NOVARTIS

Clinical Development

QGE031/Ligelizumab

CQGE031C2302E1 / NCT04210843

A multi-center, double-blinded and open-label extension study to evaluate the efficacy and safety of ligelizumab as retreatment, self-administered therapy and monotherapy in Chronic Spontaneous Urticaria patients who completed studies CQGE031C2302, CQGE031C2303, CQGE031C2202 or CQGE031C1301

Statistical Analysis Plan (SAP)

Author:	Trial Statistician, [redacted]

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Document History – Changes compared to previous final version of SAP

Date	Reason for update	Outcome for update	Section and title impacted (Current)
08-Apr-2020	Final First Version	N/A – First version	N/A
17-Nov-2021	Creation of Amendment 1	Update SAP to add an unplanned interim analysis	Section 1, 2, and 5
11-Jul-2022	Creation of Amendment 2	Update SAP for the final analysis	Section 1 and 2
27-Sep-2022	Creation of Amendment 3	Update SAP for the final analysis	Section 2 and 5

Amendment 1 change log

Section	Changes made
Section 1	Text updated: "This SAP is based on Protocol Amendment 1, dated 09-Apr-2021."
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Section 2.13	Section added to include an unplanned interim analysis for analyzing the efficacy and safety of outside-of-clinic self-administration of ligelizumab with PFS.
Section 5.4	Added a table of clinically notable criteria.

Amendment 2 change log

Section	Changes made
Section 1	Text added: "On 06 April 2022, following extensive assessment of data from the Phase III studies (CQGE031C2302, CQGE031C2303) of ligelizumab in CSU, Novartis communicated a strategic decision to discontinue further clinical development of ligelizumab in chronic urticaria (CSU and chronic inducible urticaria (CINDU)). The decision to not proceed was not based on any safety concerns with ligelizumab. As a result of this decision, this study CQGE031C2302E1 was terminated."
Section 2.2	Removed adolescent analysis, Japanese subpopulation analysis, and country or race subpopulation analysis in subgroup analysis. Added the definition of "long term treatment subpopulation." Text updated: "COVID-19 related PDev will be summarized separately based on SAF by treatment group for the entire study."
Section 2.3	Text updated: "Information on screen-failed subjects will not be included in the summaries of demographics, disease characteristics at baseline, and medical history." "Baseline proportion of AAS7 = 0" was added to the baseline disease characteristics. "Duration of a typical angioedema episode – collected at Visit 201", "Experienced angioedema within the past 4 weeks – collected at Visit 201", and "Duration of the last episode of angioedema – collected at Visit 201" were removed, because those information are not collected as per protocol. Text updated: "In addition, duration of study periods TRT1, OBS2, TRT2, FU12 and FU52 will be summarized by treatment group for FAS; duration of study period OBS1 will be summarized for ENR."
Section 2.4	Text updated: "Concomitant medications are defined as any medication given at least once between the first dose of the

	study treatment and the date of the last study visit in the extension study."
Section 2.5	For subjects rolling over from study CQGE031C2302 and CQGE031C2303, who received different treatment or different ligelizumab dose regimen, removed text: "The efficacy data for these subjects will be analyzed separately." For subjects rolling over from study CQGE031C1301, who received ligelizumab 120 mg, removed text: "The efficacy data for these subjects will be analyzed separately." For subjects rolling over from the adolescent PK/PD study CQGE031C2202, removed text: "The efficacy data for these subjects will be analyzed separately." Removed Section 2.5.4, the supportive analyses of adolescent subjects versus adult subjects. Added primary estimand, and added multiple imputation for missing data due to study early termination.
Section 2.6	Added multiple imputation for missing data due to study early termination for some key secondary endpoints.
Section 2.8	The analysis scope of AEs, AESIs, lab, ECG and vital signs was updated according to the final analysis.
[redacted]	[redacted]
[redacted]	[redacted]
Section 2.11	Removed text: "Number and proportion of subjects with values outside of the limits of quantification will be presented." Added text: "The unscheduled visit information will not be included in the summary table." Text updated: "A summary table will be provided for baseline values by treatment group. The unscheduled visit information will not be included in the summary table."
Section 2.13	Removed text: "At the End of Study, a final analysis of all data collected up to last study visit will be performed when all subjects have completed the last study visit." Added text: "Due to the early termination of study CQGE031C2302E1, the planned interim analysis IA1 and IA2 will not be performed. A final analysis of all data collected up

	to last study visit will be performed when all subjects have completed the last study visit."
Section 2.14	Section of final analysis was added.

