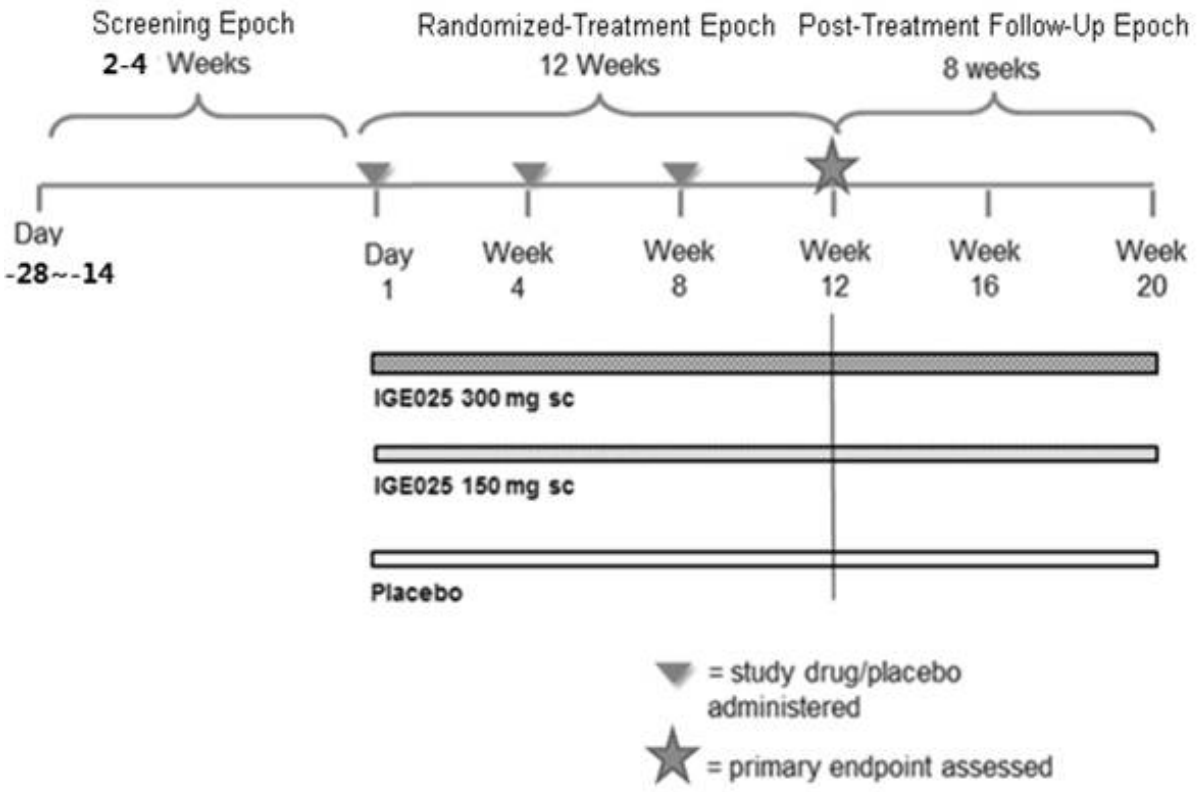
LDH	Lactate Dehydrogenase
LFT	Liver Function Tests
LOCF	Last Non Missing Weekly Score
LSM	Least Squares Means
LTRA	Leukotrine Receptor Antagonist
MAR	Missed At Random
MMRM	Mixed Effect Linear Model With Repeated Measures
MRI	Magnetic Resonance Imaging
NHS	Number of Hives Score
[redacted]	[redacted]
[redacted]	[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

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]

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.

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.

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]

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.

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.

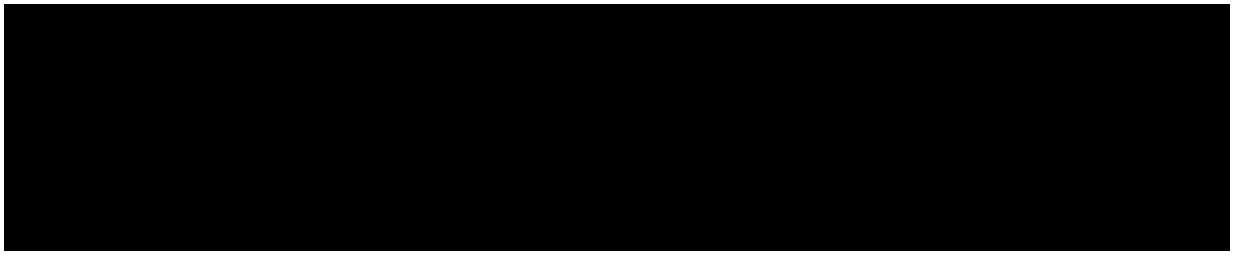
Any females with a confirmed serum positive pregnancy test during screening are not eligible for randomization.

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.

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.

				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

	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.

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

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

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.

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.

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]

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.

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).

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