NOVARTIS

Clinical Development

[QGE031/Ligelizumab]

Clinical Trial Protocol [CQGE031C2201E1] / NCT02649218

An open label, multicenter, extension study to evaluate the long-term safety of QGE031 240 mg s.c. given every 4 weeks for 52 weeks in Chronic Spontaneous Urticaria patients who completed study CQGE031C2201

Statistical Analysis Plan (SAP)

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	02MAR2018	Updated the MedDRA version information (Section 2.3.3 Medical history). [redacted]
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	15AUG2018	Remove week 100 information from eDiary derivation (table 1-2). [redacted] Updated “Table 1-6” variable information for “UAS7, HSS7 - time to achievement” related analysis.
	28AUG2018	Updated LLOQ and ULOQ derivation information for laboratory evaluations

Version	Date	Changes
		Updated section " 2.5.1.3 Deaths" to add report on deaths.
2.6	17OCT2018	[redacted]
2.7	11APR2019	Updated section "2.3.1 Patient disposition" to add duration of study follow-up report. [redacted]
2.8	03JUN2019	Updated section "2.5.1 Adverse events" to update the definition of treatment emergent adverse events, to exclude AEs which started more than 16 weeks after last dose. Also updated that follow-up epoch summaries will be for non-TEAEs. Updated section "2.5.1.1 Adverse events of special interest / grouping of AEs" to remove text "(Level 1)" after "Liver Toxicity" as per latest data. [redacted] Updated section "2.6 Analysis of the secondary objectives" to clarify when cut-off is used in time to event analysis. [redacted]
	18JUN2019	Update section 2.4.2 to add report on concomitant use of omalizumab. [redacted] Updated section 4 - added note for positively adjudicated Cerebrovascular events listing.

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Abbreviation

[redacted]	[redacted]
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CM	Concomitant medication
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical Study Report
CSU	Chronic Spontaneous Urticaria
CU	Chronic Urticaria
CV%	Coefficient of variation
DBP	Diastolic blood pressure
[redacted]	[redacted]
DRP	Data Review Plan
E1	Extension 1 of the core study
E1 FU	Post-treatment Follow-up period of the Extension 1
ECG	Electrocardiogram
[redacted]	[redacted]
H1-AH	H1-antihistamines
H2-AH	H2-antihistamines
hs-CRP	High sensitivity C-reactive protein
HSS	Hive Severity Score
[redacted]	[redacted]
INR	International Normalized Ratio
ISS	Itch Severity Score
LDH	Lactate dehydrogenase
LLOQ	Lower Limit Of Quantification
LTRA	Leukotriene Receptor Antagonist
MedDRA	Medical Dictionary for Regulatory Activities
NovDTD	Novartis Drug and Therapy Dictionary
PDev	Protocol Deviation
[redacted]	[redacted]
PT	Preferred Term
q4w	Every 4 weeks

QTc	Corrected QT Interval
QTcF	Fridericia QT Correction
s.c.	Subcutaneous
SAE	Serious Adverse Event
SBP	Systolic blood pressure
SS	Safety set
SOC	System Organ Class
TBL	Total bilirubin
TEAE	Treatment Emergent Adverse Event
UAS	Urticaria Activity Score
ULN	Upper Limit of Normal
ULOQ	Upper Limit Of Quantification
UPDD	Urticaria Patient Daily Diary
[redacted]	[redacted]

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1 Introduction

This document covers statistical and analytical plans to evaluate long-term safety as well as efficacy outcome of QGE031 240 mg subcutaneous (s.c.) administered every 4 weeks (q4w) for 12 months in patients with chronic spontaneous urticaria (CSU) who completed the CQGE031C2201 study. This document does not cover statistical analysis on pharmacogenetic data analyses which will not be presented in the Clinical Study Report (CSR).

1.1 Study design

This study is a phase 2b open label, single arm, long-term safety extension for all patients who completed the core study CQGE031C2201 and fulfill the enrollment criteria for the extension study.

Approximately 240 subjects may enroll into this extension study. Enrollment criteria require subjects to complete the treatment epoch and at least visit 201 - 203 in the follow-up epoch in study CQGE031C2201 and present with active disease, as defined by weekly Urticaria Activity Score (UAS7) $\geq$ 12.

The study consists of two epochs: open-label treatment and post-treatment follow up epoch. At or after visit 203, when the subjects become eligible to enroll in this extension study, they will complete all assessments associated with Visit 206 as a part of core study completion.

- Open-label treatment period: corresponds to 52 weeks, in which subjects are treated with QGE031 240 mg s.c. at 4-week intervals.
- Follow-up post-treatment period: in this follow-up epoch, the patients will be followed at 12-week intervals for 48 weeks.

As in the core study, patients will continue using their background medication i.e. H1-antihistamines (H1-AH) at approved or increased doses alone or in combination with H2-antihistamines (H2-AH) and/or a Leukotriene Receptor Antagonist (LTRA).

1.2 Study objectives and endpoints

1.2.1 Primary objective(s)

The primary objective of this study is to assess the long-term safety of QGE031 in adult CSU patients who completed the core study CQGE031C2201 using the following evaluations:

- Incidence and severity of non-serious and serious adverse events including any events of special interest;
- Changes in vital signs, laboratory assessments, and electrocardiograms (ECGs).

1.2.2 Secondary objectives

The secondary objective of this study is to assess the long-term efficacy of QGE031 in adult CSU patients who completed the CQGE031C2201 study by evaluation of:

- Sustained remission defined as maintaining UAS7 $\leq$ 6 over 48 weeks post-treatment follow up epoch among the subjects achieving remission at the end of treatment epoch.

2 Statistical methods

The planned analysis is described in Section 9 (Data Analysis) of the study protocol which is available in Appendix 16.1.1 of the CSR.

