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A multicenter, randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of Xolair® (omalizumab) in Chinese patients with chronic spontaneous urticaria who remain symptomatic despite antihistamine treatment

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List of abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
ANCOVA	Analysis of covariance
AR	Autoregressive
AST	Aspartate Transaminase
ATA	Anti-Therapeutic Antibodies
AV	Atrioventricular
BMI	Body Mass Index
BOCF	Baseline Observation Carried Forward
BUN	Blood Urea Nitrogen
CFDA	China Food and Drug Administration
CI	Confidence Interval
CPO	Country Pharma Organization
CQA	Clinical Quality Assurance
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CSU	Chronic Spontaneous Urticaria
CT	Computed Tomography
DAR	Dose Administration Record
DBP	Diastolic Blood Pressure
DSM	Drug Supply Management
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FcεRI	Fc Epsilon Receptor I
GCP	Good Clinical Practice
H1AH	H1 Antihistamines
HSS	Health Systems Specialist
IB	Investigators Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IN	Investigator Notification
INH	Isoniazid
ISS	Itch Severity Score
IUD	Intrauterine Device
IUS	Intrauterine System
J2R	Jump to Reference

LDH	Lactate Dehydrogenase
LFT	Liver Function Tests
LOCF	Last Non Missing Weekly Score
LSM	Least Squares Means
LTRA	Leukotrine Receptor Antagonist
MAR	Missed At Random
MMRM	Mixed Effect Linear Model With Repeated Measures
MRI	Magnetic Resonance Imaging
NHS	Number of Hives Score
[redacted]	[redacted]
[redacted]	[redacted]
PH	Proportional Hazard
PPD	Purified Protein Derivative
PRO	Patient Reported Outcome
PSUR	Periodic Safety Update Report
QFT	QuantiFERON Tuberculosis Gold Test
QM	Quality Management
QTcF	Fridericia's Correction Formula
RAN	Randomized Set
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAF	Safety Set
SBP	Systolic Blood Pressure
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA query
SOC	System Organ Class
TB	Tuberculosis
UNS	Unscheduled Treatment Discontinuation Visit
US	United States
US CFR	United States Code of Federal Regulations
WOC	Withdrawl of Consent
β-hCG	Beta Human Chorionic Gonadotropin

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (eg. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include protocol-specified concomitant background therapies when these are standard treatments in that indication
Medication pack number	A unique identifier on the label of each investigational drug package
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
UAS7	Sum of daily urticaria activity score (UAS) over 7 days prior to its assessment day. The daily UAS is average of the morning and evening UAS which is a composite score of the number of wheals (hives) and the intensity of itch.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Weekly itch severity score (ISS)	Sum of daily itch scores over 7 days prior to its assessment day. The daily itch score is average of the morning and evening itch scores. The intensity of itch score is recorded on a scale of 0 (none) to 3 (intense/severe).
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	*CIGE025E2305*
Title	A multicenter, randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of Xolair® (omalizumab) in Chinese patients with chronic spontaneous urticaria (CSU) who remain symptomatic despite antihistamine treatment
Brief title	Study of efficacy and safety of Xolair® (omalizumab) in Chinese patients with chronic spontaneous urticaria
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To evaluate the efficacy of Xolair compared with placebo in patients with refractory CSU receiving concomitant H1 antihistamine therapy as measured by the ISS and the UAS7 instrument
Primary Objective(s)	The primary objective is to demonstrate the superiority of omalizumab 300 mg or 150 mg administered subcutaneously every 4 weeks in patients with refractory CSU receiving concomitant H1AH therapy with respect to change from baseline in weekly itch severity score (ISS7) at Week 12 compared to placebo.
Secondary Objectives	Objective 1: To demonstrate that patients with refractory CSU receiving concomitant H1AH who are treated with omalizumab 300 mg or 150 mg have a greater reduction from baseline in weekly urticaria activity score (UAS7) at Week 12, compared to placebo-treated patients Objective 2: To demonstrate that patients with refractory CSU receiving concomitant H1AH who are treated with omalizumab 300 mg or 150 mg have a greater reduction from baseline in weekly number of hives score (NHS7) at Week 12 relative to placebo-treated patients Objective 3: To demonstrate that a greater percentage of patients with refractory CSU receiving concomitant H1AH who are treated with omalizumab 300 mg or 150 mg have UAS7 $\leq$ 6 at Week 12 relative to placebo-treated patients Objective 4: To demonstrate that a greater percentage of patients with refractory CSU receiving concomitant H1AH who are treated with omalizumab 300 mg or 150 mg achieve UAS7 = 0 at Week 12 relative to placebo-treated patients Objective 5: To demonstrate that a greater percentage of patients with

	refractory CSU receiving concomitant H1AH who are treated with omalizumab 300 mg or 150 mg achieve ISS7 Minimally Important Difference (MID) response at Week 12 relative to placebo-treated patients Objective 6: To demonstrate that patients with refractory CSU receiving concomitant H1AH who are treated with omalizumab 300 mg or 150 mg have a greater reduction from baseline in Dermatology Life Quality Index (DLQI) at Week 12 relative to placebo-treated patients Objective 7: To evaluate the efficacy of omalizumab compared to placebo in patients with refractory CSU receiving concomitant H1AH therapy with regards to time to ISS7 MID response by Week 12 Objective 8: To evaluate the safety of omalizumab compared with placebo in patients with refractory CSU receiving concomitant H1AH therapy with regards to the incidence and severity of adverse events (AE) and serious adverse events (SAE), vital signs and clinical laboratory evaluation at the end of the study
Study design	Randomized, multicenter, double-blind, placebo-controlled, parallel-group study
Population	A total of approximately 600 patients aged 18 to 75 years old who have been diagnosed with refractory CSU and who remain symptomatic despite conventional H1AH treatment will be screened to allow 420 patients to be randomized into this study
Key Inclusion criteria	Diagnosis of CSU refractory to H1 antihistamines at the time of randomization, as defined by all of the following • Age 18-75 years • CSU diagnosis for ≥ 6 months. • The presence of itch and hives for ≥ 6 consecutive weeks at any time prior to randomization despite current use of H1AH treatment during this time period. • UAS7 score (range 0-42) ≥ 16 and itch component of UAS7 (range 0 to 1) ≥ 8 during 7 days prior to randomization (Day 1). • In-clinic UAS ≥ 4 on at least one of the screening visit days (Day -14, Day -7, or Day 1). • Patients must have been on an approved dose of an H1AH for CSU for at least the 3 consecutive days immediately prior to the Day -14 screening visit and must have documented current use on the day of the initial screening visit.
Key Exclusion criteria	Clearly defined underlying etiology for chronic urticarias other than CSU (main manifestation being physical urticaria). Atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile

	pruritus or other skin disease associated with itch Urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary or acquired angioedema, lymphoma, leukemia, or generalized cancer
Study treatment	Omalizumab 150 mg, omalizumab 300 mg and placebo 2:2:1 randomization
Efficacy assessments	weekly itch severity score (ISS7) at Week 12 weekly urticaria activity score (UAS7) at Week 12 weekly number of hives score (NHS7) at Week 12 Percentage of patients who have UAS7 $\leq$ 6, UAS7 = 0, ISS7 MID at Week 12 DLQI
Key safety assessments	Safety of omalizumab compared to placebo with regards to the incidence and severity of adverse events and serious adverse events, vital signs and clinical laboratory evaluation at the end of the study
[redacted]	
Data analysis	Randomization will be stratified by latent tuberculosis (TB) at baseline (Yes/No). The primary efficacy variable is change from baseline in weekly itch severity score (ISS7) at Week 12. The daily itch score is the average of the morning and evening itch severity scores. The baseline ISS7 is the sum of the daily itch severity scores over the 7 days prior to the randomization Day 1 visit, and the ISS7 at Week 12 is the sum of daily itch scores over the 7 days prior to the Week 12 visit. A mixed-effect linear model with repeated measures (MMRM) will be used to obtain the least squares mean (LSM) estimate for each treatment group for change from baseline in ISS7 at Week 12. The MMRM model will include terms of treatment group, week (1 to 12), baseline score, baseline score-by-week interaction, and treatment-by-week interaction as fixed effects. Treatment group and week will be fitted as categorical variables, and baseline score as a continuous covariate. The within-patient correlation will be modeled using the unstructured covariance matrix. The difference in LSM estimates between treatment groups, together with a 95% CI, will be presented. The following secondary efficacy endpoints will be considered and analyzed accordingly. - Change from baseline in UAS7, NHS7, and overall DLQI at Week 12, respectively. For each endpoint, the treatment comparisons of 300 mg vs

	placebo and 150 mg vs placebo will be made using an MMRM model with similar terms as the primary analysis but the corresponding baseline value as a covariate. - Percentage of patients with UAS7 $\leq$ 6, UAS7 = 0, and ISS7 MID response at Week 12, respectively. For each endpoint, the treatment comparisons of 300 mg vs placebo and 150 mg vs placebo will be performed using a logistic regression model which will be fitted with treatment group as a factor and the corresponding baseline value as a covariate. - Time to ISS7 MID during the randomized-treatment epoch. Treatment comparisons of 300 mg vs placebo and 150 mg vs placebo will be performed using a Cox proportional hazard (PH) model with treatment group as a factor and baseline ISS7 as a covariate. Multiplicity adjustment will be made for testing the primary and secondary hypotheses according to the type I error control plan.
Key words	Chronic spontaneous urticaria, ISS7, UAS7, omalizumab, China

1 Introduction

1.1 Background

Urticaria is a heterogeneous group of diseases characterized by hives and/or angioedema (Zuberbier et al 2014). 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 (Zuberbier et al 2014). The prevalence of CSU is estimated as 0.5% - 1% of the population in Western countries. Women are affected twice as often as men and all age groups can develop CSU; the incidence peak of CSU is between 20 and 40 years (Maurer et al 2011).

In China, prevalence data for CSU are not available and an epidemiological survey conducted by China Dermatologist Association is ongoing. According to an epidemiological survey of urticaria conducted by Third Military Medical University in China, CSU accounted for about half of the total urticaria population. Distributions of gender and age among CSU patients were similar to those reported in Western countries (Luo Jie et al 2011). A recent hospital-based multicenter epidemiological study in the Chinese population found CSU to be the most common subtype in patients diagnosed with chronic urticaria (61% of all cases) (Zhong et al 2014).

Among the proposed etiologies of CSU include those indicating an infectious origin (e.g., *Helicobacter pylori*), non-allergic hypersensitivity reactions to foods and drugs (pseudoallergic), and autoimmunity (Fiebiger et al 1995, Tong et al 1997, Zweiman et al 1998, Fukuda et al 2004). In patients suspected of having an autoimmune etiology of CSU, urticaria symptoms are considered to result from mediator release following the cross-linking of high-affinity immunoglobulin E (IgE) receptors (FcεRI) on mast cells and basophils. Chronic spontaneous urticaria is associated with immunoglobulin G (IgG) antibodies against IgE receptor α subunit in 35-40% of patients and against IgE in an additional 5-10% (Kaplan and Greaves et al 2009).

The currently recommended treatment for CSU in the EAACI/GA2LEN/EDF/WAO guidelines (Zuberbier et al 2014) is similar to that in the Chinese Society of Dermatology guideline (CSD 2007) in which non-sedating H1 antihistamines (H1AH) are recommended as first-line treatment. In case of inadequate response to H1AH, switching to another H1AH is recommended. As general practice, use of higher, off-label doses of H1AH is uncommon in China. Other off-label used treatment options in Chinese guidelines include leukotriene receptor antagonists or H2 antihistamine therapy. For some CSU patients refractory to H1AH, the guidelines recommend the use of systemic immunosuppressants, such as systemic corticosteroids or cyclosporine. However, these drugs are associated with poor tolerability and adverse events in many patients. Further treatment options include psoralen and ultraviolet A radiation, narrow-band ultraviolet phototherapy, dapsone, plasmapheresis, and intravenous immunoglobulin.

Although approximately half or more of CSU patients are considered to be well-controlled by H1AH at approved doses, the treatment options for those who remain symptomatic on treatment with H1AH are quite limited. Some patients benefit from the addition of LTRA or H2 antihistamines, systemic corticosteroids or immunosuppressants, but there is insufficient

evidence for these therapies and many are not approved for CSU. Because chronic spontaneous urticaria has a profound negative impact on patients' quality of life (Choi WS et al 2016) there is a high unmet medical need for a new treatments in CSU patients refractory to H1AH.

Xolair® (omalizumab) is a humanized anti-IgE recombinant monoclonal antibody approved in 96 countries, including the US and the EU, to treat allergic asthma. Omalizumab binds to IgE, preventing its binding to FcεRI on the surface of mast cells and basophils. Reduction of free IgE also leads to reduced cell surface expression of FcεRI. Reduction in free IgE and in cell surface FcεRI limits the extent of release of mediators from mast cells and basophils in the allergic response.

The hypotheses for the mechanism of action of omalizumab in CSU patients are (1) lowering free IgE to near undetectable levels leads to down-regulation of IgE receptors, so that IgG autoantibody cannot cross-link the high-affinity receptor (FcεRI), and (2) the down regulation of FcεRI may be accompanied by an increase in the threshold above which degranulation of mast cells is triggered.

The main studies contributing to efficacy data for the CSU indication include a Phase II dose-finding study Q4577g and 3 Phase III placebo-controlled studies (Q4881g, Q4882g, and Q4883g). Other sources of efficacy data include an initial placebo-controlled study (ADE05) conducted locally in Germany prior to the Phase III program in CSU and small investigator-initiated placebo-controlled pilot study (Kaplan et al 2008). The studies used for pooled efficacy analysis were Q4881g and Q4882g. Efficacy was assessed using well-established and validated endpoints, based on the Urticaria Activity Score (UAS). The Phase III studies were designed to select adult and adolescent patients (12 years and older) with severe, significant impairment of quality of life and refractoriness to current standard therapy. The pivotal efficacy studies, Q4881g and Q4882g, used doses of 75 mg, 150 mg and 300 mg administered every 4 weeks during 24 weeks and 12 weeks, respectively. A consistent dose response was observed across the primary and secondary endpoints. On the basis of the efficacy observed in the Phase III program, omalizumab 300 mg and 150 mg, given subcutaneously every 4 weeks, are recommended doses for the treatment of CSU.

