

Fiebiger E, Maurer D, Holub H, et al. Serum IgG autoantibodies directed against the alpha chain of Fc epsilon RI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? J Clin Invest 1995;96:2606–12.

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210–16.

Food and Drug Administration. FDA Drug Safety Communication: FDA approves label changes for asthma drug Xolair (omalizumab), including describing slightly higher risk of heart and brain adverse events. 26 September 2014 [cited 24 October 2014]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm414911.htm.

Grattan CE, Francis DM, Hide M, et al. Detection of circulating histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. Clin Exp Allergy 1991;21:695–704.

Greaves MW. Chronic idiopathic urticaria. Curr Opin Allergy Clin Immunol 2003;3:363–8.

Hide M, Francis DM, Grattan CE, et al. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N Engl J Med 1993;328:1599–604.

Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. J Allergy Clin Immunol 2013;132:101–9.

Kozel MM, Sabroe RA. Chronic urticaria: aetiology, management and current and future treatment options. Drugs 2004;64:2515–36.

Maurer M, Rosén K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. N Engl J Med. 2013;368:924–35.

Morin CM. Insomnia: Psychological Assessment and Management. New York, NY: Guilford Press; 1993.

Niimi N, Francis DM, Kermani F, et al. Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. J Invest Dermatol 1996;106:1001–6.

Reilly MC, Zbrozek AS, Dukes E. The validity and reproducibility of a work productivity and activity impairment measure. PharmacoEconomics 1993;4:353–65.

Saini SS, Bindslev-Jensen C, Maurer M. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. J Invest Dermatol 2014 Jul 21. doi: 10.1038/jid.2014.306. [Epub ahead of print]

Saini S, Rosen KE, Hsieh HJ. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. J Allergy Clin Immunol 2011;128:567–73.

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117:391–7.

Shikiar R, Harding G, Leahy M, et al. Minimal Important Difference (MID) of the Dermatology Life Quality Index (DLQI): results from patients with chronic idiopathic urticaria. Health Qual Life Outcomes 2005;3:36.

Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092–7.

Tilles SA. Approach to therapy in chronic urticaria: when benadryl is not enough. Allergy Asthma Proc 2005;26:9–12.

Tong LJ, Balakrishnan G, Kochan JP, et al. Assessment of autoimmunity in patients with chronic urticaria. J Allergy Clin Immunol 1997;99:461–5.

Weller K, Groffik A, Church MK, et al. Development and validation of the Urticaria Control Test: a patient-reported outcome instrument for assessing urticaria control. J Allergy Clin Immunol. 2014;133:1365–72.

XOLAIR® (omalizumab) U.S. Package Insert, Genentech USA, Inc. and Novartis Pharmaceuticals Corporation. 2014 Mar [cited 2014 Apr 15]. Available from http://www.gene.com/download/pdf/xolair_prescribing.pdf.

Yang M, Morin CM, Schaefer K, et al. Interpreting score differences in the Insomnia Severity Index: using health-related outcomes to define the minimally important difference. Curr Med Res Opin. 2009;25:2487–94

Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy 2014;69:868–87.

Zweiman B, Valenzano M, Atkins PC. Modulation of serum histamine releasing activity in chronic idiopathic urticaria. Immunopharmacology 1998;39:225–34.

Appendix 1
Schedule of Assessments for Screening and Open-Label Treatment Period

	Screening [a]		Open-Label Treatment Period (Baseline to Week 24)							Follow-Up Visit for Non-Responders [c]	ET [d]
End of Study Week			Baseline	4	8	12	16	20	24 [b]		
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 [e]	x										
Vital signs (blood pressure and pulse) [f]	x		x	x	x	x	x	x	x		x
Physical examination [g]	x										
Weight/height	x										x
Pregnancy test [h]	x		x	x	x	x	x	x	x		
Concomitant medication usage	x	x	x	x	x	x	x	x	x	x	x
Adverse events [i]		x	x	x	x	x	x	x	x	x	x
Open-label omalizumab administration			x	x	x	x	x	x			
Study drug/placebo administration [b]									x [b]		
Site to contact IxRS	x		x	x	x	x	x	x	x	x	x
PROs											
Patient eDiary [j]	x	x	x	x	x	x	x	x	x		x
DLQI [k]			x			x			x	x	x
UCT [k]	x		x			x			x	x	x