2.1 Data analysis general information

Data will be analyzed [redacted] according to the data analysis Section 9 of the study protocol which is available in [Appendix 16.1.1] of the CSR. Important information is given in the following sections and details are provided, as applicable, in [Appendix 16.1.9] of the CSR.

2.1.1 Assessment windows

No assessment windows are defined for this study. Consequently, all by-visit summaries will be performed as per below scheduled visits.

Table 1-1 Assessment windows for scheduled visits

Analysis Visit	E1 Week	E1 Scheduled Day	Visit Window
E1 Baseline	Baseline	-21/-14, 1	Up to Day 1
E1 Week 4	4	29	NA
E1 Week 8	8	57	NA
E1 Week 12	12	85	NA
E1 Week 16	16	113	NA
E1 Week 20	20	141	NA

E1 Week 24	24	169	NA
E1 Week 28	28	197	NA
E1 Week 32	32	225	NA
E1 Week 36	36	253	NA
E1 Week 40	40	281	NA
E1 Week 44	44	309	NA
E1 Week 48	48	337	NA
E1 Week 52	52	365	NA
E1 Week 64	64	449	NA
E1 Week 76	76	533	NA
E1 Week 88	88	617	NA
E1 Week 100	100	701	NA

2.1.2 Definition of Study Day

The first day of administration of extension study treatment is defined as E1 Study Day 1 or Day 1.

All other study days will be labeled relative to Day 1. For event dates on or after Day 1, study day for a particular event date will be calculated as [Date of event] – [Date of first dose] +1, i.e., Day 2, Day 3, etc., will be one day, two days, etc., after Day 1, respectively. For the dates before Day 1, study day for an event date will be calculated as [Date of event] – [Date of first dose], i.e., Day -1, Day -2, etc., will be one day, two days, etc., before Day 1, respectively. Duration of an event will be calculated as (Event end date – Event start date + 1).

The descriptor “Day 0” will not be used.

2.1.3 Definition of Study Week based on eDiary

A number of efficacy outcome measures (weekly itch severity score, weekly number of hives score, UAS7, [redacted] are in the form of weekly scores derived from patient daily diary data. The extension study weeks are defined based on the study days (see Table 1-2), starting with Day 1, which is the day the patient receives the first extension study treatment. The extension study day for a particular diary date will be calculated as [Date of diary] – [Date of first extension study dose] + 1. Note that the baseline week is comprised of the 7 days prior to Day 1 (Day -7 to Day -1).

Table 1-2 Extension Study Week definition based on E1 Study Day

E1 Study Week	E1 Study Days
Baseline	(-7) - (-1)
1	1 - 7
2	8 - 14
w	7×(w−1)+1 - 7×w

2.1.4 Baseline definitions

Core study baseline definition-

Core study baseline is the last assessment (including unscheduled visits) obtained before the first dose of core study treatment.

For the following demographic information - sex, race, ethnicity and height and baseline characteristics, randomization/background medication strata and positive chronic urticaria group, core study baseline information will be used.

Extension study baseline definition –

For eDiary weekly score, the E1 baseline is the score derived from E1 study day -7 to E1 study day -1.

[redacted] If the questionnaire was completed more than once on the same date, on the last date on or before treatment start date, then the worst outcome (i.e. the highest score) of the duplicate observations on that date will be used for baseline.

For the safety analysis, the baseline will be the last assessment prior to or on the first study dose and on or after visit 206, unless otherwise specified. Note: if time is collected (i.e. hematology chemistry and ECG) the last assessment prior to or on the same time as first study dose will be used. If time is not collected then, the assessment is assumed to be prior if it's on the same date as first study dose.

2.1.5 Day of last dose of study treatment

The date of last dose will be collected via the case report form (CRF). The subject's exposure will be calculated using last dose + 28 days. If a subject discontinued early during the treatment period, then exposure will be calculated using last dose + 28 days, unless the patient dies, in which case the date of death will be used.

2.2 Analysis sets

2.2.1 Analysis set definition

Safety set (SS) will include all patients who received at least one dose of open-label study drug during this open-label study.

All safety and efficacy analyses will be performed on the safety analysis set and for the total population (not broken down by treatment) unless otherwise specified.

The protocol deviation codes leading to exclusion from the analysis sets defined above are presented in Table 1-3.

Table 1-3 Subject classification rules

Analysis set	PDev Codes that cause subject to be excluded	Non-PDev criteria that cause a subject to be excluded
Safety set	NA	No treatment taken

Note: Protocol Deviation (PDev) Codes are available from the study Data Review Plan (DRP).

Protocol deviations will be summarized by deviation category for the Safety set. The deviation categories defined in the DRP for the study are presented below:

- SELECTION CRITERIA NOT MET
- PROHIBITED CONCOMITANT MEDICATION
- TREATMENT DEVIATION
- OTHER

No major deviation will be defined in this study.

2.2.2 Subgroup of interest

Core study response status at week 20 subgroup

The following e-Diary analyses will be summarized by response status achieved at week 20 of the core study;

- achievement of UAS7=0 response, Hives Severity Score (HSS7) = 0 response and Itch Severity Score (ISS7) = 0 response,
- UAS7, HSS7 and ISS7 summary statistics.

Japanese population

Japanese population will correspond to patients screened in Japan. The following selected safety and efficacy endpoints will be evaluated using the Japanese subgroup population:

Table 1-4 Subgroup analyses for Japanese population

Endpoint/analysis
Safety
Demography table
Disposition table
Baseline characteristic table
Duration of exposure table
Efficacy
Change from baseline in UAS7
Response rate in UAS7=0
Sustained remission (i.e. Achievement of UAS7 ≤ 6)

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number of screened subjects who complete the treatment epoch in study CQGE031C2201 and complete at least Visit 203 (Week 32 of the follow-up epoch, ≥ 16

weeks after last injection) and present with active disease as defined by UAS7 ≥ 12 will be included in the Open label Treatment period.