The safety profile in CSU is consistent with that previously reported for the allergic asthma indication. Four studies, one Phase II (4577g) and three Phase III studies (Q4881g), (Q4882g), and (Q4883g), with a total of 1,068 patients, contributed data to the integrated evaluation of safety of omalizumab in CSU, including 802 patients who received one or more doses of omalizumab. There were no deaths or major organ toxicity and a similar incidence of adverse events and severe adverse events among the treatment groups was apparent, with no age-specific safety concerns. Omalizumab is now approved for the treatment of CSU in 53 countries worldwide including the US, the EU (counted as one), Canada, and Australia (as of April 2016). In the EU, only the 300 mg dose of omalizumab is approved whereas 300 mg and 150 mg are approved in most other regions.

1.2 Purpose

The purpose of this study is to demonstrate the efficacy and safety of omalizumab, compared with placebo, as an add-on to H1AH therapy in adult patients suffering from CSU who remain

symptomatic despite H1AH therapy. The results of this study will support registration of omalizumab for adult patients suffering from CSU in China, and potentially in other countries.

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To demonstrate the superiority of omalizumab 300 mg or 150 mg administered subcutaneously every 4 weeks in patients with refractory CSU receiving concomitant H1AH therapy with respect to change from baseline in weekly itch severity score (ISS7) at Week 12, compared to placebo	The primary efficacy variable is defined as the change from baseline of the ISS7 score after 12 weeks of treatment	Section 9.4
Secondary		
To demonstrate that patients with refractory CSU receiving concomitant H1AH who are treated with omalizumab 300 mg or 150 mg have a greater reduction from baseline in weekly urticaria activity score (UAS7) at Week 12, compared to placebo-treated patients To demonstrate that patients with refractory CSU receiving concomitant H1AH who are treated with omalizumab 300 mg or 150 mg have a greater reduction from baseline in weekly number of hives score (NHS7) at Week 12 relative to placebo-treated patients To demonstrate that a greater percentage of patients with refractory CSU receiving concomitant H1AH who are treated with omalizumab 300 mg or 150 mg have UAS7 $\leq$ 6 at Week 12 relative to placebo-treated patients To demonstrate that a greater percentage of patients with refractory CSU receiving concomitant H1AH who are treated with omalizumab 300 mg or 150 mg achieve UAS7 = 0 at Week 12 relative to placebo-treated patients To demonstrate that a greater percentage of patients with refractory CSU receiving concomitant H1AH who are treated with omalizumab 300 mg or 150 mg achieve ISS7 Minimally Important Difference (MID) response at Week 12 relative to placebo-treated patients To demonstrate that patients with refractory CSU receiving concomitant H1AH who are treated with omalizumab 300 mg or 150 mg have a greater	Variables and timepoint: UAS7 • Change from Baseline of UAS7 score after 12 weeks of treatment • Percentage of patients with UAS7 $\leq$ 6 at Week 12 • Percentage of patients with UAS7=0 at Week 12 NHS7 • Change from Baseline of NHS7 score after 12 weeks of treatment ISS7 • Percentage of patients with ISS7 MID at week 12 • Time to ISS7 MID response by Week 12 DLQI • Change from Baseline of DLQI score after 12 weeks of treatment Safety	Section 9.5

Objective	Endpoint	Analysis
reduction from baseline in Dermatology Life Quality Index (DLQI) at Week 12 relative to placebo-treated patients To evaluate the efficacy of omalizumab compared with placebo in patients with refractory CSU receiving concomitant H1AH therapy with regards to time to ISS7 MID response by Week 12 To evaluate the safety of omalizumab compared with placebo in patients with refractory CSU receiving concomitant H1AH therapy with regards to the incidence and severity of adverse events and serious adverse events, vital signs and clinical laboratory evaluation at the end of the study	• Percentage of patients with AE, with SAE, and who discontinue due to an AE • Exposure adjusted AE event rates • Percentage of patients with a clinically notable abnormality in Lab, ECG, and vital signs • Change from baseline in Lab, ECG, and vital signs	

[redacted]

3 Investigational plan

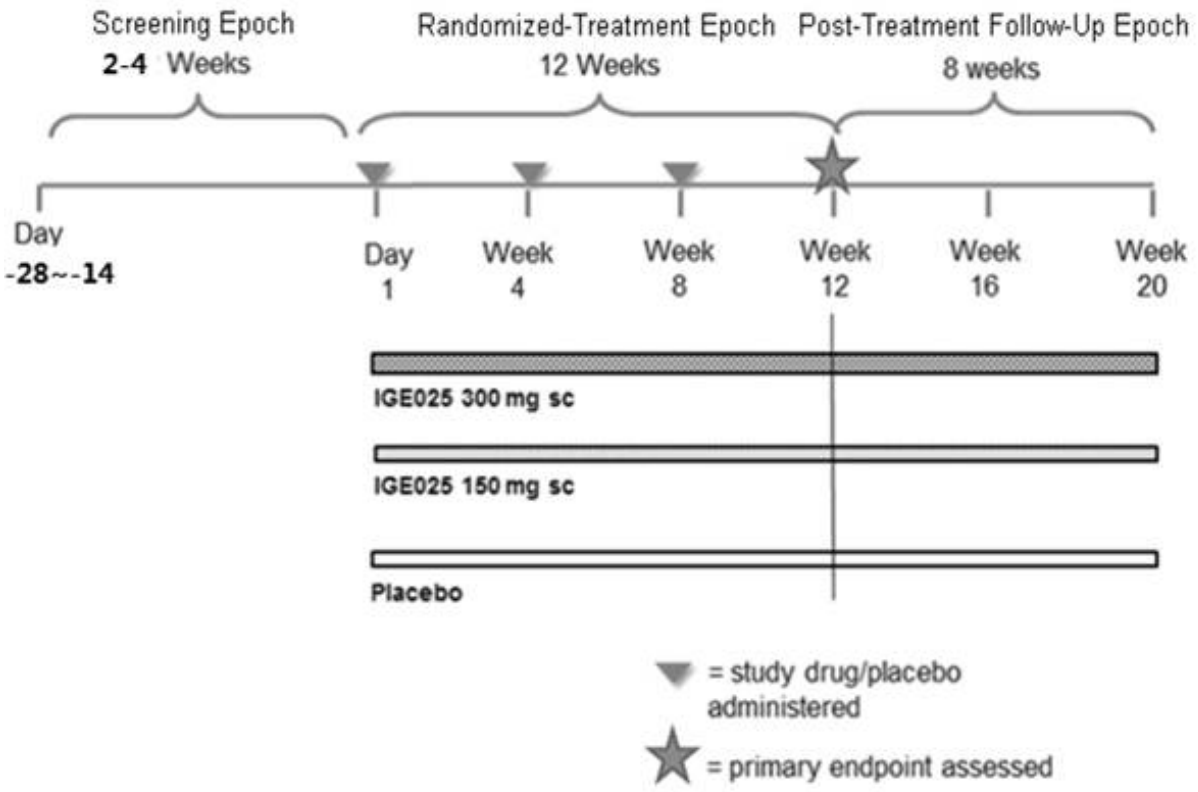
3.1 Study design

The study is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of omalizumab administered subcutaneously as an add-on therapy for the treatment of patients aged 18-75 years with the diagnosis of refractory CSU and who remain symptomatic despite approved-dosed H1AH treatment. Patients will be randomized into three treatment arms (omalizumab 300 mg s.c., omalizumab 150 mg s.c., and placebo) in a 2:2:1 ratio, stratified by latent TB status at baseline. Approximately 420 patients will be enrolled at approximately 30 study sites.

The study will consist of three distinct epochs over 24 weeks, as outlined below (see also Figure 3-1).

- Screening epoch: Day -28 to Day -1
- Randomized-treatment epoch: Day 1 to Week 12
- Post-treatment follow-up epoch: Week 12 to Week 20

Figure 3-1 Study design



Eligible patients will be required to visit at Day -28~-14 and Day -7 during the 2-4 week screening epoch. Only in cases of outstanding laboratory results will an extended screening epoch be permitted. For the duration of the screening epoch, patients are recommended to stay on a stable CSU H1AH treatment. In addition, for patients requiring treatment for latent TB, screening epoch will be extended in order to allow for a 4-Week treatment period prior to randomization.

On Day 1, eligible patients will be randomly assigned (in a 2:2:1 ratio with an Interactive Response Technology [IRT]) to receive omalizumab (150 mg or 300 mg) or placebo by subcutaneous injection every 4 weeks (on Day 1, Week 4, and Week 8) during the 12-week double-blind randomized-treatment epoch. Approximately 168 patients will be randomized to the omalizumab 150 mg, approximately 168 patients to omalizumab 300 mg and approximately 84 patients will be randomized to receive placebo. For the duration of the randomized-treatment epoch, patients are recommended to stay on the same CSU H1AH treatment that they were using during the pre-randomization period. The last dose of study drug during the randomized-treatment epoch will be administered at Week 8 study visit. The primary endpoint will be assessed at Week 12.

After the completion of the 12-week randomized-treatment epoch, all patients will enter an 8-week post-treatment follow-up epoch to allow for further characterization [redacted] of omalizumab and collection of additional efficacy and safety data. All these evaluations will

also be done for those who withdraw from the study within 12 weeks of randomization. During the post-treatment follow-up epoch, patients would be allowed to add one more H1AH therapy to their treatment regimen for CSU. This is expected to help limit patient dropout and ensure that patients return for safety evaluations during the post-treatment follow-up epoch.

For the duration of the study, patients will visit the study center at 4-week intervals. No study drug treatment will be given during the post-treatment follow-up epoch. The blind will be maintained for the full 20 weeks of the study (after randomization). For the duration of the study, all patients will be provided diphenhydramine (25 mg) tablets as rescue medication (see Section 5.5.6) for additional itch relief on an as-needed basis (up to a maximum of three doses in 24 hours or less, based on local regulations). No other medication for itch relief will be allowed during the screening and treatment phases of the study.

3.2 Rationale for study design

This is a randomized, double-blind, parallel-group, placebo-controlled study to demonstrate the efficacy and safety of omalizumab in Chinese patients with CSU who remain symptomatic despite H1AH therapy compared with placebo. The study design is aligned with previous pivotal efficacy studies Q4881g and Q4882g. Efficacy is determined using the primary endpoint of change from baseline in the weekly itch severity score at Week 12 because itching is the symptom of greatest concern to patients, with the greatest impact on their quality of life (Mathias et al 2010). As CSU is both a disease of hives and intense itch, it is appropriate to evaluate clinical response assessing hives, as well as using a composite endpoint, UAS, which incorporates assessment of both symptoms. Therefore the UAS will be incorporated as a secondary endpoint. The validity and reliability of UAS in CSU has been established in previous studies (Mylnek et al 2008, Mathias et al 2012).

The selection of Week 12 as the time point for primary efficacy assessment is consistent with previous studies conducted with omalizumab in CSU and is supported by the finding that response to omalizumab plateaued after 12 weeks in these studies. The reason for including only patients who are refractory to approved doses of H1AH therapy is that H1AH drugs are the approved first line therapy for CSU (Zuberbier et al 2009, Hide and Hiragun 2012), and the unmet medical need in CSU is highest in patients refractory to these drugs. Omalizumab will be used as an add-on therapy on top of H1AH treatment in this study.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

The doses for this study are selected based on the results of the Phase III studies Q4881g and Q4882g that tested omalizumab doses of 75 mg, 150 mg, 300 mg and placebo. The doses for these Phase III studies were selected based on the results from the Phase II dose finding study Q4577g that tested a broad array of omalizumab doses (75, 300, and 600 mg) as a single subcutaneous injection in patients with CSU refractory to H1AH. Based on the results from these studies, 300 mg and 150 mg doses are the recommended doses and have been approved in most regions worldwide. Efficacy and safety with these doses is expected to be similar in the Chinese population.

The rationale for the dose/regimen chosen for this study is summarized as follows:

- In the phase II study Q4577g, the 300 mg and 600 mg omalizumab dose groups both demonstrated efficacy superior to the placebo group, but there was no additional benefit observed for the 600 mg omalizumab group compared with the 300 mg omalizumab group. In exposure-response analysis, exposure levels at 300 mg appeared to approach the plateau of the exposure–response curve.
- In studies Q4881g and Q4882g, on the primary endpoint (change from baseline to Week 12 in weekly itch severity score), omalizumab 150 mg and 300 mg given every 4 weeks demonstrated consistent and statistically significant treatment effects relative to placebo. The 75 mg dose did not show a consistent effect on the primary endpoint and most secondary endpoints.
- The safety profile for omalizumab in CSU is consistent with the profile previously reported for the allergic asthma indication. The safety profile was similar for the 150 mg and 300 mg doses in studies Q4881g and Q4882g, and consistent with the profile for the 300 mg dose used in the safety study Q4883g.
- Based on exposure-response analysis of omalizumab in CSU, there was a dose response in efficacy (itch improvement and percent complete UAS7 responders) across the dose range tested (75 mg to 300 mg every 4 weeks), and no clear impact of body weight, body mass index (BMI) and baseline IgE on efficacy within each dose level. This result was again confirmed in phase III studies. Flat dosing (ie., without adjustment for baseline body weight and/or IgE level) is therefore supported.
- The 4 weeks dosing interval is selected because in the phase II study Q4577g maximum effect was observed 4 weeks post-dose. The appropriateness of the 4 week dosing interval was confirmed by PK/PD itch and hives time course modeling using the Phase III study data. An interval of 4 weeks is considered to minimize breakthrough CSU symptoms while avoiding accumulation resulting from dosing omalizumab more frequently than necessary.
- There was no clinically significant difference found in PK and PD of omalizumab between Chinese and Caucasian populations. Thus, Chinese subjects should respond similarly to Caucasians when omalizumab is given with the same dose/regimen as used in the previous studies (A2102, A2204 and A2206).
- Flat dosing

  Based on these findings, it is considered appropriate to select 150 mg and 300 mg doses for E2305 study. This study would attempt to further characterize the dose response profile for omalizumab in CSU with the objective of identifying the optimal dose in Chinese patients.

  The rationale for a treatment (study drug administration) period of 12 weeks is described below:

- Treatment with omalizumab results in a rapid reduction of CSU symptoms. The global phase III studies demonstrated that the time to achieve the minimally important difference response (decrease in UAS7 $\geq$ 5) was 1 to 2 weeks after the start of treatment.
- The global phase III studies showed no clear differences in therapeutic efficacy after 12 and 24 weeks of treatment, indicating that efficacy beyond Week 12 can be extrapolated from the Week 12 response.