Amendment 3 change log

Section	Changes made
Section 2.2	Definitions of Ligelizumab retreatment subpopulation and Ligelizumab responder retreatment subpopulation were updated to clarify that the subjects who switched from placebo to Ligelizumab in core studies are not included in those two subpopulations. Definitions of long term treatment subpopulation and long term treatment with a rest subpopulation were updated.
Section 2.14	Table 2-16 was refined to avoid confusion: The analysis of cumulative weeks of AAS7=0 will be conducted up to Week 12 in TRT1 in the final analysis.
Section 5.5	SAS sample code for multiple imputations were added.

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AE	Adverse event
AAS	Angioedema Activity Score
AC	Adjudication Committee
[redacted]	[redacted]
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BLA	Biologics License Application
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CDLQI	Children's Dermatology Life Quality Index
CFR	Code of Federal Regulation
CIU	Chronic Idiopathic Urticaria
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSU	Chronic Spontaneous Urticaria
CT	Computed Tomography
CTC	Common Toxicity Criteria
CU Index	Chronic Urticaria Index
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EOOBS1	End of Observation Period 1
EOOBS2	End of Observation Period 2
EOS	End of Study
EOT	End of Treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FcεRI	High Affinity Immunoglobulin E Receptor
FcεRII	Low Affinity Immunoglobulin E Receptor
FDA	Food and Drug Administration
FU	Follow-Up period
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
H1-AH	H1-Antihistamine
hCG	Human Chorionic Gonadotropin
HRQoL	Health Related Quality of Life

HSS	Hives Severity Score
HSS7	Weekly Hives Severity Score
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions For Use
[redacted]	[redacted]
IgE	Immunoglobulin E
IgG	Immunoglobulin G
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISS	Itch Severity Score
ISS7	Weekly Itch Severity Score
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLOQ	Lower Limit of Quantification
LTRA	Leukotriene Receptor Antagonist
MCP-Mod	Multiple Comparison Procedure Modeling
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NSD	Needle Safety Device
PD	Pharmacodynamic(s)
PDev	Protocol Deviation
PFS	Pre-Filled Syringe
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcome
PT	Prothrombin Time
q4w	once every 4 weeks
QoL	Quality of Life
QTcF	Fridericia QT Correction Formula
RBC	Red Blood Cell(s)
RDO	Retrieved Dropout
s.c.	Subcutaneous
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TEAESI	Treatment Emergent Adverse Event of Special Interest
TESAE	Treatment Emergent Serious Adverse Event
UAS	Urticaria Activity Score
UAS7	Weekly Urticaria Activity Score

[redacted]	[redacted]
ULN	Upper Limit of Normal
UPDD	Urticaria Patient Daily Diary
UPV	Unplanned Visit
WBC	White Blood Cell(s)
WHO	World Health Organization

1 Introduction

The purpose of Statistical Analysis Plan (SAP) is to describe the statistical analysis planned in the protocol for the clinical study report. The clinical study report will describe the results from this SAP.

This SAP is based on Protocol Amendment 1, dated 09-Apr-2021.

1.1 Study design

This is a Phase IIIb multi-center, double-blinded and open-label, extension study to evaluate efficacy and safety of ligelizumab 72 mg and 120 mg s.c. q4w as add-on therapy to H1-AHs with an option for monotherapy i.e. with discontinuation of background H1-AH in adult and adolescent CSU subjects who have completed one of the CQGE031C2302, CQGE031C2303, CQGE031C2202 or CQGE031C1301 studies ("preceding studies"), in the setting of retreatment and self-administration.