The number and percentage of subjects in the SS who completed/discontinued the full 52-week treatment epoch, and the reason for discontinuation will be presented. The number and percentage of subjects in the SS who entered/completed/discontinued the follow-up epoch, and the reason for discontinuation during the follow-up epoch will also be presented. Patient disposition during the treatment and follow-up epochs will be listed.

A separate duration of study follow-up report will be created. Duration of follow-up in weeks will be calculated as (the date of the follow-up epoch end date - the date of the follow-up epoch start date + 1) / 7.

2.3.2 Demographic and baseline characteristics

Demographic information will be summarized based on the Safety Set population.

The following demographic information will be reported from CQGE031C2201 core study baseline:

- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Unknown, Other)
- Ethnicity (Hispanic or Latino, East Asian, South Asian, Russian, Mixed ethnicity, Unknown, Other)
- Height (cm)

And the rest of the below mentioned demographic information will be reported from extension study baseline information:

- Age (years) (derived using date of first extension study dose)
- Age group (< 65, >= 65 years)
- Weight (kg)
- Body Mass Index (BMI) – calculated as weight (kg) / (height (m))^2
- BMI group (< 25, 25 - < 30, >= 30 kg/m^2)

Summary statistics will also be provided for demographics and baseline characteristics for Japanese population.

Baseline characteristics will also be summarized based on the Safety Set population.

The following baseline information will be reported from core study baseline data:

- Randomization strata (background medication)
- Positive Chronic Urticaria (CU) test (i.e. test result > 10): Yes or No
- Weekly urticaria activity score
- Weekly itch severity score
- Weekly hives severity score
- Duration of CSU (years)
- [redacted]

The following baseline characteristics information will be reported from extension study baseline information.

[redacted]

And the following baseline characteristics information will be reported from extension study baseline (over 7 days prior to extension treatment start) data.

- Weekly itch severity score
- Weekly hives severity score
- Weekly UAS

2.3.3 Medical history

Any condition entered on the *Medical history* CRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 20.1 or later. Listings will be provided for the overall medical histories including listings of; cardiovascular history, urticaria related history, malignancy medical history and other relevant medical history.

Listings will be based on the Safety set.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Patients will receive two subcutaneous injections every 4 weeks at 13 visits during the open label treatment epoch (i.e. at Day 1, Week 4, Week 8, Week 12 to Week 48).

Compliance is assured as study drug needs to be administered by study personnel every 4 weeks via subcutaneous injection. Administration of study drug, date, time and injection site will be recorded in the source documents and on the Drug Administration Record eCRF for each injection.

The analysis of study treatment data will be based on the Safety set.

The duration of exposure to study treatment in weeks will be summarized by Safety set. Duration of exposure is defined as the date of the last treatment minus the date of first extension study drug administration plus 4 weeks (28 days).

2.4.2 Prior and concomitant therapies

Prior and concomitant medication / surgery and medical procedures

Prior medications are defined as treatment taken and stopped prior to first dose of the core study drug. Prior medications were reported and analyzed in the core study and will not be reported in the extension study.

Listings will be provided for the medications and for the significant surgeries and medical procedures which were ongoing at the end of the core study or started after the end of the core study, and ended prior to first dose of the extension study drug.

Concomitant medications are defined as any medication given at least once after the first day of first extension study drug dose, and will be summarized on the safety set.

In case of missing end date the medication will be considered as concomitant. If it is partially missing, then the medication month and year will be compared to the month and year of the

first injection date, to know if the medication stopped prior to the drug or not. In case of uncertainty the medication will be considered as concomitant.

Medications will be identified using the Novartis Drug and Therapy Dictionary (NovDTD) including the Anatomical Therapeutic Chemical (ATC) code. Medications will be presented in alphabetical order, by ATC code.

Concomitant medications for CSU starting or continuing during the treatment epoch or during the follow-up epoch will be summarized for each epoch, by type of therapy, ATC code, preferred term and symptom treated. Non-urticaria related concomitant medications starting or continuing during the treatment epoch or during the follow-up epoch will be summarized for each epoch, by ATC code and preferred term.

Concomitant significant surgeries and medical procedures starting or continuing during the treatment epoch or during the follow-up epoch will be summarized for each epoch, by primary system organ class and MedDRA preferred term.

Concomitant use of rescue medication

Concomitant use of rescue medication (using eCRF information) starting during the treatment epoch or during the follow-up epoch will be summarized for each epoch, by ATC code and preferred term.

The number of tablets of rescue medication used over the past 24 hours to control conditions such as itch or hives is recorded once daily in the eDiary by the patient. The total weekly number of tablets of rescue medication from the e-Diary data will be summarized by study week. Median with quartiles will be displayed graphically over time to describe the score change during the study. The total weekly number of tablets of rescue medication will be calculated as the sum of the number of tablets per day, over 7 days.

If rescue medication use was not recorded (due to not completing the eDiary entry) on one or more days over the week, then the total weekly number of tablets will be missing.

Concomitant use of omalizumab

The use of omalizumab is allowed during study, concomitant use of omalizumab (using eCRF information) starting during the treatment epoch or during the follow-up epoch will be listed.

2.5 Analysis of the primary objective

The primary objective of this study is to obtain data on the long-term safety and tolerability of QGE031 for 12 months of treatment in CSU patients.

The primary variables which will be analyzed are: for AEs/ Serious Adverse Events (SAEs), ECGs, laboratory assessments, vital signs data and events of special interest such as hypersensitivity reactions, anaphylaxis, cardio-cerebrovascular events, and pre-malignancies and malignancies.

2.5.1 Adverse events

All adverse events which start after the first dose of study medication in the extension study and within 16 weeks of last dose, or events present prior to the first dose of extension study treatment

and increased in severity (within 16 weeks of last dose), will be considered as a treatment emergent adverse events. Treatment emergent adverse events (TEAEs) will be presented overall (including those that started during treatment and follow-up epoch) and those which started during the treatment epoch. Non-TEAEs will be presented for those which started during the follow-up epoch.