The rationale for establishing an 8-week follow-up epoch after the end of the treatment epoch is that this is deemed sufficient to provide safety data and assessment of anti-therapeutic antibodies (ATA).

3.4 Rationale for choice of comparator

In this trial, omalizumab is investigated as add-on therapy to H1AHs and compared to placebo to determine the efficacy and safety of omalizumab as add-on therapy.

During the 12 weeks of the treatment epoch, placebo will be given to the 150 mg group (150 mg omalizumab and 150 mg placebo) and placebo group (150 mg placebo x 2) (Table 3-1).

All patients must take study-defined H1AH medications at approved doses during the screening, treatment, and post-treatment follow-up epochs, which is typical for placebo-controlled trials where an add-on therapy is studied for a disease with a pre-existing standard of care.

Patients should remain on a stable H1AH treatment regimen throughout the study.

Diphenhydramine will be allowed as rescue medication (see Section 5.5.6). Diphenhydramine 25 mg will be provided and used on an as-needed basis (up to a maximum of three doses of 25 mg in 24 hours according to the Chinese label) during the screening, randomized treatment, and post-treatment follow-up epochs. Patients will be permitted to add up to one additional H1AH therapy after the primary endpoint has been assessed at Week 12 to reduce patient dropout during the post-treatment follow-up epoch.

The use of placebo arm in this trial is deemed mandatory to demonstrate the efficacy and safety of Xolair in Chinese patients suffering from CSU. The 2:2:1 randomization serves to limit the proportion of patient that will receive placebo during the study to 20% of patients. Moreover, patients in the placebo arm will receive standard of care treatment with H1AH therapy throughout the study and will be allowed to receive rescue medication.

Table 3-1 Number of study drug administrations at Day 1 and at Weeks 4 and 8

Treatment Arm	Omalizumab 300 mg	Omalizumab 150 mg	Placebo
Active drug (omalizumab 150 mg/vial)	2	1	0
Placebo (150 mg/vial)	0	1	2

3.5 Purpose and timing of interim analyses/design adaptations

Interim analyses or design adaptation are currently not planned.

3.6 Risks and benefits

Based on results from multiple global studies, omalizumab treatment has a positive benefit-risk ratio for severe, refractory CSU patients at either of the proposed doses. Patients treated with omalizumab can achieve a clinically relevant reduction in persistent and debilitating symptoms associated with the disease, while maintaining a safety profile consistent with the known safety profile in allergic asthma.

Omalizumab has been approved for allergic asthma in 96 countries worldwide based on the positive benefit-risk ratio from the submitted clinical trials. Omalizumab was approved for the treatment of CSU in the EU and in the US in 2014. As of May 2016, omalizumab is approved for CSU in 83 countries worldwide including USA, EU, Switzerland, Canada, and Australia.

For CSU, significant and consistent results were apparent across all the Phase III studies. On the basis of the efficacy observed in the phase III program, omalizumab doses of 300 mg and 150 mg administered every 4 weeks, result in a fast onset of treatment effect (within 1-2 weeks) for the majority of patients, with significant improvement relative to placebo being demonstrated for itch, hives and associated CSU symptoms. There were no reported deaths, and few serious adverse events. Omalizumab was well-tolerated in all the clinical studies and the observed adverse events were broadly similar across each treatment group. Overall no new safety concerns were raised when these data are compared with the adverse reactions (AR) listed in the current prescribing information for omalizumab.

The safety profile for omalizumab in CSU is consistent with the profile previously reported for the allergic asthma indication. There were no deaths or major organ toxicity in any SOC and a similar incidence of AEs and SAEs among the treatment groups with no age specific safety concerns. However, small imbalances were observed in some SOCs, as listed below with the event(s) that contributed to the imbalance bracketed:

General disorders and administration site disorders (injection site reactions), Infections and infestations (upper respiratory tract infection, urinary tract infection), Musculoskeletal and connective tissue disorders (arthralgia), Nervous system disorders (headache), and Respiratory, thoracic and mediastinal disorders (coughing, bronchospasm) were reported more frequently in the omalizumab treatment groups than in the placebo group.

The preferred terms noted above are not necessarily the same events identified as adverse reactions (ARs). These were identified from candidate events where the incidence on any omalizumab dose was ≥2% higher than in the placebo group. The events noted as ARs in the pooled CSU safety database are nasopharyngitis, viral upper respiratory tract infection, sinusitis, arthralgia, and headache.

Apart from a few specific preferred terms, the other relatively small imbalances observed were in line with the well characterized safety profile of omalizumab in the severe allergic asthma indication, and with events listed in the adverse reaction (AR) table in the SmPC.

Among the more commonly reported AEs, headache was the only notable event that was reported more frequently relative to placebo in the omalizumab 150 mg and 300 mg dose groups. Most events seen were mild to moderate in severity, and no meaningful difference between treatment groups was seen for severe events during the treatment periods.

The percentage of patients with AEs suspected by the investigator to be related to study drug was slightly higher in the omalizumab groups (range 7.5% to 9.2%) compared to placebo (5.8%). The small imbalance with omalizumab 300 mg was partly due to preferred terms headache, and injection site reactions.

The incidence of SAEs, discontinuations from study due to an AE, and withdrawals from treatment were similar or lower with omalizumab treatment compared to placebo, so do not present an incremental risk to patients.

Among a range of AEs of special interest examined, hypersensitivity, injection site reaction, and hematopoietic cytopenia were reported at higher rates with omalizumab 300 mg treatment, and were consistent with previous clinical experience with omalizumab.

There were no clinically relevant differences observed between treatment groups for hematology or vital signs, and no meaningful differences between treatment groups were observed for new abnormalities.

During the follow-up period, imbalances were seen in the omalizumab groups compared to placebo in the SOCs of infections and infestations (150 mg and 300 mg omalizumab groups), and skin and subcutaneous tissue disorders (all omalizumab groups). An increase in skin and subcutaneous events was likely due to the re-emergence of symptoms present at baseline, while the imbalance in infections was similar or lower to the difference seen under active treatment, and showed no clear dose-dependence.

The safety profile is subject to regular review (PSUR 21, Feb 2016) and updates to the existing risk management plan omalizumab for allergic asthma and CSU. No new risks were identified in the latest version of the risk management plan (Core RMP 11, April 2016),

Other treatment alternatives to omalizumab for patients that have failed the standard treatment paradigm of H1 antihistamines at approved, or multiple doses include immunosuppressive agents such as cyclosporine, or repeated exposure to oral glucocorticoids. There are significant potential adverse effects associated with both of these alternatives and due to safety concerns can only be administered over short periods of time.

Therefore, the benefit of treatment with omalizumab is that it could improve itch, hives and associated CSU symptoms in a patient population that is refractory to current standard of care. The risks for patients participating in this study include the potential for known safety issues associated with omalizumab, which includes anaphylaxis, with an estimated incidence of at least 0.2%, as well as the potential for additional risks outlined in the Investigator's Brochure.

Based on the proposed mechanism of action of omalizumab, there is no clear scientific rationale to suspect a decrease in immunity to tuberculosis (TB) associated with its use, nor clinical data suggesting relapse or worsening of TB in patients treated with omalizumab. Nevertheless, given the high incidence of TB in China that is up to 20-fold as high as those in EU and US (WHO 2015), TB screening will be performed in the study. Patients screened with latent TB will need to receive tuberculosis prophylaxis for at least 4 weeks prior to study drugs (for details, see Section 6.2.1).

4 Population

A total of approximately 600 patients from approximately 30 sites in China mainland, aged 18 to 75 years old who have been diagnosed with refractory CSU and who remain symptomatic despite conventional H1AH treatment will be screened to allow 420 patients to be randomized into this study. This accounts for approximately 30% screening failures. If the maximum early discontinuation rate of 10% is assumed for this study, then approximately 375 subjects are expected to be able to complete the 12-week randomized-treatment epoch with primary efficacy data available at the endpoint.

4.1 Inclusion criteria

Patients/subjects eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Aged 18-75 years.
3. Diagnosis of CSU refractory to H1AH at the time of randomization, as defined by all of the following:
   - CSU diagnosis for ≥ 6 months.
   - The presence of itch and hives for ≥ 6 consecutive weeks at any time prior to randomization despite current use of H1AH treatment during this time period.
   - UAS7 score (range 0-42) ≥ 16 and itch component of UAS7 (range 0-21) ≥ 8 during 7 days prior to randomization (Day 1).
   - In-clinic UAS ≥ 4 on at least one of the screening visit days (Day -14, Day -7, or Day 1).
   - Patients must have been on an approved dose of an H1AH for CSU for at least the 3 consecutive days immediately prior to the Day -14 screening visit and must have documented current use on the day of the initial screening visit.
4. Willing and able to complete a daily symptom eDiary for the duration of the study.
5. Patients must not have had any missing eDiary entries in the 7 days prior to randomization.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator in order to ensure that the study population will be representative of all eligible patients/subjects.

1. Clearly defined underlying etiology for chronic urticarias other than CSU. This includes the following:
   - Acute, solar, cholinergic, heat, cold, aquagenic, delayed pressure or contact urticarias;
   - Any of the following diseases, which may have symptoms of urticaria and/or angioedema: urticarial vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary or acquired angioedema, lymphoma, leukemia, or generalized cancer
2. Patients with a stool examination positive for ova or parasites (at screening) (patients should be cautioned and instructed to apply appropriate hygienic measurements when travelling to areas where helminthic infections are endemic).
3. Any skin disease other than CSU with chronic itching that could confound the results of the study (e.g., atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, or senile pruritus).
4. Previous treatment with omalizumab.
5. Contraindications to diphenhydramine:

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

6. History of anaphylactic shock.
7. Patients with platelet count ≤ 100,000 /μL at Visit 1.
8. Patients who are sucrose-intolerant (e.g., the glucose-galactose malabsorption syndrome, fructose intolerance or sucrose-isomaltase deficiency).
9. Presence of clinically significant cardiovascular, neurological, psychiatric, metabolic, hepatic, or other pathological conditions that could interfere with the interpretation of the study results and or compromise the safety of the patients.
10. 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 will be reviewed with the investigator.
11. Inability to comply with study and follow-up procedures.
12. History or evidence of ongoing alcohol or drug abuse, within the last 6 months prior to randomization.
13. Patients who have been previously randomized into this study.
14. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
15. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.
16. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients/subjects participating in the study such as:
    - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
    - History of familial long QT syndrome or known family history of Torsades de Pointes
17. Patients taking medications prohibited by the protocol (see Section 5.5.8, Table 5-1)
18. History of malignancy of any organ system regardless of whether there is evidence of local recurrence or metastases (except basal cell carcinoma, actinic keratosis, or Bowen's disease [squamous carcinoma *in situ*] that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma *in situ* of the cervix or non-invasive malignant colon polyps that have been removed treated or untreated, within the past 5 years)
19. Pregnant or nursing (lactating) women
20. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of investigational drug. Basic contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps).
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS).

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

21. Patients with evidence of latent TB infection, as defined by a positive QuantiFERON TBGold Test (QFT), who are unwilling to be treated with TB treatment according to local country guidelines, or cannot, demonstrate documented compliance with prior treatment of latent TB infection according to local country guidelines. Patients with a positive QFT are required to have a chest X-ray, computerized tomography (CT scan), or MRI, obtained within 12 weeks prior to baseline, to evaluate for the potential for prior or current active TB by a qualified physician. Patients with evidence of prior or current active TB cannot participate further in the trial.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

- Name: Omalizumab (IGE025)
- Formulation: Lyophilized powder for solution for injection
- Appearance: White cake, reconstituted solution: colorless to pale yellow and clear to slightly opalescent

- Unit dose: 150 mg/vial
- Packaging: Glass vial

  The appearance of omalizumab vial differs from that of placebo vial, and the viscosity of omalizumab differs from that of placebo. Omalizumab matching placebo provided in 5ml glass vial.

5.1.2 Additional treatment

Except for the concurrent use of H1AH and diphenhydramine as rescue medication (see Section 5.5.6), no additional treatment beyond investigational treatment is requested for this trial. The long-acting non-sedating H1AH agents are allowed during the study.

Dosage and administration should follow local regulations

5.2 Treatment arms

Patients will be randomized to one of the following three treatment arms in a ratio of 2:2:1.

- Omalizumab 300 mg arm will receive a dose of omalizumab 300 mg s.c. which consists of two injections of omalizumab 150 mg vials every 4 weeks.
- Omalizumab 150 mg arm will receive a dose of omalizumab 150 mg s.c. which consists of one injection of omalizumab 150 mg vial and one injection of placebo 150 mg vial every 4 weeks.
- Placebo arm will receive placebo s.c. which consists of two injections of placebo 150 mg vials every 4 weeks.

A detailed schedule of administration is described in Section 6. As this is a double-blind study, the dispensing and administration of the study treatments will be performed by suitably qualified personnel who are otherwise not involved in study conduct. Further details are provided in Section 5.3,Section 5.4 and Section 5.5.

5.3 Treatment assignment and randomization

At Visit "101," all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The unblinded authorized staff will contact IRT at Visit 101 after confirming that the patient fulfills all the inclusion/exclusion criteria. Also, the unblinded authorized staff will contact the IRT at Visits 102 and 103. The blinded staffs must not contact the IRT at the above visits. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to any of the site staff.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients/subjects and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the

responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Randomization will be stratified by latent TB at baseline (Yes/No).

The randomization scheme for patients/subjects will be reviewed and approved by a member of the Randomization Group.