Per study protocol, the definition of the disease states for CSU, for purposes of this study protocol and used for decisions described in this section is:

- Urticaria-free (Completely controlled disease): UAS7 = 0;
- Well controlled disease: UAS7 ≤ 6;
- Mild Disease: UAS7 > 6 and < 16 and
- Moderate to severe disease: UAS7 ≥ 16.

As depicted in Figure 1-1 the study consists of 5 distinct periods

- Screening period (Day -28 to Day -7), duration 1 to 4 weeks;
- First observation period, duration up to 36 weeks;
- Treatment period, duration of 2 years (104 weeks);
- Second observation period, duration up to 52 weeks;
- Post-treatment follow-up period, duration of 12 weeks or 52 weeks.

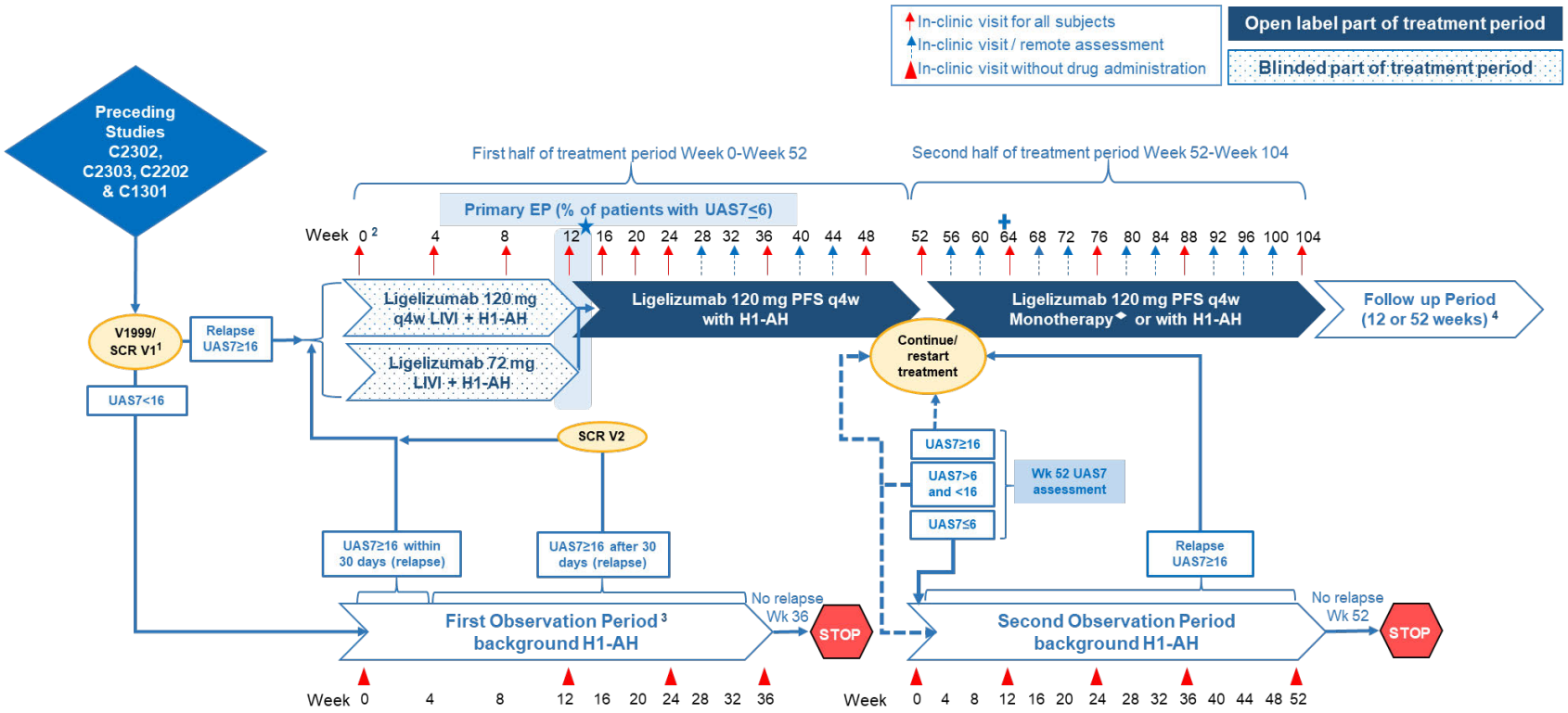
If the study site is ready to enroll subjects in the extension study, and the subject completed the preceding study's End of Study Visit (EOS, Visit 1999), the subject can "roll-over" into this extension study. When the site is ready to enroll subjects, the subject should be enrolled into the extension study in as short a timeframe as possible. All assessments done as a part of Visit 1999 for preceding studies will be considered for screening for the extension study. These subjects will have their Screening Visit 1 for the extension study on the same day as Visit 1999 of the preceding study.