APPENDIX 1 (cont'd)
Schedule of Assessments for Screening and Open-Label Treatment Period

	Screening [a]		Open-Label Treatment Period (Baseline to Week 24)							Follow-Up Visit for Non-Responders [c]	ET [d]
End of Study Week			Baseline	4	8	12	16	20	24 [b]		
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		
U-AIM [k]	x		x			x			x	x	x
ISI [k]			x			x			x	x	x
GAD-7 [k]			x			x			x	x	x
WPAI [k]			x			x			x	x	x
P-GIC scale [k]									x		
IC-UAS [k]	x	x	x						x	x	x
C-GIC scale [k]									x		
Laboratory tests [l]											
Hematology [m]	x								x		x
Stool ova and parasite evaluation [n]		x									
Chemistry [o]	x										
Urinalysis [p]	x										
Thyroperoxidase antibody	x										
CU index	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

APPENDIX 1 (cont'd)
Schedule of Assessments for Screening and Open-Label Treatment Period

	Screening [a]		Open-Label Treatment Period (Baseline to Week 24)							Follow-Up Visit for Non-Responders [c]	ET [d]
End of Study Week			Baseline	4	8	12	16	20	24 [b]		
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		
Blood RNA (optional) [q]	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.

[a] 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.

[b] 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 (see Appendix 2).

[c] 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.

[d] 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."

[e] 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.

[f] 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.

[g] 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.

[h] 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.

[i] 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 (see Section 5.6). 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.

[j] 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.

[k] 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.

[l] Samples for laboratory tests will be taken pre-dose on dosing days.

[m] 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).

[n] 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.

[o] 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.

[p] 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).

[q] 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 2
Schedule of Assessments for Double-Blind Randomization Period and Follow-Up Period

	Double-Blind Randomization Period [a] (Week 24 to Week 48)							Follow-Up Period [b] (Week 48 to Week 60)			ET
End of Study Week	24 [c]	28	32	36	40	44	48 [d,e]	52 [e]	56 [e]	60 [e]	
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) [f]	x	x	x	x	x	x	x			x	x
Weight/height										x	x
Pregnancy test [g]	x	x	x	x	x	x					
Concomitant medication usage	x	x	x	x	x	x	x	x	x	x	x
Adverse events [h]	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 [i]	x	x	x	x	x	x	x	x	x	x	x
DLQI [j]	x			x			x			x	x
UCT [j]	x			x			x			x	x
U-AIM [j]	x			x			x			x	x
ISI [j]	x			x			x			x	x
GAD-7 [j]	x			x			x			x	x
WPAI [j]	x			x			x			x	x
P-GIC scale [j]	x						x				
IC-UAS [j]	x			x			x			x	x
C-GIC scale [j]	x						x				

APPENDIX 2 (cont'd)
Schedule of Assessments for Double-Blind Randomization Period and Follow-Up Period

	Double-Blind Randomization Period [a] (Week 24 to Week 48)							Follow-Up Period [b] (Week 48 to Week 60)			ET
End of Study Week	24 [c]	28	32	36	40	44	48 [d,e]	52 [e]	56 [e]	60 [e]	
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 [k]											
Hematology [l]	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) [m]	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.

[a] 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 according to Appendix 3.

[b] The 12-week follow-up period applies only to patients who have completed the first 48 weeks of the study.

[c] 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 (see Appendix 1) and do not need to be repeated for the double-blind randomization period.

[d] The Week 48 visit is the end of the double-blind randomization period and the beginning of the follow-up period.

[e] 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.

[f] 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.

[g] 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.

[h] 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 (see Section 5.6). 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.

[i] 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.

[j] 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.

[k] Samples for laboratory tests will be taken pre-dose on dosing days.