5.4 Treatment blinding

All data up to final database lock will be collected with the Novartis clinical trial team, investigator / site personnel evaluating subjects, and subjects blinded to treatment allocation. The Novartis clinical team will be blinded during the study until the final database is locked, and all site personnel including the assessor performing the study assessments, will also remain blinded to individual treatment allocation until after final database lock. This excludes the unblinded pharmacist and unblinded health care professional who will dispense and / or administer the study drug and not be involved in the study assessments. An unblinded pharmacist and an unblinded health care professional are required because they will be able to determine whether the study drug is active or not from the appearance of vial and the viscosity of the drug. Blinding will be maintained using the following methods:

1. Randomization data will be kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:
    - Drug Supply Management (DSM), Drug Safety & Epidemiology (DS&E) and specific vendors whose role in trial conduct requires their unblinding
    - Unblinded pharmacist and unblinded health care professional at each site
    - Unblinded monitor
    - [redacted]
2. Placebo and active treatment will be dispensed by an unblinded pharmacist (or other authorized unblinded staff) who is independent of those involved in the assessment of study subjects. In addition, the unblinded pharmacist (or other authorized unblinded staff) will store study medication and keep medication records containing unblinded information in a secure area where blinded staff would not have access.
3. Study treatments will be administered by an unblinded suitably authorized individual (health care professional) who is not responsible for any aspect of subject assessment or follow-up.
4. The procedural details relating to treatment blinding and unblinded drug administration will be described in the Pharmacist Manual which will be provided separately.

In the event that the packaging of a study treatment has a broken seal, this information will be documented in the IRT, along with a reason (if applicable) and the medication number so that the vial will not be available to dispense to another subject.

[redacted]

Unblinding will only occur in the case of subject emergencies (see Section 5.5.9) and at the conclusion of the study.

The appropriate personnel from the study site and Novartis will assess whether the study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason. Study treatment must be discontinued after emergency unblinding.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Patient numbering,

Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the CRF book with a matching Subject Number from the EDC system to enter data.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the Screening epoch Study Disposition CRF.

5.5.2 Dispensing the study drug

Each study site will be supplied with open-label study drug.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the omalizumab 150 mg or placebo. Unblinded site personnel will identify the investigational treatment package(s) to dispense to the patient by matching medication numbers obtained from IRT. Immediately before dispensing the package to the patient, unblinded site personnel will detach the outer part of the label from the packaging and affix it to the Investigational Product accountability log source document (Drug Label Form) for that patient's unique subject number.

The study drugs will be dispensed by the unblinded pharmacist (or other unblinded authorized site personnel) appointed at the study site.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and

designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. The study drugs should be received by unblinded staff only. The blinded team should not have access to storage location or should not be involved in receipt of IP. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels will include Chinese and comply with the legal requirements of China. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

The background treatment H1AH will be provided by the study site. For the use of H1AH please refer to Section 5.5.7.

5.5.4 Instructions for prescribing and taking study treatment

Active or placebo omalizumab will be administered by subcutaneous injection. The first administration of drug will take place at Visit 101 once all eligibility criteria have been confirmed and all other assessments performed.

The lyophilized product takes 15-20 minutes to dissolve. The fully reconstituted product will appear clear or slightly opalescent and may have a few small bubbles or foam around the edge of the vial. Detailed instructions on how to reconstitute omalizumab vials can be found in the separate Pharmacist Manual. Reconstituted omalizumab vials should be protected from direct sunlight.

Administration

Study medication will be administered by an unblinded suitably authorized individual (qualified health care professional) who is not responsible for any aspect of subject assessment or follow-up. This individual will be identified at site as the “independent study drug administrator”. The independent study drug administrator will administer the study treatment to the corresponding subject by s.c. injection during the study visit without engaging in any unnecessary interactions that may have the potential to unblind the subject or any of the site study personnel.

Study drug is administered to the patient using a disposable 25-gauge needle and a disposable plastic tuberculin-type syringe. The injections are administered in the deltoid region on the right arm and/or left arm, avoiding urticarial lesions. Alternatively, the injections can be administered in the thigh if reasons preclude administration in the deltoid region. The injections are administered subcutaneously after aspiration of the plunger of the syringe. If

blood is withdrawn, the needle is removed without administration of the dose and the injection site is changed.

All kits of study treatment assigned by the IRT will be recorded/databased in the IRT.

The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment (omalizuamb, placebo, background H1AH or diphenhydramine) as prescribed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Investigational drug dose adjustments and/or interruptions are not permitted.

If a dose (omalizumab or placebo) was dispensed by IRT but not administered to a subject at a visit at which the subject attended, this deviation event must be recorded on the Dosage Administration Record eCRF.

5.5.6 Rescue medication

Diphenhydramine 10 mg or 25 mg tablet will be provided and used on an as-needed basis (up to a maximum of 75 mg/day) during the screening, randomized-treatment, and post-treatment follow-up epochs.

Use of rescue medication must be recorded on the Concomitant medications form in the CRF.

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies eCRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

Permitted concomitant medications (for CSU)

Subjects should remain on a stable non-sedating H1AH treatment regimen throughout the study.

During the post-treatment follow-up epoch (after Week 12 visit) subjects are permitted to add up to one additional approved non-sedating H1AH or to up-dose the non-sedating H1AH within approved dose levels if multiple doses are available and a lower dose was used as a background therapy.

Dosage and administration should follow local regulations.

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-1 that could confound the efficacy is NOT allowed during the study for indication and wash-out periods for these treatments are indicated in Table 5-1.

The investigator or authorized site staff must instruct the subject to notify them about any new treatments he/she takes after enrollment. All prohibited treatments taken after enrollment must be recorded in eCRF.

If a prohibited treatment listed in Table 5-1 was used during the study, the subject should discontinue use of the prohibited treatment. At the discretion of the investigator or authorized site staff, if the subject's use during the study of a prohibited treatment listed in Table 5-1 presents undue safety risk for the subject, the subject should be discontinued from study treatment as per Section 5.5.9.

Table 5-1 Prohibited medication

Medication	Wash out period
Anti-IgE therapy	No prior use allowed
Routine (daily or every other day during 5 or more consecutive days) doses of systemic corticosteroids	30 days
Routine (daily or every other day during 5 or more consecutive days) doses of hydroxychloroquine	30 days
Routine (daily or every other day during 5 or more consecutive days) doses of immunosuppression (e.g. methotrexate, cyclosporine, tacrolimus, mycophenolate mofetil, cyclophosphamide, or triperygium wilfordii Hook)	30 days
Intravenous immunoglobulin G	30 days
Plasmapheresis	30 days
Regular (daily or every other day) doxepin (oral)	14 days
Any H2 antihistamine	7 days
Any leukotriene receptor antagonist (LTRA)	7 days
Any H1 antihistamine at greater than approved doses	3 days
vaccination with inactivated pathogen	48 hours prior to visits 101, 102, and 103
Oral Chinese traditional medicine prescribed for CSU *	30 days
Subjects taking either LTRAs or H2 antihistamine for disease other than CSU (e.g., asthma or gastroesophageal reflux disease, respectively) will be permitted to continue their use during the study. These diseases must be recorded as part of the medical history collected during the screening epoch. Inhaled asthma controllers, including corticosteroids, are also permitted during the study. *Subject receiving oral Chines traditional medicine for another indication and for at least 2 months will be allowed to continue this treatment.	

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency

condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- patient number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that unblinding can be performed at any time.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol.

Continuing care should be provided by investigator and/or referring physician based on patient availability for follow-up.

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (see Section 6.5.6 and Section 7.6)
- Use of prohibited treatment as per recommendations in Table 5-1
- Any situation in which study participation might result in a safety risk to the patient
- Individual serum creatinine increase ≥ 50% compared to baseline, unless the event is not drug related, related to disease progression, or if the benefit / risk assessment supports continuing study treatment.
- Emergence of the following adverse events: adverse events that in the judgment of the investigator, taking into account the subject's overall status, prevent the subject from continuing participation in the study (for example, sepsis)

- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study.

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. The patient should return to the clinic as soon as possible, after discontinuation of study drug, for a study treatment discontinuation visit. Treatment discontinuation visit assessments detailed in the "unscheduled treatment discontinuation visit" (UNS) in Table 6-1 should be completed and recorded in the eCRF. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the Dosage Administration eCRF.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone visits:

- new / concomitant treatments
- adverse events / serious adverse events

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9.

5.6.3 Withdrawal of informed consent

Patients/subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (e.g., telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table below.

5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed, an "s" indicates the data remain in the source documents only.

Patients/subjects must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients/subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

Patients/subjects will be contacted for safety evaluations during the 30 days following the last administration of study treatment.

Table 6-1 Assessment schedule

Epoch	Screening			Randomized treatment					Post-treatment follow-up		
Visit Number	**1**	**2**		**101**	**102**	**103**	**199[a]**		**201**	**299[a]**	
Visit Name	**Week -4 to -2**	**Week -1**	**Epoch disposition**	**Randomization**	**Week 4**	**Week 8**	**Week 12**	**Epoch disposition**	**Week 16**	**Week 20**	**Epoch disposition**
Day	**Day -28 to -14**	**Day -7**		**Day 1**	**Day 29**	**Day 57**	**Day 85 or DISC**		**Day 113**	**Day 141 or DISC**	
Obtain informed consent	x										
Inclusion/ exclusion criteria	x	x		x							
In-clinic assessment of UAS[b]	x	x		x							
Demographic data	x										
Medical/surgical history including urticaria and angioedema history and prior treatments	x										
Physical Exam[c]	s			s	s	s	s		s	s[*]	
Height	x										
Weight	x										
Vital signs	x			x	x	x	x		x	x	
ECG	x										
QuantiFERON®TB-Gold In-Tube test	x										
Chest X-ray[k]	x										
Concomitant medication usage	x	x		x	x	x	x		x	x[*]	
Adverse events	x	x		x	x	x	x		x	x[*]	
Study drug/placebo administration				x	x	x					
Randomization				x							

[redacted]

Epoch	**Screening**			**Randomized treatment**					**Post-treatment follow-up**		
Visit Number	**1**	**2**		**101**	**102**	**103**	**199[a]**		**201**	**299[a]**	
Visit Name	**Week -4 to -2**	**Week -1**	**Epoch disposition**	**Randomization**	**Week 4**	**Week 8**	**Week 12**	**Epoch disposition**	**Week 16**	**Week 20**	**Epoch disposition**
Day	**Day -28 to -14**	**Day -7**		**Day 1**	**Day 29**	**Day 57**	**Day 85 or DISC**		**Day 113**	**Day 141 or DISC**	
Contact IRT	x			x	x	x				x	
Patients' eDiary[d]	x	x		x	x	x	x		x	x*	
PROs											
DLQI				x	x		x			x*	
Laboratory tests											
Serum pregnancy test[e]	x										
Urine pregnancy test[e]				x	x	x	x			x*	
Stool ova and parasite evaluation[f]		s									
Hematology[g]	x			x	x		x			x*	
Chemistry[h]	x			x	x		x			x*	
Urinalysis (local)[i]	x			x						x	
Sample collection											
[redacted]											
Anti-omalizumab antibody				**x**						**x**	
Epoch Deposition[l]			x					x			x

DLQI = Dermatology Life Quality Index

NOTE: PROs must be completed prior to other assessments.

NOTE: Unless otherwise indicated, all assessments should be performed pre-administration.

* These assessments are also to be conducted for patients who discontinue treatment.

[a] Subjects who discontinue study treatment early will be expected to perform 4 weeks after their last dose, the Day 85 (Visit 199) assessments. These subjects will subsequently be expected to perform Post-treatment follow-up the Day 113, 141 evaluations (Visit 201, and 299). Subjects who enter the Post-treatment follow-up epoch but wish to terminate early will be expected to perform the Day 141 (Visit 299) assessments.

[redacted]

Epoch	Screening			Randomized treatment					Post-treatment follow-up		
Visit Number	**1**	**2**		**101**	**102**	**103**	**199[a]**		**201**	**299[a]**	
Visit Name	**Week -4 to -2**	**Week -1**	**Epoch disposition**	**Randomization**	**Week 4**	**Week 8**	**Week 12**	**Epoch disposition**	**Week 16**	**Week 20**	**Epoch disposition**
Day	**Day -28 to -14**	**Day -7**		**Day 1**	**Day 29**	**Day 57**	**Day 85 or DISC**		**Day 113**	**Day 141 or DISC**	

[b] In-clinic UAS is assessed by the investigator (for hives) and patient (for itch) at Day -14, Day -7 and Day 1.

[c] Physical exam on Day -14 is comprehensive but subsequent physical exams maybe limited.

[d] Includes UAS7 (itch score and number of hives), largest size of hives, [redacted], [redacted], rescue medication (diphenhydramine) use, angioedema episodes, calls to doctor or nurse. Daily diary completed twice or once a day by the patient. The eDiary will be given to patients on Day -14, and the patients will be trained by the site staff how to use the eDiary

[e] All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test during the screening epoch and urine pregnancy test prior to randomization. If the serum pregnancy test during the screening epoch is positive, the patient will be a screening failure. If urine pregnancy test results are positive during the randomized-treatment epoch, dosing should be held and a serum pregnancy test will be performed by the central laboratory. If urine pregnancy test results are positive during the post-treatment follow-up epoch, a serum pregnancy test will be performed by the central laboratory. Urine pregnancy tests will be performed at the site.

[f] Note that stool ova and parasite examination should be performed on Day -7 in patients with an eosinophil count > 2 times the upper limit of normal on Day -14 AND risk factors for parasitic disease.

Stool ova and parasite examination will be performed at the site.

[g] Hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent and absolute differential count (neutrophils, bands, eosinophils, lymphocytes monocytes, basophils other cells).

[h] Sodium, potassium, chloride, bicarbonates, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatinine phosphokinase, and uric acid.

[i] A midstream urine sample (approximately 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments. Semi quantitative 'dipstick' evaluation for the following parameters will be performed. Specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leucocyte and blood.

[redacted]

[K] Chest X ray will be performed only in case of positive QFT

[l] If the patient will continue into the next phase of the trial or if the study is terminated by the sponsor at any time for any reason, the patient are expected to perform the assessment at the last visit of each respective epoch. Epoch disposition page may look slightly different in the content depending the epoch.

[redacted]

6.1 Information to be collected on screening failures

All patients/subjects who have signed informed consent but not entered into the next epoch will have the study completion page for the screening epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include date of birth, age, sex, race, ethnicity. Relevant medical history/current medical condition present before signing the informed consent will be captured. Where possible, diagnoses, and not symptoms, will be recorded. In addition, data on patient's family history on malignancies is collected on the respective CRF page to assess possible risk factors related to any malignancies.