Adverse events that started during the core study were reported and analyzed in the core study and will not be included in tables of the extension study unless they become more severe. They will, however, be included in listings with additional collected information (e.g., outcome) as applicable.

Adverse events that started in the core study but became more severe in the extension study will be reported and analyzed as new events.

Treatment emergent adverse events with the number and percentage of patients having any adverse event by system organ class (SOC) and preferred term (PT) will be provided for:

- All adverse events
- Adverse events by maximum severity
- Adverse events suspected by the investigator as study drug-related
- Serious adverse events
- Adverse events leading to permanent discontinuation of study drug (only for treatment epoch)

Also, a separate summary table for most frequently reported TEAEs during the study, by SOC and PT, will be produced. Most frequent TEAEs will be those with their PT representing at least 5% of subjects.

Clinicaltrials.gov and EudraCT

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on <on-treatment/treatment emergent> adverse events which are not serious adverse events with an incidence greater than 5% and on <on-treatment/treatment emergent> serious adverse events and SAE suspected to be related to study treatment, will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non-SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block. If at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.5.1.1 Adverse events of special interest / grouping of AEs

Adverse events of special interest will be summarized and also will be listed. AEs of special interest include the following, specified as compound-level risk factors defined in the Case Retrieval Strategy (CRS):

- Anaphylaxis (including Hypersensitivity reactions)
- Parasitic (Helminthic) Infection
- [redacted]
- Serum Sickness Syndrome/Serum Sickness Like Disease
- Neoplastic conditions
- Eosinophilic Conditions / Churg-Strauss Syndrome
- Arterial Thromboembolic Events (ATEs) / Cardiovascular toxicity
- Injection site reactions
- Thrombocytopenia
- Reduction in Vaccine Efficacy
- Liver Toxicity
- Contraceptive measures

2.5.1.2 Adjudication committee (AC)

Hypersensitivity assessment

All hypersensitivity reactions that are possible cases of anaphylaxis will be adjudicated by an independent committee. All adjudicated hypersensitivity reactions will be listed, and the treatment emergent adjudicated hypersensitivity reactions will be flagged.

Cardio- and Cerebrovascular events

All cardio- and cerebrovascular events will be adjudicated by an independent committee. All positively adjudicated events will be listed, and the treatment emergent adjudicated events will be flagged.

Malignancies

Adjudicated malignancies whether newly detected or worsening of existing malignancies will be listed, treatment emergent adjudicated events will be flagged.

Liver events and renal events

Liver events and renal events will be listed.

2.5.1.3 Deaths

Death while on study will be listed and reported by SOC and PT.

2.5.2 Laboratory data

The following hematology criteria will be assessed: Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count. Also, coagulation will be assessed by International Normalized Ratio (INR).

The following biochemistry criteria will be assessed: Albumin, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), chloride, calcium, sodium, potassium, magnesium, lactate dehydrogenase (LDH), creatinine, inorganic phosphorus, urea/BUN, uric acid and high sensitivity C-reactive protein (hs-CRP) will be measured.

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 and maximum/minimum value will be presented for quantitative criteria. For qualitative criteria frequencies by categories at each visit will be summarized. These descriptive summaries will be presented by test group and laboratory test.

Change from baseline will only be summarized for subjects having both baseline and post baseline values. The maximum and minimum values could come from post-baseline scheduled, unscheduled or premature discontinuation visits. For laboratory test values below Lower Limit of Quantification (LLOQ) or above Upper Limit of Quantification (ULOQ) will be imputed as LLOQ or ULOQ value at the time of testing, respectively. The numerical part of the reported result will be treated as the actual LLOQ or ULOQ. These laboratory values will be displayed in listings using the standard unit with the reported sign i.e. “<” or “>”.

For hematology and serum chemistry, a shift table from baseline to the worst value during the treatment epoch will be presented based on normal range. The same shift table will be done with the worst value during the post-treatment follow-up epoch.

The notable criteria for platelet count (<75,000µL), for serum creatinine (>= 50% increase compared to baseline), for AST, ALT or INR above 1.5x Upper Limit of Normal (ULN), for creatinine above ULN and stool test result positive for ova or parasites, will be used to calculate number and percentage of patients with newly occurring or worsening notable abnormalities occurring during the treatment epoch and also occurring during the post-treatment follow-up epoch. A case will be considered as newly occurring if the value for a laboratory evaluation is not notable or missing at baseline but is notable thereafter; a case will be considered as worsening if the value for a laboratory evaluation is notable at baseline and at least one post-baseline value is worse than baseline.

To evaluate potential drug-induced liver injury, newly occurring liver enzyme abnormalities at any time post-baseline will also be summarized for treatment epoch and for post-treatment follow-up epoch based on the event criteria given below defined in the protocol [Section 13.2].

Table 1-5 Liver-related events

Parameter	Notable criterion
ALT	>3xULN; >5xULN; >8xULN; >10xULN; >20xULN
ALT or AST	>3xULN; >5xULN; >8xULN; >10xULN; >20xULN
(ALT or AST) & TBL	>3xULN & (TBL>1.5xULN; >2xULN)
(ALT or AST) & INR	>3xULN & INR>1.5

Parameter	Notable criterion
TBL	>1xULN; >1.5xULN; >2xULN
ALP	>1.5xULN, >2xULN; >5xULN
ALP & TBL	>3xULN; >5xULN & TBL>2xULN
(ALT or AST) & TBL & ALP	ALT or AST>3xULN & TBL>2xULN & ALP≤2xULN (potential Hy's Law case)
(ALT or AST) and (nausea or vomiting or fatigue or general malaise or abdominal pain or (rash and eosinophilia))	> 3 x ULN and (nausea or vomiting or fatigue or general malaise or abdominal pain or (rash and eosinophilia))

AST = Aspartate aminotransferase; also known as SGOT, ALT = Alanine aminotransferase; also known as SGPT, INR=International Normalized Ratio, ALP = Alkaline phosphatase, TBL = Total bilirubin

For potential Hy's Law case, all the elevations must occur at the same post-baseline time point. A case will be considered as newly occurring if a criterion is not met or missing at baseline but is met thereafter. Laboratory data will be listed by patient and time point and values outside the normal ranges or satisfying the notable criterion will be flagged.