Subjects who complete Visit 1999 of the preceding studies prior to the study site being ready to enroll subjects in the extension study, will have a gap between their Visit 1999 and Screening Visit 1 i.e. Visit 1999 and screening Visit 1 will not occur on the same day. Informed consent for the extension study will be signed off prior to or at Screening Visit 1. If this gap between the two visits is less than or equal to 30 days, all Visit 1999 assessments can still be used to

determine eligibility into the extension study. If this gap between the two visits exceeds 30 days, subjects will be re-assessed for eligibility into the trial at Screening Visit 1. During this gap between completion of preceding studies and enrolment into extension study:

- Subjects can use second generation H1-AH as per CSU treatment guidelines.
- Subjects can use omalizumab, if needed, provided there is at least 16 weeks between last dose of omalizumab and Screening Visit 1.
- Subjects can use oral corticosteroids, if needed, provided there is at least 30 days between last dose of oral corticosteroid and Screening Visit 1 of this study.

Figure 1-1 Study design



[1] After screening, UAS7 score will be assessed via eDiary
[2] Subjects from C2302/2303 72 mg dose arm will receive the 72 mg; all other subjects will receive ligelizumab 120 mg
[3] Blinded to core study treatment group but unblinded to observation period
[4] Subjects completing 104 continuous weeks of treatment enter 52-week follow up; All other subjects enter 12-week follow up
EP = Endpoint; SCR = screening; LIVI = liquid in vial; PFS = prefilled syringe

Treatment continuation decision: PI reassessment in discussion with subject
★ **Week 12 Self-admin:** Qualifying subjects starts self-admin in clinic at Wk 12 and transitions at Wk 24 to out of the clinic setting
✚ **Week 64 Repeat & new self-admin:** Subjects re-starting self-admin at Week 64 and subjects who newly qualify, will start self-admin in clinic at Week 64 and transition at Week 76 to out of the clinic setting
◆ **Ligelizumab monotherapy:** Subjects with UAS7 ≤ 6 at Week 52, who re-enter 2nd half of treatment period from the 2nd observation period, will have a possibility to discontinue H1-AH background medication at Week 64, per investigator's discretion taking into account if CSU symptoms are well controlled