6.2.1 Tuberculosis screening and management

6.2.1.1 QuantiFERON TB-Gold In-tube assay

A QFT to screen a population for latent tuberculosis infection (Doherty et al 2008) will be used at screening to evaluate the subjects' eligibility for the study. This blood-based assay is specific for Mycobacterium tuberculosis and is not influenced by previous Bacillus Calmette-Guérin vaccination or by exposure to other Mycobacteria species. Furthermore, this test, in contrast to the purified protein derivative (PPD) skin test, is also insensitive to a booster effect since the subject is not exposed to the vaccine. The assay measures the production of interferon-gamma and presents it relative to a negative and a positive control sample (Manuel and Kumar 2008). The QFT kit will be supplied by the central laboratory. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the study-specific laboratory manual.

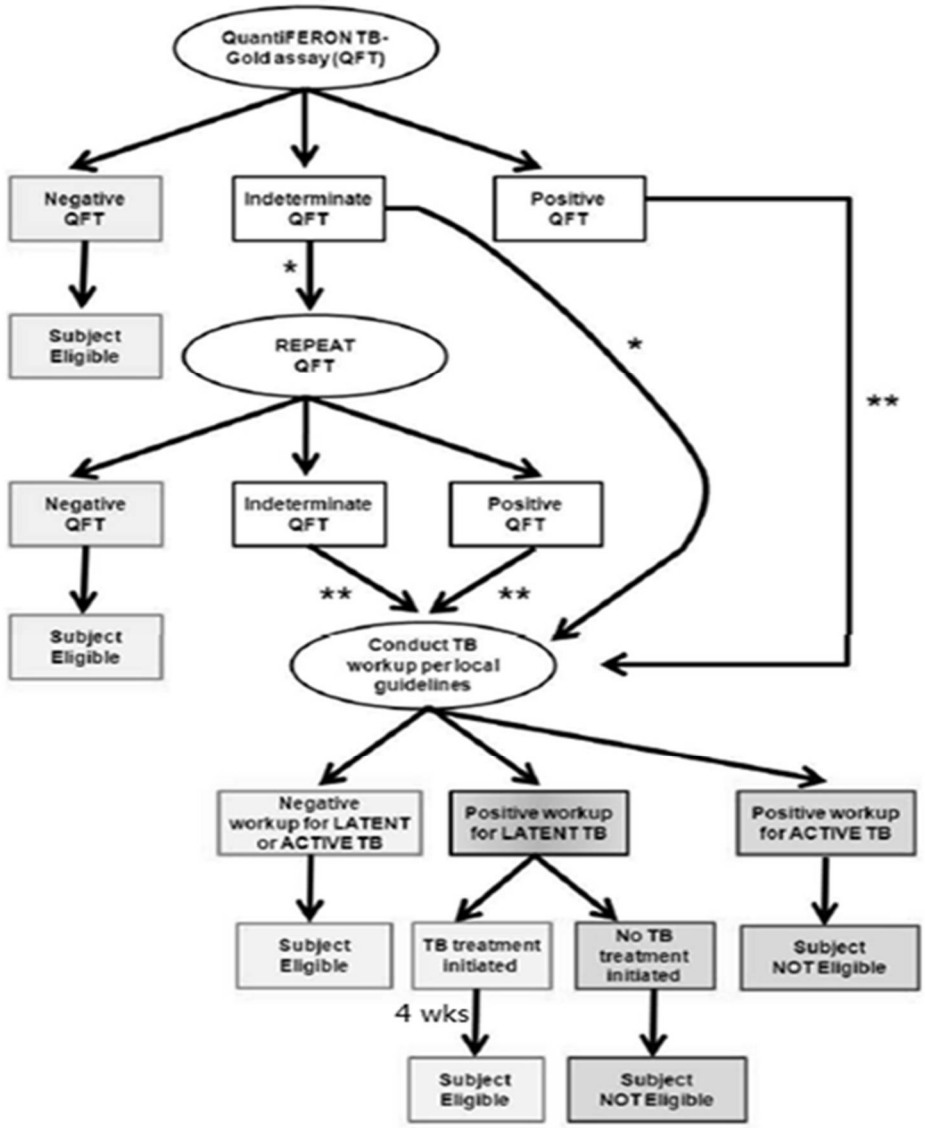
6.2.1.2 Chest X-ray

For patients with a positive QFT, a chest X-ray is required; no new chest X-ray is needed in subjects with chest X-ray, chest CT scan and/or chest MRI performed within 12 weeks of screening. If the chest X-ray, chest CT scan, and/or chest MRI evaluated by a qualified health care professional reveals past or present active TB, the subject will not be enrolled into the study.

6.2.1.3 Protocol for tuberculosis screening

Screening for TB will be performed according to Figure 6-1, below. Positive or indeterminate QFTs must be entered on the Tuberculosis assessment eCRF.

Figure 6-1 Tuberculosis screening flowchart



The subject will not be eligible for randomization if "active tuberculosis is present" or if "latent tuberculosis is present and is untreated as per local guideline"

*If the first QuantiFERON® TB-Gold In-Tube test (QFT) is indeterminate, the investigator may choose to perform a second QFT or refer the subjects for tuberculosis workup per local guidelines.

**If the result of any QFT is "positive" or the results of 2 sequential QFTs are "indeterminate", the subject must be referred to have a tuberculosis workup per local guidelines (if no workup within 12 weeks prior to randomization is available.)

The approach to screening is as follows:

- If the QFT result is negative, the subject may be randomized.
- If the QFT result is positive, the investigator should perform further evaluation to rule out active TB, as per local procedures. If a TB workup was conducted prior to screening the

subject, results of the workup can be used to assess eligibility if the workup was conducted within 12 weeks prior to randomization.

- Subjects with latent TB may be randomized if treatment for latent TB has been performed for 4 weeks prior to randomization and subject agrees to continuous treatment according to local guidelines.
- Subjects positive for active TB per workup are not eligible for the study.

- If the QFT result is **indeterminate**, the investigator **may repeat the test once or may proceed directly to perform workup** for TB as per local procedures. This action is at the discretion of the investigator. If a TB workup was conducted prior to the screening the subject, results of the workup can be used to assess eligibility if the workup was conducted within 12 weeks prior to randomization.
  - If the second test is negative, the subject may be randomized.
  - If the second test is positive or indeterminate, the investigator should perform further evaluation to rule out active TB, as per local guidelines. Subject positive for **latent** TB per workup may be randomized to the trial if treatment for latent TB has been performed for 4 weeks prior to randomization and subject agrees to continuous treatment according to local guidelines. Subjects positive for active TB per workup **are not eligible** for the study.
- If eligibility is being assessed with only 1 test result and a TB workup (i.e., no second TB test will be performed), the TB test to assess eligibility must have been done via the central laboratory for the study within the screening epoch (within 4 weeks prior to randomization) and TB workup will only be considered if it was completed within 12 weeks prior to randomization. Subjects positive for latent TB per workup may be randomized to the trial if sufficient treatment has been initiated according to local routine clinical practice for at least 4 weeks prior to randomization and will be maintained for the prescribed duration. Subjects positive for active TB per workup are not eligible for the study. Subjects negative for TB per workup (no signs of latent or active TB) may be randomized to the trial.

6.2.1.4 Treatment of latent TB and safety monitoring

In case of latent TB, patients who elect to remain in the trial will receive TB prophylaxis treatment according to local guidelines. The following recommendations are based on WHO guidelines and are considered guidance, unless local regulations suggest different approaches.

If a 6 month 5 mg/kg/per day INH TB prophylaxis is prescribed according WHO guidelines used in China (WHO 2015), patients are required to undergo monthly LFT monitoring. The INH treatment will be continued for 6 months.

The INH treatment should be halted in the following situations:

- ALT $\geq$ 5 x ULN
- ALT $\geq$ 3 x ULN and presence of symptoms (e.g. general malaise, fatigue, abdominal pain, nausea, or vomiting)

- ALT ≥ 2-3 x ULN and AST ≥ 3 x ULN

In patients whose INH is discontinued, after ALT normalization, TB prophylaxis will be resumed with an alternative regimen (e.g., 10 mg/kg/per day rifampicin) for 3-4 months.

If regimens that don't include INH are chosen to treat latent TB, then monitoring of LFTs will be necessary in the case of regimens including rifamycins (e.g., rifampicin, rifapentine, or rifabutine), pyrazinamide, or their analogs; in such cases, management of abnormal LFTs should be performed using the example for INH, above.

6.2.2 Other baseline characteristics

Baseline characteristic data to be collected on all subjects include (all laboratory results are central except where indicated): ECG, vital signs; hematology; clinical chemistry; local urinalysis; local stool ova and parasite evaluation; serum pregnancy test; medical history of anaphylactic; history of contraindications to diphenhydramine; immunogenicity; [redacted] in clinic UAS; DLQI.

6.3 Treatment exposure and compliance

All doses of study treatment administration will be recorded on the appropriate Dosage Administration Record eCRF page. Compliance will be assessed by unblinded field monitor at each visit using vials (omalizumab and omalizumab placebo) counts and information provided by the unblinded pharmacist or unblinded authorized site staff responsible for treatment dispensation and preparation.

6.4 Efficacy

A number of efficacy variables will be assessed during the study. During each visit, the assessment will be started with patient reported outcomes (PRO) (DLQI) and then move to other assessments and laboratory assessment.

6.4.1 eDiary assessments

6.4.1.1 Number of hives, intensity of itch, and Urticaria Activity Score (UAS)

The number of hives, and intensity of itch score will be recorded by the patient twice daily (morning and evening) in their eDiary, on a scale of 0 (none) to 3 (intense/severe) (see Table 6-2). The UAS is a composite score of the number of wheals (hives) (Hives Severity Scores, HSS); and the severity of the itch (Itch Severity Scores, ISS).

Table 6-2 Urticaria Activity Score (UAS)

Score	Wheals (Hives)	Pruritus (Itch)
0	None	None
1	Mild (1-6 hives/12 hours)	Mild (minimal awareness, easily tolerated)
2	Moderate (7-12/12 hours)	Moderate (definite awareness, bothersome but tolerable)
3	Severe (> 12 hives/12 hours)	Severe (difficult to tolerate)

6.4.1.1.1 Hives Severity Score (HSS)

The wheals (hives) severity score (HSS), defined by number of hives, will be recorded by the patient twice daily in their eDiary, on a scale of 0 (none) to 3 (intense/severe) (see Table 6-2). A weekly score (HSS7) is derived by adding up the average daily scores of the 7 days preceding the visit. The possible range of the weekly score is therefore 0 – 21.

Complete hives response is defined as HSS7 = 0.

When either the morning or evening score is missing, the non-missing score for that day (morning or evening) will be used as the daily score. When one or more of the daily scores are missing, the following principles will be applied to handle the missing data: If a patient has at least 4 non-missing daily scores within the 7 days prior to the study visit, the weekly score is calculated as the sum of the available eDiary scores in that week, divided by the number of days that have a non-missing diary score, multiplied by 7. If there are less than 4 non-missing daily scores within the prior 7 days, then the weekly score is missing for the week.

6.4.1.1.2 Itch Severity Score (ISS)

The severity of the itch will be recorded by the patient twice daily in their eDiary, on a scale of 0 (none) to 3 (intense/severe) (see Table 6-2). A weekly score (ISS7) is derived by adding up the average daily scores of the 7 days preceding the visit. The possible range of the weekly score is therefore 0 – 21. Partially missing diary entries will be handled in the same way as described for the hives severity score.

Complete itch response is defined as ISS7 = 0.

Weekly itch severity score MID response is defined as a reduction from baseline in weekly itch severity score of at least 5 points.

Time to weekly itch severity score MID response is the time (in weeks) from the date of the first dose to the date where weekly itch severity score MID response is first achieved.

6.4.1.1.3 The weekly Urticaria Activity Score (UAS7)

The UAS7 is the sum of the HSS7 score and the ISS7 score. The possible range of the weekly UAS7 score is 0 – 42.

Complete UAS7 response is defined as UAS7 = 0.

UAS7 MID response is defined as a reduction from baseline in UAS7 of at least 11 points.

Time to UAS7 MID response is the time (in weeks) from the date of the first dose to the date where UAS7 MID response is first achieved.

Week 12 responders are defined as patients who achieve an absolute UAS7 less than or equal to 6 at Week 12.

6.4.1.6 Calls to doctor or nurse

Calls to doctor, nurse or nurse practitioner because of the patient's skin condition will be recorded once daily in the eDiary by the patient.

6.4.2 Patient reported outcome assessment

6.4.2.1 Dermatology Life Quality Index (DLQI)

DLQI is a 10-item dermatology-specific health-related quality of life measure (Finlay and Khan 1994). Patients rate their dermatology symptoms as well as the impact of their skin condition on various aspects of their lives. 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, Treatment. The minimally important difference of the overall DLQI score for patients with CSU has been estimated to be 2.24−3.10 (Shikiar et al 2005). DLQI questionnaire will be provided in Chinese language, and be assessed at the site; The questionnaire will be completed by the patients unobserved.

6.4.3 Appropriateness of efficacy assessments

Efficacy will be determined using the primary endpoint of change from baseline in the weekly itch severity score at Week 12. Assessment of itch is the symptom of greatest concern to patients, with greatest impact on their quality of life (Mathias et al 2010). Because the chief CSU symptoms are hives and intense itch, it is appropriate to evaluate clinical response through use of the UAS, a composite endpoint that measures both of these symptoms. UAS7 is therefore incorporated as a secondary endpoint.

Time to onset of the clinical effect (ISS7 MID and UAS7 MID) of treatment with omalizumab will be evaluated during the treatment epoch. Time to onset of clinical effect is important to establish so that guidance can be given to patients regarding when a response should be expected.

Disease recurrence after study drug is withdrawn will be measured during this study. For all patients, symptom scores will be measured during both the treatment and post-treatment follow-up epochs. This important information will be used along with data from other studies to provide guidance for the duration of therapy.

6.5 Safety

6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A short physical exam will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse). A short physical exam will be at all visits starting from visit 3 except where a complete physical examination is required (see above).

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after first administration of investigational drug which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF.

6.5.2 Vital signs

Vital signs include BP and pulse measurements. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using an automated validated device, e.g., OMRON, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

Clinically notable vital signs are defined in Appendix 1.

6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential counts, and platelet count will be measured.

6.5.4.2 Clinical chemistry

Sodium, potassium, chloride, bicarbonates, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatinine phosphokinase, and uric acid will be measured.