[redacted]

2.5.3 Vital signs

Vital signs (i.e. blood pressure and pulse rate) will be summarized by presenting summary statistics of values and change from baseline by visit. Change from baseline will only be summarized for patients having both baseline and post-baseline values. In addition, frequency of patients with clinically notable values will be presented for both the treatment and follow-up epochs. Patients with notable vital signs as defined below will also be listed.

A notable value is defined as follows:

- Pulse rate below 60 bpm (bradycardia)
- Pulse rate above 100 bpm (tachycardia)
- Systolic blood pressure (SBP) greater than or equal to 140 mmHg
- SBP lower than 90 mmHg
- Diastolic blood pressure (DBP) greater than or equal to 90 mmHg
- DBP lower than 60 mmHg.

2.5.4 ECG

ECG intervals will be summarized by presenting summary statistics for values and change from baseline values by visit. ECGs are planned to be performed in triplicate (other than baseline ECG results, which has been collected once), therefore the mean of the patients' scheduled measurements, by visit, will be used in the summary statistics.

Count and frequency of clinically notable ECG abnormalities or changes will be presented for patients with newly occurring or worsening notable abnormalities occurring post-baseline. For

ECGs, a notable corrected QT Interval (QTc) value is defined as a QTcF (Fridericia's) interval of greater than 450 msec for males and greater than 460 msec for females. The categories used for the change (increase) in QTcF are - greater than 30 msec and greater than 60 msec.

ECG evaluation for all subjects with at least one visit, with the most common interpretation of that visit is abnormal, will be listed. ECG interval data will be listed for all patients and abnormal value flagged based on clinically notable ranges.

A shift table from baseline to the worst post-baseline value will be presented based on the overall ECG interpretation.

2.5.5 Statistical model, hypothesis, and method of analysis

No hypotheses will be tested as per the protocol. All the analysis will have a descriptive purpose.

2.5.6 Handling of missing values/censoring/discontinuations for the safety endpoints

All available data, regardless of concomitant use of omalizumab, for the safety endpoints outlined in protocol [Section 9.4.1] will be reported. Missing data for these endpoints will not be imputed, except for the missing date as described in appendix 5.

2.6 Analysis of the secondary objectives

Secondary efficacy variables will be summarized by visit with descriptive statistics, which include absolute and relative frequencies for categorical variables and arithmetic mean, standard deviation, minimum, maximum, median and first and third quartile for continuous variables. Time to event variables will be summarized using Kaplan-Meier estimates. Time to event variables that are only analyzed during the treatment epoch will be cut-off at Week 52, otherwise all data available will be included in the analysis (no cut-off at Week 100).

Table 1-6 Secondary [redacted] efficacy variables

Domain	Variable	Analyzed in treatment epoch	Analyzed in follow-up epoch
Clinical symptoms: total	Complete UAS7 response (UAS7 = 0)	Y	Y
	Achievement of UAS7 <= 6	Y	Y
	Change from Baseline in Urticaria Activity Score (UAS7)	Y	Y
	Time to achievement of complete UAS7 response for patients without response at extension study baseline	Y	N

Domain	Variable	Analyzed in treatment epoch	Analyzed in follow-up epoch
	Time to loss of complete UAS7 response for patients having achieved complete UAS7 response in E1 treatment period at Week 52	N	Y
	[redacted]		
	Time to UAS7 > 6 for patients having achieved UAS7 ≤ 6 in E1 treatment period at Week 52	N	Y
Clinical symptoms: hives	Complete hives response (HSS7 = 0)	Y	Y
	Change from Baseline in HSS7	Y	Y
	Time to achievement of complete hives response for patients without response at extension study baseline	Y	N
	Time to loss of complete hives response for patients having achieved complete hives response in E1 treatment period at Week 52	N	Y
Clinical symptoms: itch	Complete itch response (ISS7 = 0)	Y	Y
	Change from Baseline in Itch Severity Score (ISS7)	Y	Y
[redacted]			

Note: Y: yes, N: no

2.6.1 Hives Severity Score (HSS7)

The number of hives will be recorded by the patient twice daily in their eDiary on a scale of 0 (none) to 3 (severe (greater than 12 hives)).

A weekly score (HSS7) will be derived by adding up the average daily scores of the 7 days. The weekly score will therefore range from 0 to 21. If one of the morning or evening scores is missing, then the non-missing score for that day (morning or evening) will be used as the daily score. Complete hives response is defined as HSS7 = 0.

Changes from baseline in HSS7 score will be computed and will be summarized along with the absolute values at each visit. Mean with 95% confidence interval will be displayed graphically over time to describe the score change during the study. In addition, HSS7 descriptive statistics will be summarized, [redacted].

For HSS7=0 response, summary tables and graphs by visit will display, the response rate with the 95% Clopper-Pearson exact confidence interval. In addition, HSS7=0 response will be summarized, [redacted].

Kaplan-Meier estimates of the time to first HSS7=0 response and of the time to first loss of response for patients having achieved response at Week 52, will be plotted and will be tabulated at defined time points.

For patients with concomitant use of omalizumab, HSS scores will be censored at the date of start of omalizumab and treated as missing onward.

2.6.2 Itch Severity Score (ISS7)

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).

A weekly score (ISS7) will be derived by adding up the average daily scores of the 7 days preceding the visit. The weekly score will therefore range from 0 to 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.

Changes from baseline in ISS7 score will be computed and will be summarized along with the absolute values at each visit. Mean with 95% confidence interval will be displayed graphically over time to describe the score change during the study. In addition, ISS7 descriptive statistics will be summarized, [redacted].