[l] 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).

[m] 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 3
Schedule of Assessments for Patients Who Transition to Open-Label Omalizumab after Randomization

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

APPENDIX 3 (cont'd)
Schedule of Assessments for Patients Who Transition to Open-Label Omalizumab After Randomization

	First Day of Transition	Post-Randomization Open-Label Treatment Period [a]		Follow-Up Period [b]			ET
		Every 4 Weeks Until 48 Weeks of Total Treatment	Week 48 [c]	Week 52 [c]	Week 56 [c]	Week 60 [c]	
Visit Window (days)		±3	±3	±3	±3	±3	±3
IC-UAS [h]	x		x			x	x
C-GIC scale [h]	x		x				
Laboratory tests [i]							
Hematology [j]	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) [k]	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.

[a] 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.

[b] The 12-week follow-up period applies only to patients who have completed the first 48 weeks of the study.

[c] 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.

[d] 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.

[e] 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.

[f] 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 (see Section 5.6). 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.

[g] 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.

[h] 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.

[i] Samples for laboratory tests will be taken pre-dose on dosing days.

[j] Hematology to include hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent, and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells).

[k] 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 4
Study Drug Preparation and Administration

An unblinded pharmacist or other qualified designated individual will prepare the study drug (omalizumab or placebo) injection as outlined below.

RECONSTITUTION

The supplied study drug must be reconstituted with Sterile Water for Injection (SWFI), USP, using the following instructions:

1. Before reconstitution, determine the number of vials that will need to be reconstituted (each vial delivers 150 mg of study drug).
2. Draw 1.4 mL SWFI, USP, into a 3-mL syringe equipped with a 1-inch, 18-gauge needle.
3. Place the vial upright on a flat surface and, using standard aseptic technique, insert the needle and inject the SWFI, USP, directly onto the product.
4. Keeping the vial upright, gently swirl the upright vial for approximately 1 minute to evenly wet the powder. Do not shake.
5. Gently swirl the vial for 5 to 10 seconds approximately every 5 minutes in order to dissolve any remaining solids. **The lyophilized product takes 15 to 20 minutes to dissolve.** If it takes longer than 20 minutes to dissolve completely, gently swirl the vial for 5 to 10 seconds approximately every 5 minutes until there are no visible gel-like particles in the solution. Do not use if the contents of the vial do not dissolve completely in 40 minutes.
6. After reconstitution, the study drug solution is somewhat viscous and will appear clear or slightly opalescent. It is acceptable if there are a few small bubbles or foam around the edge of the vial; there should be no visible gel-like particles in the reconstituted solution. Do not use if foreign particles are present.
7. Invert the vial for 15 seconds to allow the solution to drain toward the stopper.
8. **Use the study drug solution within 8 hours following reconstitution when stored in the vial at 2 to 8°C (36 to 46°F), or within 4 hours of reconstitution when stored at room temperature.** Reconstituted study drug vials should be protected from sunlight.
9. Using a new 3-mL syringe equipped with a 1-inch, 18-gauge needle, insert the needle into the inverted vial. Position the needle tip at the very bottom of the solution in the vial stopper when drawing the solution into the syringe. The reconstituted product is somewhat viscous; in order to obtain the full 1.2-mL dose, **all of the product must be withdrawn** from the vial before expelling any air or excess solution from the syringe. Before removing the needle from the vial, pull the plunger all the way back to the end of the syringe barrel to remove all of the solution from the inverted vial.
10. Replace the 18-gauge needle with a 25-gauge needle for subcutaneous (SC) injection.

11. Expel air, large bubbles, and any excess solution in order to obtain the required 1.2-mL dose. A thin layer of small bubbles may remain at the top of the solution in the syringe.

ADMINISTRATION

Administer study drug by SC injection. The injection may take 5–10 seconds to administer because the solution is slightly viscous. Do not administer more than 150 mg (contents of one vial) per injection site.

Cap the syringe. Label the syringe with the patient number, kit number details, and protocol number (ML29510). The syringe is now ready for use.