6.5.4.3 Urinalysis

A midstream urine sample (approximately 30 ml) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments. Semi quantitative 'dipstick' evaluation for the following parameters will be performed. Specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leucocyte and blood.

6.5.4.4 Anti-omalizumab antibodies

At Visit 101 an anti-omalizumab antibody level will be measured on all patients prior to first dosing. Patients are also instructed to return to the clinic for an anti-omalizumab antibody blood sample 12 weeks after their last administration (Visit 299). The 12-week waiting period

decreases the interference of anti-omalizumab antibody detection due to the presence of omalizumab. Refer to the blood log in Appendix 2, Table 13-2 for sample collection and volumes.

6.5.5 Electrocardiogram (ECG)

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12 lead ECGs are collected. The original ECGs and a certified copy on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site.

Each ECG tracing must be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs must be performed to confirm the safety finding. Clinically significant ECG findings at baseline must be discussed with the sponsor before administration of study treatment.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE CRF / e(CRF) page as appropriate.

6.5.6 Pregnancy and assessments

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

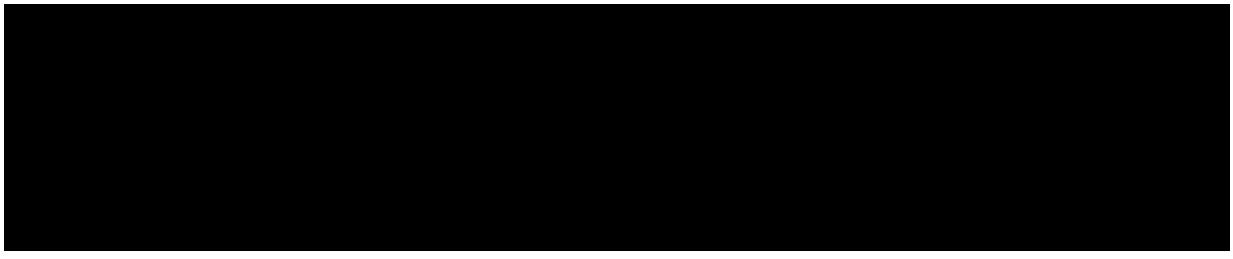
Any females with a confirmed serum positive pregnancy test during screening are not eligible for randomization.

All pre-menopausal females who are not sterile at screening will also have a urine pregnancy test performed locally at Visits 101, 102, 103, 199 and 299.

A positive urine pregnancy test during the treatment epoch of the study requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If the serum β-hCG test is positive, study treatment must be discontinued, as described in Section 5.5.9.

6.5.7 Appropriateness of safety measurements

The safety assessments selected in this study are reliable and standard measured for a biologic immunomodulating agent in adult and adolescent subjects with CSU.



[redacted]

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment
  - Yes
  - No
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.

- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding [investigational] treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- investigational treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification (IN) or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the patient's general condition

- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE omalizumab and complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

As omalizumab is not associated with hepatotoxic potential no specific liver safety monitoring is needed in this trial in patients who do not require treatment for latent TB.

7.4 Renal safety monitoring

As omalizumab is not associated with kidney toxicity potential no specific renal safety monitoring is needed in this trial.

7.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

7.6 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data, identify risks and trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or

assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients/subjects will be disclosed.

8.2 Data collection

Novartis will supply the investigator site with a computer loaded with Electronic Data Capture (EDC) software that has been fully validated and conforms to US CRF 21 Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained by Novartis personnel. Designated investigator staff will enter the data required by the protocol into the Novartis CRFs using the Novartis-supplied computer. Automatic validation programs check for data discrepancies in the CRFs and, by generating appropriate error messages, allow the data to be confirmed or corrected by the investigator staff before transfer of the data to Novartis via a secure Virtual Private Network. The investigator must certify that the data entered are complete and accurate by signing a memo generated at the end of the trial that will be sent to him by Novartis personnel. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff [or CRO working on behalf of Novartis] review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Diary data will be entered into an electronic diary by the patient OR Patients/subjects will fill in their patient reported outcome (PRO) data in a site based tablet. The system will be

supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

An independent adjudication committee will be used to monitor anaphylaxis. The events will be reviewed in a blinded manner and adjudicated as they occur during the conduct of the study. Details regarding the adjudication process are available in the relevant Anaphylaxis Adjudication Committee charter.

9 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

Randomized population (RAN): The RAN will include all randomized subjects, regardless of whether they took any study medication. Patients in RAN will be analyzed according to the treatment assigned at randomization.

Full analysis set (FAS): The FAS will include all randomized subjects who receive at least one dose of study drug. Following the intent-to-treat principle, subjects will be analyzed according to the treatment they are assigned to at randomization. This analysis population will be used for all efficacy analyses unless otherwise specified.

Safety set (SAF): The SAF consists of all subjects in the FAS who take at least one dose of study medication. Subjects will be analyzed according to the actual treatment received during the randomized treatment epoch, as follows:

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

9.2 Patient demographics and other baseline characteristics

The analysis will be based on the RAN, unless otherwise specified.

Demographic and baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristic variables for each treatment group. The number and percentage of patients in each category will be presented for categorical variables for each treatment group and all patients.

The randomized treatment groups will be summarized by the following demographic variables: gender, age, ethnicity, race, weight, height, and BMI.

Baseline disease characteristics will also be summarized for the following variables, including but not limited to: duration of CSU, previous number of CSU medications, previous use of systemic steroids for CSU, in-clinic UAS, weekly urticaria activity score (UAS7), weekly itch severity score (ISS7), weekly number of hives score (NHS7), weekly size of largest hive score (LHS7), and presence of angioedema.

Medical history

Any condition entered on the Medical history eCRF will be coded using the MedDRA dictionary. The number of patients with medical history will be summarized by primary system organ class, preferred term and treatment group for the RAN. Protocol solicited medical history will be also summarized.

9.3 Treatments

The analysis of study treatment data will be based on the SAF, unless otherwise specified.

Study treatment

The duration of exposure to study treatment will be summarized by treatment group. In addition, the number of doses and total cumulative dosage will be presented.

Duration of exposure is defined as the date of the last treatment minus the date of first study drug administration plus 4 weeks (28 days).

Prior and concomitant medication

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized

study treatment and the date of the last study visit will be a concomitant medication, including those which were started pre-baseline and continued into the period where study treatment is administered.

Prior and concomitant medications will be summarized by treatment separately for CSU related and non-CSU related medications. CSU-related medications will be summarized by pre-specified categories, route of administration, and preferred term. Non-CSU related concomitant medications will be summarized by the preferred term. Concomitant medications will be also summarized by epoch; the randomized treatment epoch and newly onset during post-treatment follow-up epoch.

Significant surgery and medical procedures will be summarized by primary system organ class and MedDRA preferred term.

9.4 Analysis of the primary variable(s)

Analyses will be based on the patients in FAS, unless otherwise specified.

9.4.1 Variable(s)

The primary efficacy variable is change from baseline in weekly itch severity score (ISS7, a component of the UAS7, see Section 6.4.1.1) at Week 12.

The daily itch score is the average of the morning and evening itch severity scores. The baseline ISS7 is the sum of the daily itch severity scores over the 7 days prior to the randomization Day 1 visit, and the ISS7 at Week 12 is the sum of daily itch scores over the 7 days prior to the Week 12 visit. The same principles of calculating baseline and Week 12 weekly scores will be applied to each weekly outcome unless otherwise stated.

9.4.2 Statistical model, hypothesis, and method of analysis

A mixed-effect linear model with repeated measures (MMRM) will be used to obtain the least squares mean (LSM) estimate for each treatment group for change from baseline in ISS7 at Week 12 (the primary endpoint). The MMRM model will include terms of treatment group, week (1 to 12), baseline score, baseline score-by-week interaction, and treatment-by-week interaction as fixed effects. Treatment group and week will be fitted as categorical variables, and baseline score as a continuous covariate. The within-patient correlation will be modeled using the unstructured covariance matrix (Mallinckrodt et al 2001). If the model does not converge, the compound symmetry covariance structure will be used. The occurrence of missing data will be assumed to be missing at random (MAR).

The difference in LSM estimates between treatment groups, together with a 95% CI, will be presented.

A multiplicity adjustment for two primary efficacy comparisons based on above model will be made according to the overall study testing strategy provided in Section 9.5.1. The statistical analyses will test the null hypothesis of no difference between the placebo and each omalizumab dose group.

9.4.3 Handling of missing values/censoring/discontinuations

The primary endpoint will be analyzed using an MMRM which is valid under the MAR (Missing-At-Random) assumption (Rubin 1976). Patients who have at least one post-baseline are included in the MMRM analysis. This includes not only the patients who have completed 12 weeks of treatment (with a complete 12-week longitudinal data), but also those who discontinue from study treatment early (although only able to contribute to a partial time profile). This is under the assumption that dropouts would follow the similar data pattern like other patients who complete the treatment period in the same treatment group, as if they had not discontinued from the study treatment.

Patients who discontinue from study treatment early will remain in the study and follow the procedures described in Section 5.5.9. Nevertheless, the data on and post the date of the last treatment + 4 weeks will be treated as missing in the primary analysis.

The ISS7 is the sum of the average daily itch scores over 7 days each week. The daily itch scores are calculated based on daily eDiary entries for itch. The daily itch score is then calculated as the average of the morning and evening itch scores.

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

- If a patient has at least 4 non-missing daily itch scores within the 7 days prior to the study visit, the ISS7 score is calculated as the sum of the available eDiary itch scores in that week, divided by the number of days that have a non-missing diary itch score, multiplied by 7.
- If there are less than 4 non-missing daily itch scores within the prior 7 days, then the ISS7 score is missing for the week.

9.4.4 Sensitivity analyses

The impact of missing data on the primary analysis results will be assessed by repeating the analysis using different missing data assumptions to handle missing data. The supportive analyses may include, but are not limited to:

- An analysis of covariance (ANCOVA) model with missing Week 12 itch scores imputed by carrying forward the patients' baseline scores (BOCF). The ANCOVA model would include treatment group as a factor, and baseline score as a covariate.
- An ANCOVA model with missing Week 12 itch scores imputed by carrying forward the patients' last non-missing weekly score (LOCF). The ANCOVA model would include treatment group as factors, and baseline score as a covariate.
- Jump-to-Reference (J2R) multiple imputation approach

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

All of the secondary efficacy variables will be analyzed using the FAS unless otherwise specified.

Testing strategy

The following primary and secondary hypotheses will be included in the testing strategy. To ensure the family-wise type I error rate (α) is kept at an overall level of less than 5%, a flexible gate-keeping procedure (Bretz et al 2009) will be employed as described below. The procedure allows the type-one error rate associated with a rejected hypothesis to be reallocated among the remaining (un-rejected) hypothesis tests according to a set of pre-specified rules. The hypotheses are organized to describe the order in which different sets of hypotheses will be tested.

Primary objectives (as described in Section 9.4):

H_1: Omalizumab 300 mg is not different to placebo with respect to change from baseline in ISS7 (weekly itch severity score) at Week 12

H_2: Omalizumab 150 mg is not different to placebo with respect to change from baseline in ISS7 (weekly itch severity score) at Week 12

Secondary objectives:

H_3: Omalizumab 300 mg is not different to placebo with respect to change from baseline in UAS7 (weekly urticaria activity score) at Week 12

H_4: Omalizumab 150 mg is not different to placebo with respect to change from baseline in UAS7 (weekly urticaria activity score) at Week 12

H_5: Omalizumab 300 mg is not different to placebo with respect to change from baseline in NHS7 (weekly number of hives score) at Week 12

H_6: Omalizumab 150 mg is not different to placebo with respect to change from baseline in NHS7 (weekly number of hives score) at Week 12

H_7: Omalizumab 300 mg is not different to placebo with respect to the percentage of patients with UAS7 $\leq$ 6 response at Week 12

H_8: Omalizumab 150 mg is not different to placebo with respect to the percentage of patients with UAS7 $\leq$ 6 response at Week 12

H_9: Omalizumab 300 mg is not different to placebo with respect to the percentage of patients with UAS7 = 0 response at Week 12

H_{10}: Omalizumab 150 mg is not different to placebo with respect to the percentage of patients with UAS7 = 0 response at Week 12

H_{11}: Omalizumab 300 mg is not different to placebo with respect to the percentage of patients with ISS7 MID response at Week 12

H_{12}: Omalizumab 150 mg is not different to placebo with respect to the percentage of patients with ISS7 MID response at Week 12

H_{13}: Omalizumab 300 mg is not different to placebo with respect to change from baseline in overall DLQI score at Week 12

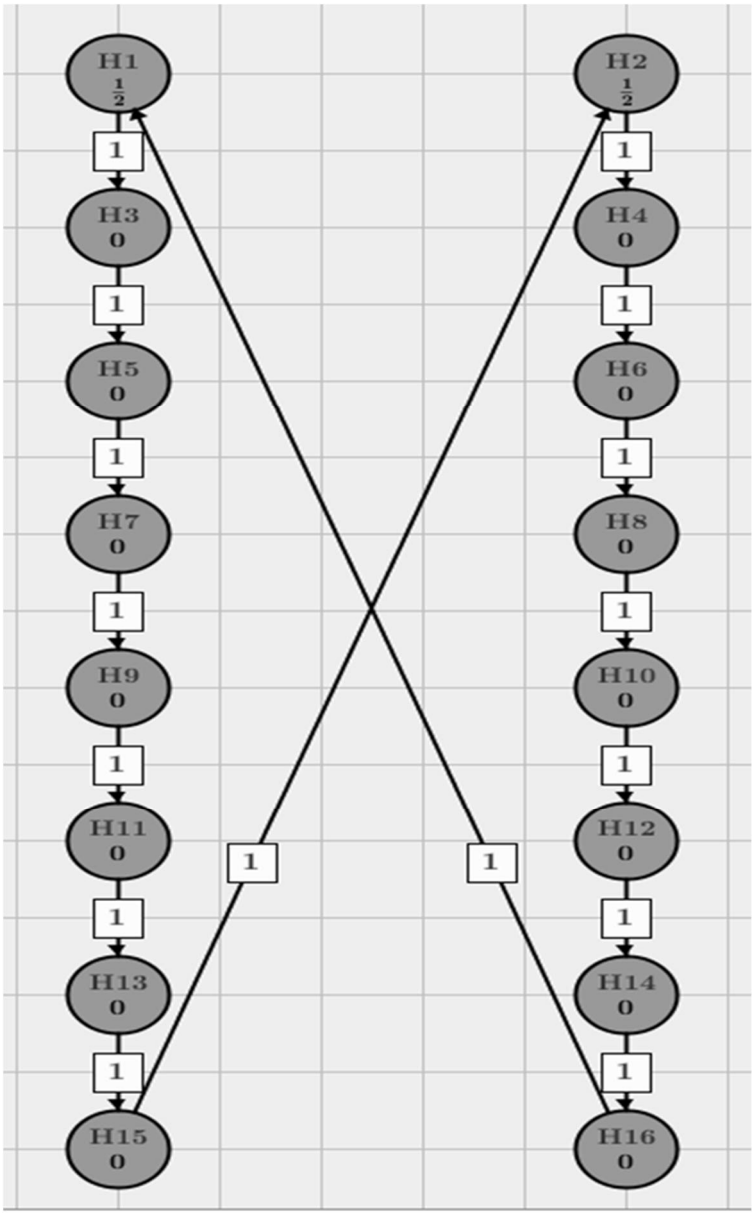
H_{14}: Omalizumab 150 mg is not different to placebo with respect to change from baseline in overall DLQI score at Week 12

H_{15}: Omalizumab 300 mg is not different to placebo with respect to the time to ISS7 MID during the randomized treatment epoch

H_{16}: Omalizumab 150 mg is not different to placebo with respect to the time to ISS7 MID during the randomized treatment epoch

The graphical approach of (Bertz et al 2009) for sequentially rejective testing procedures is used to illustrate the testing strategy in Figure 9-1.