ISS7=0 response will be summarized and plotted by visit and response rate with the 95% Clopper-Pearson exact confidence interval will be included in the analysis. In addition, ISS7=0 response will be summarized, [redacted].

For patients with concomitant use of omalizumab, ISS scores will be censored at the date of start of omalizumab and treated as missing onward.

2.6.3 The weekly Urticaria Activity Score (UAS7)

The UAS7 is the sum of the HSS7 score and the ISS7 score. The weekly UAS7 score will then range from 0 to 42. Complete UAS7 response is defined as UAS7 = 0.

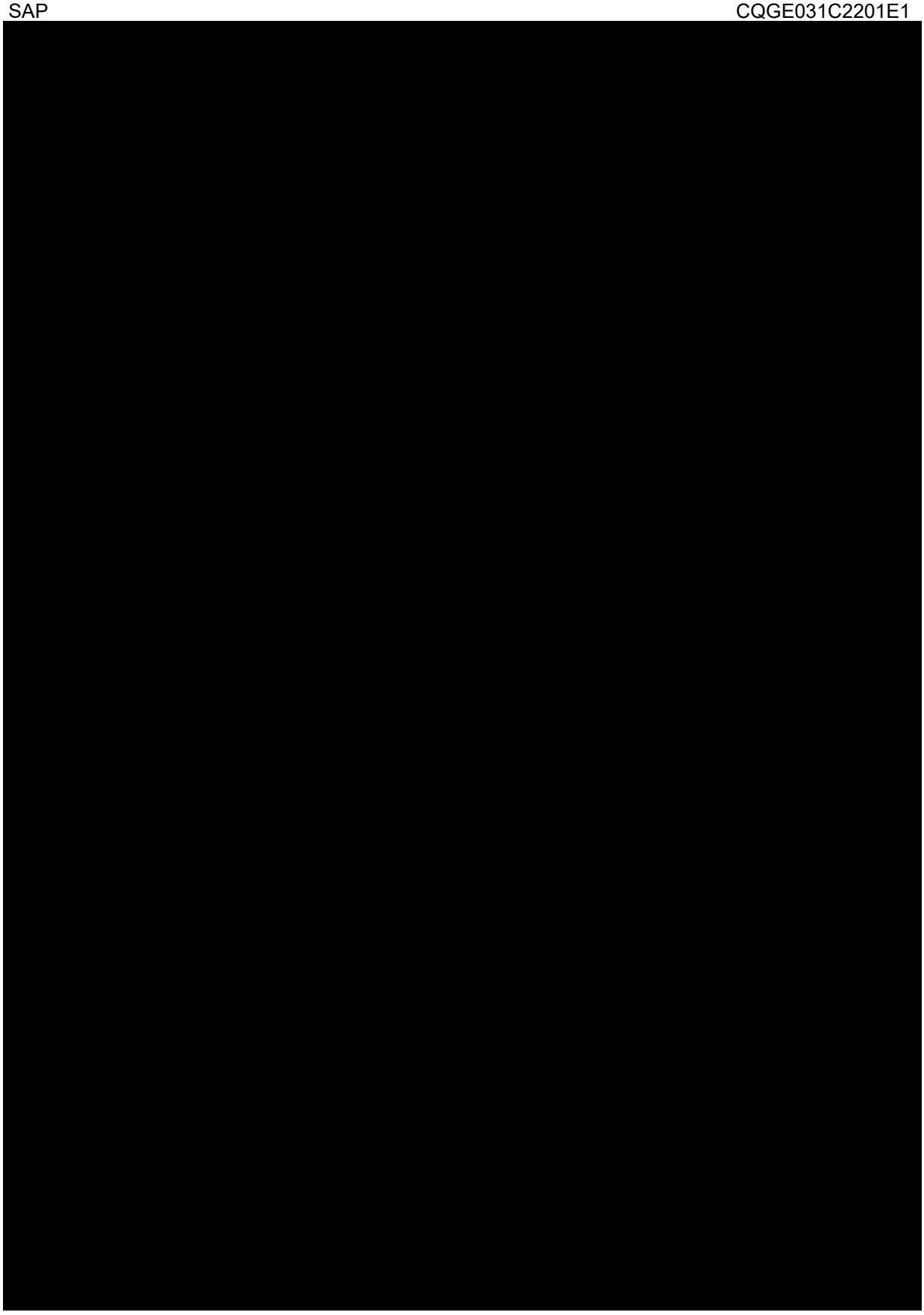
Changes from baseline in UAS7 score will be computed and will be summarized along with the absolute values at each visit. Mean with 95%confidence interval will be displayed graphically over time to describe the score change during the study. In addition, UAS7 descriptive statistics will be summarized, [redacted].