Appendix 5
Study Drug Dosing and Scheduling Table

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

Dose (mg)	Number of Injections	Total Volume Injected (mL) [a]
300	2 injections: 1.2 mL omalizumab + 1.2 mL omalizumab	2.4
Placebo	2 injections: 1.2 mL placebo + 1.2 mL placebo	2.4

[a] 1.2 mL maximum delivered volume per vial.

Appendix 6
Patient Electronic Diary (eDiary)

Note: The patient eDiary is also referred to as the Urticaria Patient Daily Diary (UPDD).

GENERAL INSTRUCTIONS

Please answer each question to the best of your ability.

There are no right or wrong answers.

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

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

INSTRUCTIONS FOR COUNTING THE NUMBER OF HIVES AND MEASURING THE SIZE OF THE LARGEST HIVE

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

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

APPENDIX 6 (cont'd)
Patient Electronic Diary (eDiary)

Today's Date

		-				-				

Day **Month** **Year**

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

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

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

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

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

APPENDIX 6 (cont'd)
Patient Electronic Diary (eDiary)

Today's Date

		-				-				

Day **Month** **Year**

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

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

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

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

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

APPENDIX 6 (cont'd)
Patient Electronic Diary (eDiary)

Today's Date

		-				-				
Day			**Month**				**Year**			

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

(Please circle only one response.)

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

   0 No interference

   1 Mild, little interference with sleep

   2 Moderate, awoke occasionally, some interference with sleep

   3 Substantial, woke up often, severe interference with sleep

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

   0 No interference

   1 Mild, little interference with daily activities

   2 Moderate, some interference with daily activities

   3 Substantial, severe interference with daily activities

APPENDIX 6 (cont'd)
Patient Electronic Diary (eDiary)

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

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

   0 = 0 pills

   1 = 1 pill

   2 = 2 pills

   3 = 3 pills

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

   0 = No (**GO TO Question 7**) 1 = Yes

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

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

   1 Took some prescription or non-prescription medication

   2 Called my doctor, nurse, or nurse practitioner

   3 Went to see my doctor, nurse, or nurse practitioner

   4 Went to the emergency room at the hospital

   5 Was hospitalized

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

   0 = No 1 = Yes

Appendix 7
Dermatology Life Quality Index (DLQI)

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

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

Please check you have answered EVERY question. Thank you.

Appendix 8
Urticaria Control Test (UCT)

Patient name: _____ Date: (dd mmm yyyy): ___ ____ _____

Date of birth (dd mmm yyyy): ___ ____ _____

Instructions: You have urticaria. The following questions should help us understand your current health situation. Please read through each question carefully and choose an answer from the five options that *best fits* your situation. Please limit yourself to *the last four weeks*. *Please don't think about the questions for a long time*, and do remember to answer *all questions* and to provide *only one answer to each question.*

1. How much have you suffered from the **physical symptoms of the urticaria (itch, hives (welts) and/or swelling)** in the last four weeks?

   O very much O much O somewhat O a little O not at all

2. How much was your **quality of life** affected by the urticaria in the last 4 weeks?

   O very much O much O somewhat O a little O not at all

3. How often was the **treatment** for your urticaria in the last 4 weeks **not enough** to control your urticaria symptoms?

   O very often O often O sometimes O seldom O not at all

4. **Overall**, how well have you had your urticaria **under control** in the last 4 weeks?

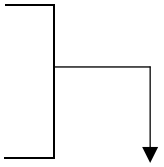
   O not at all O a little O somewhat O well O very well

Appendix 9
Urticaria Activity and Impact Measure (U-AIM)

This questionnaire asks you about your **urticaria** and how it may have affected your life **in the past 7 days**. Please answer each question to the best of your ability. There are no right or wrong answers. For each question, mark an ☒ in the one box that best describes your experience.

1. Thinking about your urticaria in the past 7 days, on average, **how severe was your itch**?

☐ 0 None (skip to question 2)
☐ 1 Mild
☐ 2 Moderate
☐ 3 Severe

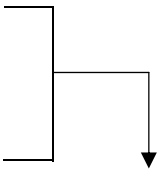


1a. In the past 7 days, how much of the time did your **itch bother** you?