Figure 9-1 Testing strategy for primary and secondary endpoints



Note: As shown in the above graph, initially each H_1 and H_2 will be assigned $\alpha/2$ to test the individual hypotheses simultaneously and move forward.

The family-wise error rate will be set to $\alpha = 5\%$ (2-sided) and will be controlled using the proposed hierarchical testing strategy as illustrated in Figure 9-1.

First, each of the hypotheses (H_1 and H_2) for the primary objective (based on change from baseline in ISS7 at Week 12) for omalizumab 300 mg and 150 mg versus placebo will be tested simultaneously at $\alpha/2$.

If at least one of H_1 and/or H_2 is rejected, then H_3 and/or H_4, respectively, will be tested at $\alpha/2$. If at least one of H_3 and/or H_4 is rejected, then H_5 and/or H_6, will be tested, respectively. A similar process applies until H_{15} and H_{16}. Once all hypotheses for an omalizumab dose are rejected, then the respective $\alpha/2$ can be passed on to the other dose's hypotheses, if they are not already rejected at $\alpha/2$. In the description above, rejection of a hypothesis refers to rejection of the two-sided hypothesis; however the significance level of a rejected hypothesis is only passed on according to the graphical procedure for the test of another hypothesis if the treatment effect is in favor of omalizumab.

Change from baseline in weekly urticarial activity score (UAS7) at Week 12

The urticaria activity score (UAS) is a composite score (itch severity score and number of hives score) described in Section 6.4.1.1. For each of the morning and evening UAS score, it is calculated as the sum of the itch severity score and number of hives score according to eDiary entries. The daily UAS is the average of the morning and evening UAS scores, and UAS7 is the sum of daily UAS scores over 7 days.

The missing data will be handled in the same way as described in Section 9.4.3.

Treatment comparisons of 300 mg vs placebo (H_3) and 150 mg vs placebo (H_4) in change from baseline to Week 12 in the UAS7 will be made using an MMRM model with similar terms as the primary analysis but baseline UAS7 as a covariate (Refer to Section 9.4.2).

Change from baseline in weekly number of hives score (NHS7) at Week 12

The weekly number of hives score (NHS7) will be handled using the same principles as described for the primary endpoint in Section 9.4.1 and Section 9.4.3.

Treatment comparisons of 300 mg vs placebo (H_5) and 150 mg vs placebo (H_6) in change from baseline to Week 12 in the NHS7will be made using an MMRM model with similar terms as the primary analysis but baseline NHS7 as a covariate (Refer to Section 9.4.2).

Percentage of patients with UAS7 ≤ 6 at Week 12

Treatment comparisons of 300 mg vs placebo (H_7) and 150 mg vs placebo (H_8) in the percentage of patients with UAS7 ≤ 6 at Week 12 will be made using a logistic regression model with treatment group as a factor and baseline UAS7 as a covariate.

A patient with missing data at Week 12 will be imputed as a responder if the patient was a responder at Week 10 and Week 11, otherwise as a non-responder.

Percentage of patients with UAS7 = 0 at Week 12

Treatment comparisons of 300 mg vs placebo (H_9) and 150 mg vs placebo (H_{10}) in the percentage of patients with UAS7 = 0 at Week 12 will be made using a logistic regression model with treatment group as a factor and baseline UAS7 as a covariate.

A patient with missing data at Week 12 will be imputed as a responder if the patient was a responder at Week 10 and Week 11, otherwise as a non-responder.

Percentage of patients with ISS7 MID response at Week 12

The ISS7 MID response is defined as a reduction from baseline in ISS7 of ≥ 5 points.

Treatment comparisons of 300 mg vs placebo (H_{11}) and 150 mg vs placebo (H_{12}) in the percentage of patients with ISS7 MID response at Week 12 will be made using a logistic regression model with treatment group as a factor and baseline ISS7 as a covariate.

A patient with missing data at Week 12 will be imputed as a responder if the patient was a responder at Week 10 and Week 11, otherwise as a non-responder.

Change from baseline in overall DLQI at Week 12

DLQI is a PRO instrument, described in Section 6.4.2.1. An overall score will be calculated according to the scoring manual given in Appendix 3. The baseline and up to Week 12 overall DLQI scores will be derived from the questionnaires assessed at the Day 1 and up to Week 12 visits.

Treatment comparisons of 300 mg vs placebo (H_{13}) and 150 mg vs placebo (H_{14}) in change from baseline to Week 12 in overall DLQI score will be made using an MMRM model with similar terms as primary analysis but baseline DLQI as a covariate (Refer to Section 9.4.2).

Time to ISS7 MID response during the randomized treatment epoch

The ISS7 MID response is defined as a reduction from baseline in ISS7 of ≥ 5 points. Time to ISS7 MID response is the time (in weeks) from the date of the first dose to the date where ISS7 MID response is first achieved during the randomized treatment epoch. If no ISS7 MID response is achieved during the randomized treatment period, the patient will be treated as censored at the last dose date + 28 days – 1.

Treatment comparisons of 300 mg vs placebo (H_{15}) and 150 mg vs placebo (H_{16}) will be performed using a Cox proportional hazard (PH) model with treatment group as a factor and baseline ISS7 as a covariate. The ratio of event rate and 95% CI will be reported.

Kaplan-Meier analysis stratified by treatment group will be also presented with log-rank test and displayed graphically.

9.5.2 Safety variables

All safety evaluations will be performed on the safety set (SAF).

Adverse events

All the AEs occurring after providing written informed consent will be recorded on the Adverse Event eCRF page. AEs starting on or after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term will be classified as treatment emergent AEs. Overall AEs, SAEs, AEs by severity will be also summarized for each epoch (randomized-treatment and post-treatment follow-up) when necessary. Non-treatment emergent AEs (occurring after providing written informed consent but before first dose of study treatment) will not be summarized but listed only.

Treatment emergent AEs will be summarized by presenting, for each treatment group, the number and percentage of patients having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will be also presented for treatment emergent AEs by severity and for study treatment related AEs. If a patient reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable. Separate summaries will be provided for death, serious adverse event, and adverse events leading to discontinuation.

Treatment emergent AEs of special interest for omalizumab treatment will be also summarized. AEs of special interest for omalizumab treatment will be specified as compound-level risk factors defined in the Case Retrieval Strategy.

Summary tables that present numbers and percentages of patients with the AEs of special interest will be presented by standardized MedDra Query (SMQ) (if applicable), preferred term and treatment. In addition, the hepatic disorders events will be tabulated by latent TB at baseline (Yes/No).

Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, serum chemistry and urinalysis). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline values.

The hepatic-related laboratory tests will also be tabulated by latent TB at baseline (Yes/No).

Anti-omalizumab antibody

A summary of anti-omalizumab antibodies will be provided.

Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for subjects with both baseline and post-baseline values. Subjects with notable vital signs as defined below will be listed.

- Hypertension (systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg) or hypotension (systolic blood pressure or < 90 mmHg and/or diastolic blood pressure of < 60 mmHg).
- Pulse rate below 60 bpm (bradycardia) or above 100 bpm (tachycardia)

Other

Healthcare utilization (calling a doctor, nurse, or nurse practitioner) based on patient daily diary data will be summarized for each treatment group.

For patients reporting angioedema, the action(s) taken in response to their angioedema based on patient daily diary data will be summarized for each treatment group.

9.5.3 Resource utilization

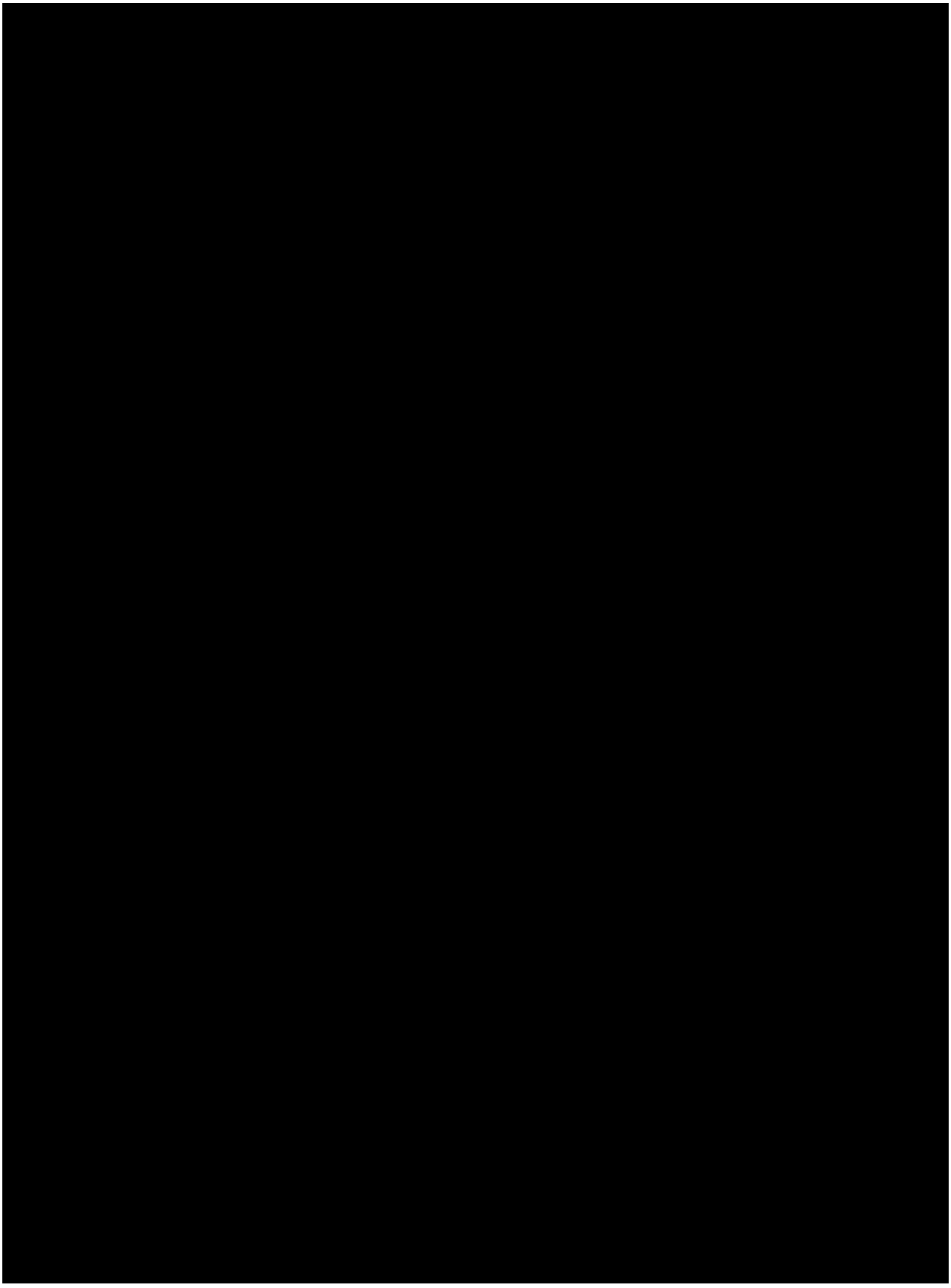
Not applicable.