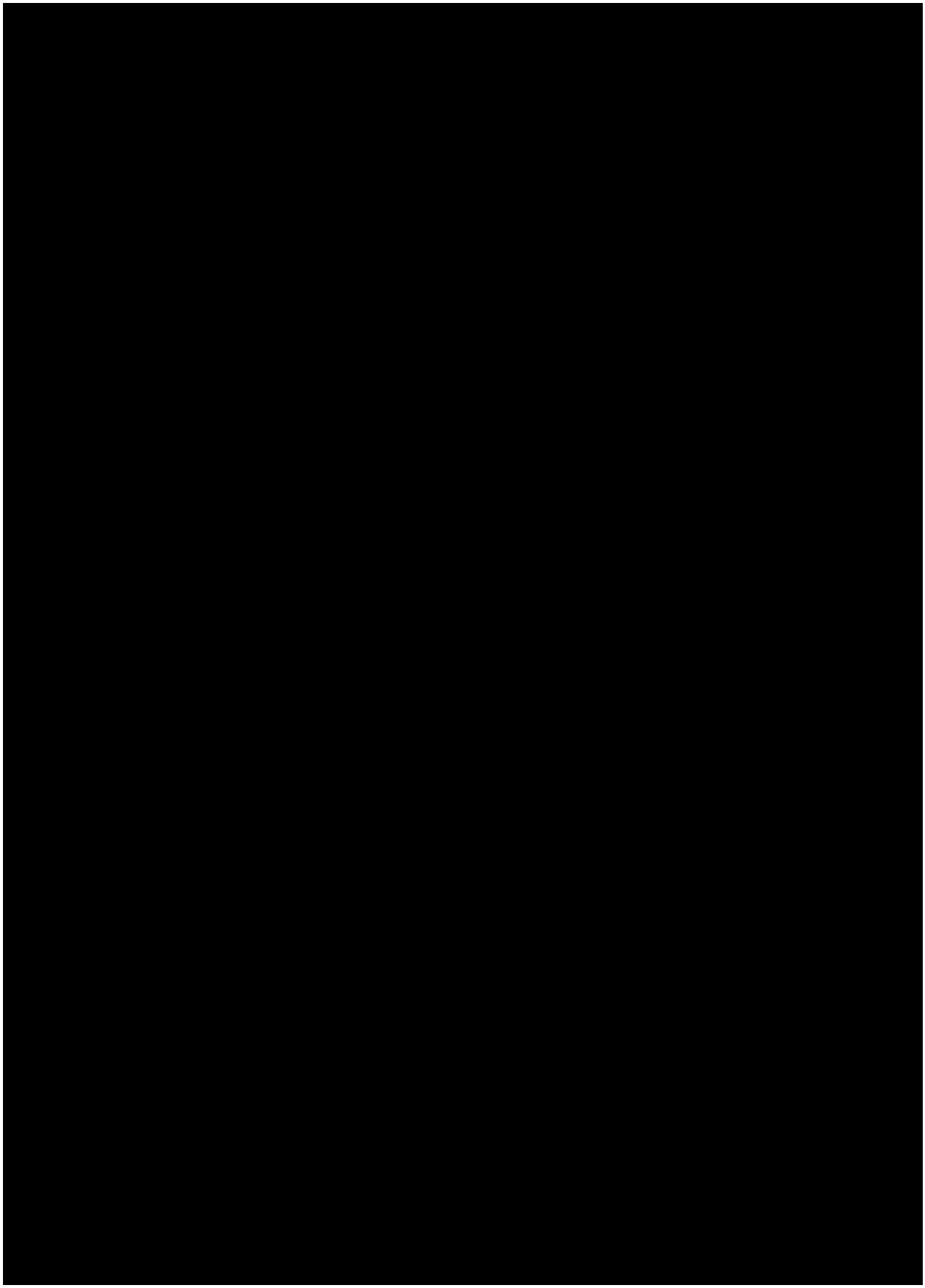
UAS7=0 response will be summarized and plotted by visit and response rate with the 95% Clopper-Pearson exact confidence interval will be included in the analysis. In addition, achievement of UAS7 <= 6 will be summarized similarly. Also, UAS7=0 response will be summarized, [redacted].

Kaplan-Meier estimates of the time to first UAS7=0 response and of the time to first loss of response for patients having achieved response at Week 52, will be plotted and will be tabulated at defined time points. In addition, Kaplan-Meier estimates of the time to first UAS7 > 6 for patients having achieved UAS7 ≤ 6 at Week 52 [redacted], will be tabulated at defined time points.

For patients with concomitant use of omalizumab, UAS scores will be censored at the date of start of omalizumab and treated as missing onward.

[redacted]





[redacted]

2.6.10 Missing data handling and censoring process

There are 17 patients taking concomitant medication of omalizumab post treatment, which would have impact on the estimated efficacy during the post treatment period, especially for the patients stay in the follow-up period until the end of the study. In order to exclude the potential bias causing by the omalizumab use during post-treatment period, the efficacy data observed after start concomitant use of omalizumab will be set as missing.

Missing data handling of all weekly score coming from UPDD [redacted].

The weekly score (HSS7, ISS7, sleep/activitiy interference scores) will be derived by adding up the average daily scores of the 7 days preceding the visit. The weekly score will then range from 0 to 21. If one of the morning or evening score is missing, then the non-missing score for that day (morning or evening) will be used as the daily score.

For each weekly score from UPDD [redacted], except weekly total rescue medication, if one or more of the daily scores are missing, then 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, then the weekly score will be calculated as the sum of the available eDiary scores of that week, divided by the number of non-missing days multiplied by 7.
- If there are less than 4 non-missing daily scores within the prior 7 days, then the weekly score will be missing for that week.

For rescue medication, if one or more of the daily number of tablets are missing, then the total weekly number of tablets will be missing.

The weekly Urticaria Activity Score is the sum of both the HSS7 score and the ISS7 score and will be missing if at least one of them is missing.

For all display of response rate by week, the rate will be obtained by dividing the number of responses by the total number of patients in the group analyzed, whatever if some of these patients analyzed have missing data on this week or not.

For the response rate analysis, for patients with missing data either due to discontinuation or due to insufficient eDiary data during that week or the start concomitant use of omalizumab, data imputation of the response will be done using the worst-case scenario (i.e. non-responder). For the patients completing the study, there will be no more imputation applied after the end of study visit. For the patients discontinuing the study early or start concomitant use of omalizumab, the imputation will be applied up to Week 100.

[redacted]

Duplicate data handling of questionnaires

For HSS7, ISS7 and UAS7, the daily score is derived from the average of morning and evening scores. All other questionnaires are completed either daily or at visits. If any of those questionnaires are completed more than once per day or visit (depending on the questionnaire schedule), then the worst outcome (i.e. the highest score) of the duplicate observations will be used in the analysis.

Censoring of time to response.

Time endpoints, such as time to first complete hives response, will be considered censored at the date of the last non-missing weekly score up to E1 Week 52, for any non-responder.

Censoring of time to loss of response.