☐ 0 None of the time
☐ 1 A little of the time
☐ 2 Some of the time
☐ 3 Most of the time
☐ 4 All of the time

2. Thinking about your urticaria in the past 7 days, on average, **how many hives** did you have per day? Count *each hive separately* even if you had more than one hive grouped together with other hives.

☐ 0 None (skip to question 3)
☐ 1 Between 1 and 6 hives
☐ 2 Between 7 and 12 hives
☐ 3 Greater than 12 hives



2a. In the past 7 days, how much of the time did your **hives bother** you?

☐ 0 None of the time
☐ 1 A little of the time
☐ 2 Some of the time
☐ 3 Most of the time
☐ 4 All of the time

3. In the past 7 days, how many days did you have any **rapid swelling** on your face, (especially your eyelids or lips), inside your mouth (including your throat or tongue), or elsewhere on your body? This rapid swelling, also called **angioedema**, is at a deeper level under your skin than hives.

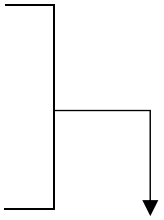
☐ 0 Did not experience angioedema (skip to question 4)

☐ 1 1 – 2 days

☐ 2 3 – 4 days

☐ 3 5 – 6 days

☐ 4 7 days



3a. In the past 7 days, how much of the time did this **rapid swelling (angioedema) bother** you?

☐ 0 None of the time

☐ 1 A little of the time

☐ 2 Some of the time

☐ 3 Most of the time

☐ 4 All of the time

4. In the past 7 days, how much of the time did urticaria symptoms **interfere with your daily activities**? This could include work, school, sports, hobbies, and activities with friends and family.

☐ 0 None of the time

☐ 1 A little of the time

☐ 2 Some of the time

☐ 3 Most of the time

☐ 4 All of the time

5. In the past 7 days, how much of the time did urticaria symptoms **interfere with your sleep**?

☐ 0 None of the time

☐ 1 A little of the time

☐ 2 Some of the time

☐ 3 Most of the time

☐ 4 All of the time

APPENDIX 9 (cont'd)
Urticaria Activity and Impact Measure (U-AIM)

6. How would you rate your **urticaria control** in the past 7 days?

- ☐ 0 Completely controlled
- ☐ 1 Well controlled
- ☐ 2 Somewhat controlled
- ☐ 3 Poorly controlled
- ☐ 4 Not controlled at all

Please check that you answered *every* question. Thank you for your answers!

Appendix 10
Insomnia Severity Index (ISI)

Subject ID: _____ Date: _____

For each question below, please circle the number corresponding most accurately to your sleep patterns in the last **two weeks.**

For the first three questions, please rate the **SEVERITY** of your sleep difficulties.

1. Difficulty falling asleep:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

2. Difficulty staying asleep:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

3. Problem waking up too early in the morning:

None	Mild	Moderate	Severe	Very Severe
0	1	2	3	4

4. How **SATISFIED/DISSATISFIED** are you with your current sleep pattern?

Very Satisfied	Satisfied	Neutral	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. To what extent do you consider your sleep problem to **INTERFERE** with your daily functioning (e.g., daytime fatigue, ability to function at work/daily chores, concentration, memory, mood).

Not at all Interfering	A Little Interfering	Somewhat Interfering	Much Interfering	Very Much Interfering
0	1	2	3	4

6. How **NOTICEABLE** to others do you think your sleeping problem is in terms of impairing the quality of your life?

Not at all Noticeable	A Little Noticeable	Somewhat Noticeable	Much Noticeable	Very Much Noticeable
0	1	2	3	4

7. How **WORRIED/DISTRESSED** are you about your current sleep problem?

Not at all	A Little	Somewhat	Much	Very Much
0	1	2	3	4

APPENDIX 10 (cont'd)
Insomnia Severity Index (ISI)