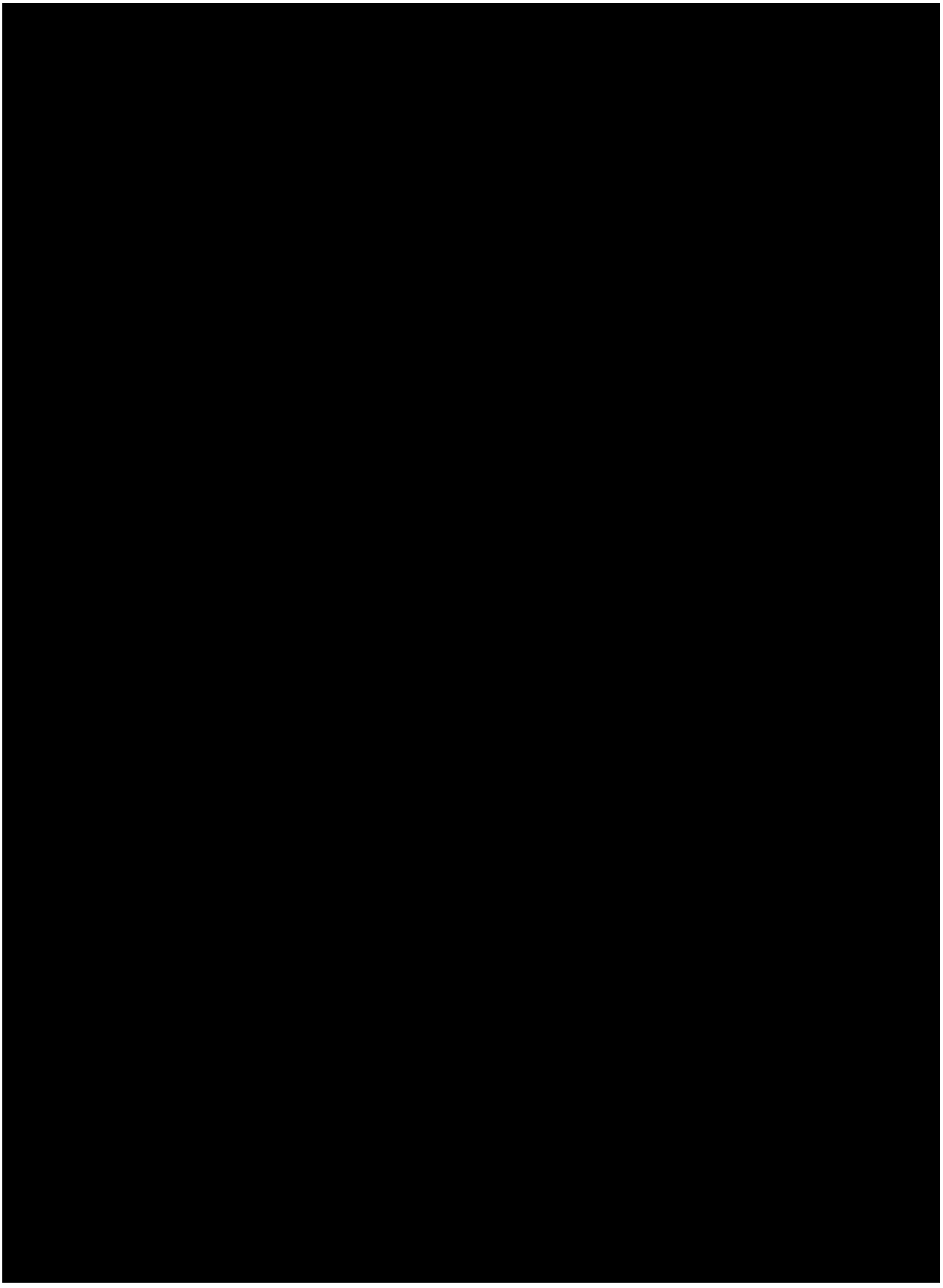
9.5.4 Biomarkers

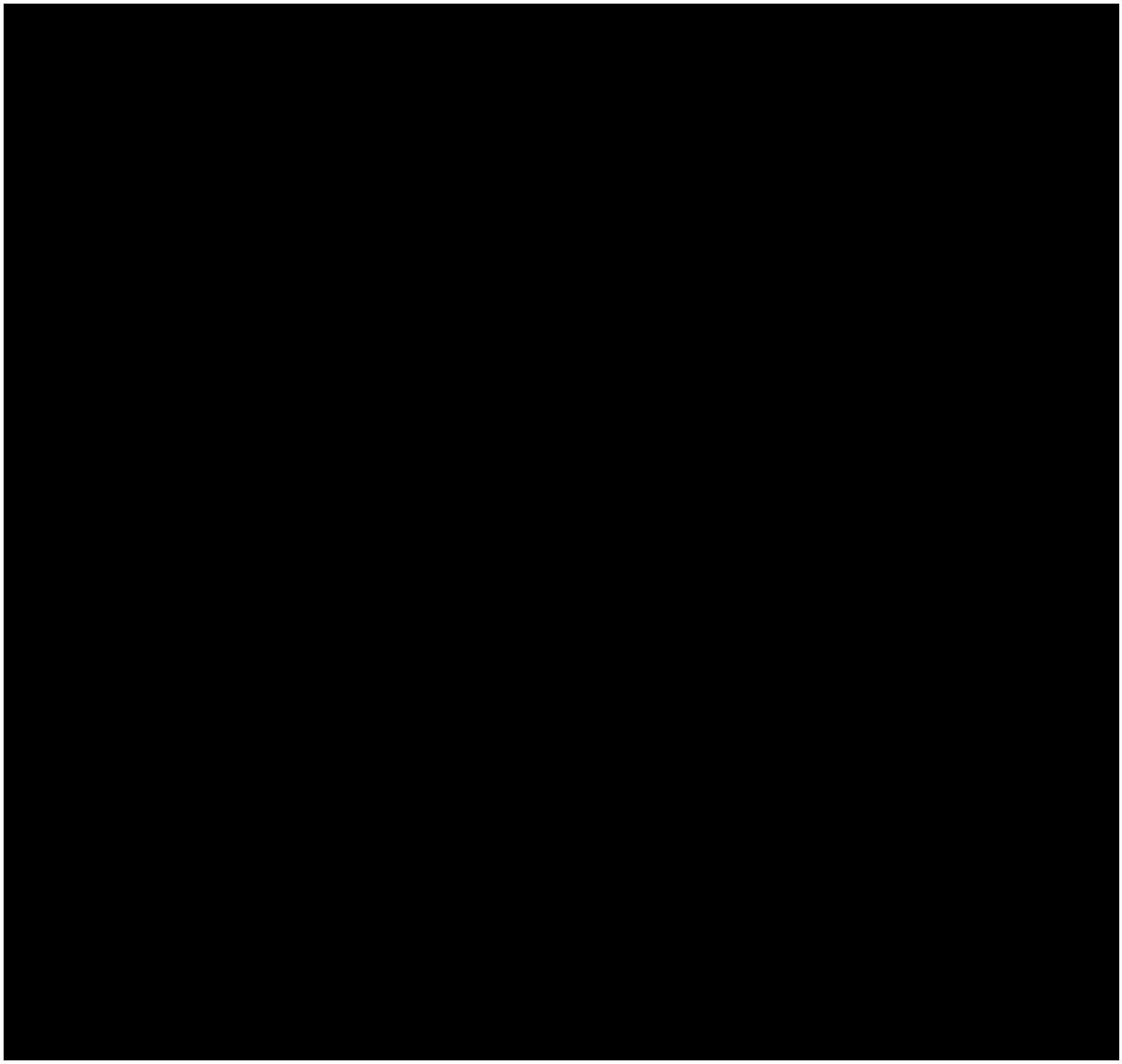
Not applicable.

9.5.5 DNA

Not applicable.







9.7 Interim analyses

No interim analysis is planned in this study.

9.8 Sample size calculation

The study is sized to ensure sufficient power to demonstrate meaningful efficacy based on the data from the full analysis set. In addition, for registration of a biologic compound the China health authority (China Food and Drug Administration, CFDA) requires at least 300 patients to be treated in the test drug as the minimum for safety evaluation. Assuming 10% dropout rate by week 12, the study will randomize 420 patients in a ratio of 2:2:1 to omalizumab 300 mg, omalizumab 150 mg, and placebo to ensure 375 patients completing Week 12 with 300 patients in the two omalizumab dose groups.

The below power evaluation for the planned hypothesis tests is based on a sample size of 375 (2:2:1) patients who complete 12 weeks of treatment duration. The powers are examined according to the hierarchy order of the multiplicity type I error control plan with the overall alpha level controlled at 0.05 (2-sided) as outlined in Figure 9-1. It is assumed Study E2305 will repeat the performance of the previous pivotal studies (Q4881g, Q4882g, and E2306). Except for ethnicity, these 3 studies have a similar patient population with consistent results for the primary and secondary endpoints. There is no statistical evidence suggesting heterogeneity among the studies. A meta-analysis with fixed-effects model was performed based on summary data from these studies to combine the estimates of the treatment effect and standard deviation (SD). The obtained pooled estimates on the treatment effect size and SD are then used as the assumed values for the alternative hypotheses to evaluate the power for each endpoint. To understand the impact of the strength of dependency between endpoints on the power, the power was evaluated under 3 scenarios of correlation (0, 0.5, 0.9), i.e. completely independency, moderate dependency, and strong dependency. The results are summarized in Table 9-1.

For the primary endpoint (change from baseline weekly itch score at Week 12), the study will offer

- a power of > 99.9% to detect a difference of 4.73 between 300 mg and placebo with the assumed SD of 5.28
- a power of > 93% to detect a difference of 2.73 between 150 mg and placebo with the assumed SD of 5.55

The power was evaluated for the primary and secondary endpoints as a whole according to the testing strategy defined in Section 9.5.1 (Figure 9-1) using the gMCP package in the R software.

According to Table 9-1, the power evaluation is summarized as follows.

- The power for 300 mg is maintained at nearly 95% and above for all testing hypotheses regardless of the strength of dependency between endpoints.
- The power for 150 mg is at least 80% for the testing hypotheses up to the endpoint of percentage of patients with UAS7 ≤ 6 at Week 12. The power for the rest of endpoints is decreased to 65% and below, and can be as low as 18% if the dependency between endpoints is none.

By reviewing and using clinical data from previous studies in the power assessment for the targeted hypothesis tests for the current study, the total sample size of 420 (including 10% dropout) with 2:2:1 assignment ratio is considered appropriate to allow sufficient power to achieve the primary objective and all the first four secondary objectives for both 300 mg and 150 mg. The study also has high power to achieve the last four secondary objectives for 300 mg, although the power is < 65% and below for 150mg.

Table 9-1 Power analysis of primary and key secondary endpoints

Endpoint	Hypo-thesis	Comparison	Parameter assumptions[1]	Power[2]
				Correlation between endpoints

				None (0)	**Moderate (0.5)**	**Strong (0.9)**
Change from baseline in ISS7 at W12	H_1	300 mg vs Placebo	Δ=4.73 SD=5.28	>0.999	>0.999	>0.999
	H_2	150 mg vs Placebo	Δ=2.73 SD=5.55	0.933	0.931	0.932
Change from baseline in UAS7 at W12	H_3	300 mg vs Placebo	Δ=11.16 SD=11.54	>0.999	>0.999	>0.999
	H_4	150 mg vs Placebo	Δ=6.31 SD=11.84	0.899	0.906	0.925
Change from baseline in NHS7 at W12	H_5	300 mg vs Placebo	Δ=6.22 SD=6.82	>0.999	>0.999	>0.999
	H_6	150 mg vs Placebo	Δ=3.52 SD=6.77	0.859	0.880	0.917
% of patients with UAS7 ≤ 6 at W12	H_7	300 mg vs Placebo	Log OR=2.09 SD=2.48 (~ p_{300}=61%, p_0=16%)	>0.999	>0.999	>0.999
	H_8	150 mg vs Placebo	Log OR=1.32 SD=2.46 (~ p_{150}=41%, p_0=16%)	0.830	0.864	0.914
% of patients with UAS7 = 0 at W12	H_9	300 mg vs Placebo	Log OR=2.27 SD=3.46 (i.e. p_{300}=41%, p_0=7%)	0.992	0.992	0.991
	H_{10}	150 mg vs Placebo	Log OR=1.21 SD=3.63 (~ p_{150}=19%, p_0=7%)	0.540	0.616	0.654
% of patients with ISS7 MID at W12	H_{11}	300 mg vs Placebo	Log OR=1.57 SD=2.34 (~ p_{300}=81%, p_0=47%)	0.986	0.986	0.989
	H_{12}	150 mg vs Placebo	Log OR=0.78 SD=2.09 (~ p_{150}=65%, p_0=47%)	0.408	0.537	0.631
Change from baseline in Overall DLQI at W12	H_{13}	300 mg vs Placebo	Δ=3.55 SD=5.86	0.965	0.969	0.977
	H_{14}	150 mg vs Placebo	Δ=1.91 SD=6.25	0.237	0.404	0.536
Time to ISS7 MID	H_{15}	300 mg vs Placebo	Log HR=0.7 SD=1.14 (~ S_{300}=6%, S_0=25%)	0.947	0.955	0.970
	H_{16}	150 mg vs Placebo	Log HR=0.43 SD=1.15 (~ S_{150}=12%, S_0=25%)	0.179	0.372	0.530

Endpoint	Hypo-thesis	Comparison	Parameter assumptions[1]	Power[2]		
				Correlation between endpoints		
				None (0)	Moderate (0.5)	Strong (0.9)

[1] Parameter assumptions are based on a meta-analysis of Studies Q4881g, Q4882g, and E2306

Δ= Difference; OR=Odds Ratio; HR: Hazard Ratio (i.e. ratio of event rate)

p_{300}, p_{150}, p_0: the probability of an event occurrence at Week 12 for Omalizumab 300mg, 150mg, and placebo

S_{300}, S_{150}, S_0: the probability of not having an event at and prior to Week 12 for Omalizumab 300mg, 150mg, and placebo

SD= Standard deviation for the data either normally distributed or on the scale with a normal approximation, e.g. logit(p) for binary data and log-log(S) for time-to-event data

[2] Power is calculated based on the total sample size of 420 assigned to treatment group 300 mg, 150 mg and placebo in ratio of 2:2:1 with 10% dropout rate during 12 weeks of treatment period, according to the hierarchy order of the multiplicity Type I error control scheme with overall alpha level controlled at 0.05 (2-sided).

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by

the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients/subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance (CQA), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients/subjects

should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients/subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

12 References

References are available upon request

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13 Appendices

13.1 Appendix 1: Clinically notable laboratory values and vital signs

The following criteria will be used to define expanded limit and notable abnormalities.

Hematology value

Platelet count: ≤ 100,000 /μL

No specific action is pre-defined within this protocol to respond to specific abnormal laboratory values, as it will be decided by the investigator /qualified site staff whether and which specific action needs to be taken to respond to any abnormal values, taking into account the overall status of the subjects.

For all other laboratory assessments, the Central Laboratory will flag laboratory values falling outsides of the normal ranges on the Central Laboratory Report (which the investigator should review and sign off) and the investigator will report any values considered clinically significant in the CRF.

Vital signs

Notable values of vital signs are described in Section 9.5.2.

13.2 Appendix 2 Blood log

[redacted]

Table 13-2 Blood log for immunogenicity

		Immunogenicity
Matrix		Serum
Visit	Sample No.	Volume (mL)
Visit 101 (pre-dose)	401	2
Visit 299	402	2
Sub total (mL)		4

13.3 Appendix 3 Dermatology Life Quality Index (DLQI) questionnaire

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: N/A Date:

Name: N/A Score:

Address: N/A Diagnosis:

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	Yes	❒

	you from **working** or **studying**?	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.