For any patient maintaining response, the time to loss, such as time to first loss of complete hives response for patients who completed the treatment epoch and achieved complete hives response at Week 52, will be considered censored at the date of the last non-missing weekly score or at the date of start concomitant use of omalizumab.

Note that time to loss of response will be missing for all patients without having achieved the response in the E1 treatment period at study week 52.

[redacted]

[redacted]

2.8 Interim analysis

The study is planned with one interim analysis occurring when all patients have completed the treatment epoch. In particular, the summary will include baseline characteristics, adverse events, exposure, concomitant medication, ECG, vital signs, safety laboratory data and the weekly symptom scores, derived responder status, [redacted].

Study procedures will not be modified as a result of this interim analysis.

[redacted]

3 Sample size calculation

The sample size calculation is defined in the protocol [section 9.7].

4 Change to protocol specified analyses

- The definition of the safety set (SS) was updated - no additional check needed for subjects “who had at least one post-baseline (Visit 301) safety assessment”.
- Medical history will consist of medical conditions which started before the start of the core study, instead of before the start of the open-label extension study and will therefore only be listed and not tabulated.
- Adjudicated AEs will only be listed and not summarized, since few adjudicated AEs are expected.
- [redacted]

[redacted]

- The definition of TEAE is updated as: all adverse events which start after the first dose of study medication in the extension study and within 16 weeks of last dose, or events present prior to the first dose of extension study treatment and increased in severity (within 16 weeks of last dose).
- All adverse events which start after the first dose of study medication in the extension study or events present prior to the first dose of extension study treatment and increased in severity, will be considered TEAEs, similar to the core study definition. TEAEs will be summarized by treatment epoch and over all, which will be based on the epoch derivation that depends on the patient's visit dates which might not occur exactly on last dose + 4 weeks.
- For patients with concomitant use of omalizumab, efficacy variables (HSS/ISS/UAS/[redacted] will be censored at the last visit prior to the date of start of omalizumab and treated as missing onward.
- Only positively adjudicated Cerebrovascular events will be listed.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

No imputation of missing/partial start date of study drug. If missing the time of study drug end date will be imputed to 23:59:59.

5.1.2 AE date imputation

Rules for imputing the AE end date:

- If the AE end date month is missing, the imputed end date should be set to the earliest of the (study end date, 31DECYYYY, date of death).
- If the AE end date day is missing, the imputed end date should be set to the earliest of the (study end date, last day of the month, date of death).
- If AE year is missing, the end date will not be imputed.

Rules for imputing the AE start date:

- If imputing end dates, this should be done prior to calculating imputed start dates

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.c) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min(informed consent date, earliest visit date).
2. If (imputed) AE end date is complete and (imputed) AE end date >= Treatment period 1 start date i.e. TR01SDT but before Extension Treatment start date i.e. TR02SDT (or Extension Treatment start date is missing) then AE start reference = treatment period 1 start date i.e. TR01SDT.
3. Else if (AE start year > Extension Treatment start year) or (AE start year = Extension Treatment start year and AE start month >= Extension Treatment start month) then AE start reference = Treatment Period 2 start date i.e. TR02SDT. Else AE start reference = Treatment Period 1 start date i.e. TR01SDT.

Impute AE start date

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).

3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the treatment start date year value:
    a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
    b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
    c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.3 Concomitant medication date imputation

No imputation of numeric date will be performed for the dates of medication recorded on the Trial Rescue Medication CRF page or the Prior urticaria therapy CRF page. All therapies on the Prior urticaria therapy CRF page will be considered as prior.

Rules for imputing the concomitant medication (**CM) end date (including on-going records):**

- If imputing end dates, this should be done prior to calculating imputed start dates.
- When the medication is on-going at the end of the study, no numeric end date is derived.
- If the end date is completely missing no numeric end date is derived.

a) If CM end day is missing and CM month/year are non-missing, then impute CM date as the minimum of study end date and the last day of the month.

b) If CM end day/month are missing and CM year is non-missing, then impute CM date as the minimum of study end date and the end of the year (31DECYYYY).

c) If imputed CM end date is less than the complete CM start date, use the complete CM start date as the imputed CM end date.

Rules for imputing the CM start date:

- If imputing end dates, this should be done prior to calculating imputed start dates.

The following table explains the notation used in the logic matrix.

	Day	Month	Year
Partial CM Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	**(1))** Uncertain	**(1))** Uncertain	**(1))** Uncertain	**(1))** Uncertain
YYYY < TRTY	**(2.a))** Before Treatment Start	**(2.b))** Before Treatment Start	**(2.b))** Before Treatment Start	**(2.b))** Before Treatment Start
YYYY = TRTY	**(4.a))** Uncertain	**(4.b))** Before Treatment Start	**(4.a))** Uncertain	**(4.c))** After Treatment Start
YYYY > TRTY	**(3.a))** After Treatment Start	**(3.b))** After Treatment Start	**(3.b))** After Treatment Start	**(3.b))** After Treatment Start

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to *Treatment start date (TR01SDT)*.
2. If the CM start date year value is less than the *Treatment start date (TR01SDT)* year value, the CM started before treatment. Therefore:
    a) If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
    b) Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the *Treatment start date (TR01SDT)* year value, the CM started after treatment. Therefore:
    a) If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).
    b) Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the *Treatment start date (TR01SDT)* year value:
    a) And the CM month is missing or the CM month is equal to the *Treatment start date (TR01SDT)* month, then the imputed CM start date is set to one day prior *Treatment start date (TR01SDT).*
    b) Else if the CM month is less than the *Treatment start date (TR01SDT)* month, the imputed CM start date is set to the mid-month point (15MONYYYY).
    c) Else if the CM month is greater than the *Treatment start date (TR01SDT)* month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the complete (imputed) CM end date, then imputed CM start date should be set to the complete (imputed) CM end date.

5.1.3.1 Prior therapies date imputation

This section will refer to the concomitant medication date imputation.

6 Reference

There is no statistical reference for the study.