Guidelines for Scoring/Interpretation:

Add scores for all seven items = _____

Total score ranges from 0–28

0–7 = No clinically significant insomnia

8–14 = Subthreshold insomnia

15–21 = Clinical insomnia (moderate severity)

22–28 = Clinical insomnia (severe)

Appendix 11
Generalized Anxiety Disorder 7 Item (GAD-7) Scale

GAD-7				
Over the <u>last 2 weeks</u>, how often have you been bothered by the following problems? *(Use "✓" to indicate your answer)*	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

(For office coding: Total Score T____ = ____ + ____ + ____)

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

Appendix 12
Work Productivity and Activity Impairment Questionnaire: Chronic Urticaria V2.0 (WPAI:CU)

The following questions ask about the effect of your chronic urticaria on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? ____ No ____ Yes

   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your chronic urticaria? *Include hours you missed on sick days, times you went in late, left early, etc., because of your chronic urticaria. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____ HOURS

4. During the past seven days, how many hours did you actually work?

   _____ HOURS (*If "0", skip to question 6.*)

APPENDIX 12 (cont'd)
Work Productivity and Activity Impairment Questionnaire: Chronic Urticaria V2.0 (WPAI:CU)

5. During the past seven days, how much did your chronic urticaria affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If chronic urticaria affected your work only a little, choose a low number. Choose a high number if chronic urticaria affected your work a great deal.

   Consider only how much chronic urticaria affected productivity while you were working.

Chronic urticaria had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Chronic urticaria completely prevented me from working

   CIRCLE A NUMBER

6. During the past seven days, how much did your chronic urticaria affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If chronic urticaria affected your activities only a little, choose a low number. Choose a high number if chronic urticaria affected your activities a great deal.

   Consider only how much chronic urticaria affected your ability to do your regular daily activities, other than work at a job.

Chronic urticaria had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Chronic urticaria completely prevented me from doing my daily activities

   CIRCLE A NUMBER

Appendix 13
Patient Global Impression of Change (P-GIC) Scale

Please rate how your chronic idiopathic urticaria has changed since the beginning of the study:

1. ☐ Very much improved
2. ☐ Much improved
3. ☐ Minimally improved
4. ☐ No change
5. ☐ Minimally worse
6. ☐ Much worse
7. ☐ Very much worse

Appendix 14
In-Clinic Urticaria Activity Score (IC-UAS) (Max 6)

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

Pruritus:

0 = None

1 = Mild – minimal awareness, easily tolerated

2 = Moderate – definite awareness, bothersome but tolerable

3 = Severe – difficult to tolerate

Number of Hives:

0 = none

1 = 1–6

2 = 7–12

3 = >12

Appendix 15
Clinician Global Impression of Change (C-GIC) Scale

Please rate how patient's chronic idiopathic urticaria has changed since the beginning of the study:

1. ☐ Very much improved
2. ☐ Much improved
3. ☐ Minimally improved
4. ☐ No change
5. ☐ Minimally worse
6. ☐ Much worse
7. ☐ Very much worse

Appendix 16
Sampson's Criteria of Anaphylaxis

ANAPHYLAXIS: Sampson definition of anaphylaxis (clinical definition) is the acute onset of illness which involves **SKIN, MUCOSAL TISSUE, or BOTH** (e.g., generalized hives, pruritus or flushing, swollen lips- tongue uvula) **with one OR more of the following:**

- **RESPIRATORY:** Airway compromise (e.g. dyspnea, wheeze, or bronchospasm, stridor and reduced PEF)
- **CIRCULATORY:** Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope)

OR

TWO or MORE of the following that occur rapidly after exposure:

- **SKIN, MUCOSAL TISSUE:** e.g. generalized hives, itch-flush, swollen lips- tongue-uvula
- **RESPIRATORY:** Airway compromise (e.g. dyspnea, wheeze, or bronchospasm, stridor and reduced PEF)
- **CIRCULATORY:** Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia, syncope)
- **GASROINTESTINAL:** Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting, nausea, diarrhea)