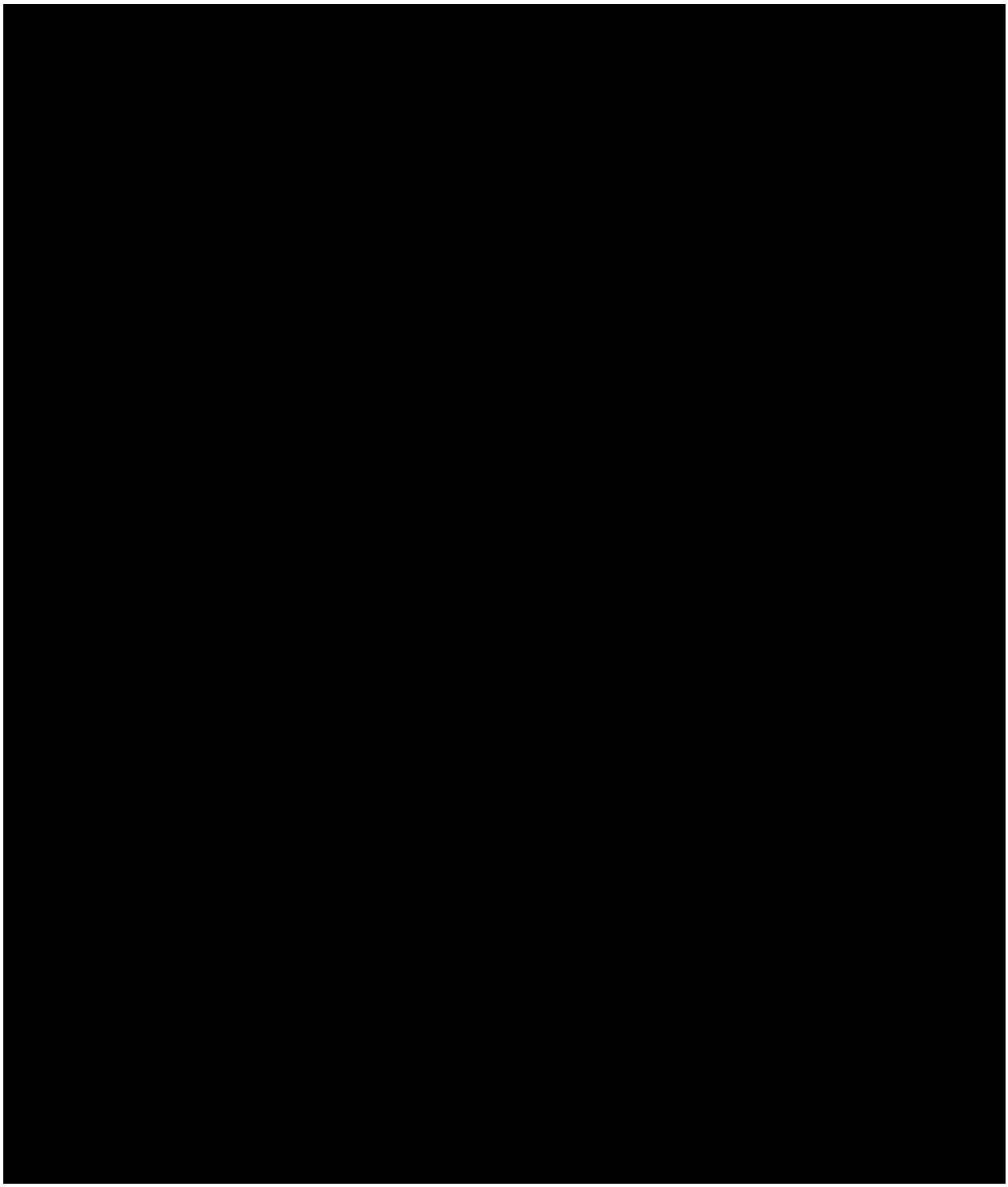
1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the efficacy of retreatment with ligelizumab 72 mg or 120 mg q4w in subjects previously treated in the core studies (CQGE031C2302/CQGE031C2303) • To evaluate the efficacy of retreatment with ligelizumab in the subgroup of these subjects who achieved a weekly urticaria activity score (UAS7) ≤ 6 after 12 weeks of treatment in these core studies	• The proportion of subjects with well-controlled disease (UAS7 ≤ 6) at Week 12
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
For retreatment efficacy evaluation:	
• To describe the efficacy of ligelizumab 72 mg or 120 mg q4w in achieving complete control of chronic spontaneous urticaria (CSU) at Week 12 when used as retreatment for subjects previously treated in the core studies (CQGE031C2302/CQGE031C2303)	• The proportion of subjects with completely controlled disease (UAS7 = 0) at Week 12
• To describe the efficacy of ligelizumab with respect to a reduction from extension study baseline in the UAS7 and its components (weekly itch severity score (ISS7) and weekly hives severity score (HSS7) at Week 12 in all subjects receiving the same dose regimen as in the core studies, i.e. 72 mg or 120 mg q4w	• Absolute change from extension study baseline in the UAS7 and its components (ISS7 and HSS7) at Week 12
• To describe the efficacy of ligelizumab in achieving an angioedema-free period at Week 12 in all subjects receiving the same dose regimen as in the core studies, i.e. 72 mg or 120 mg q4w	• Cumulative number of weeks that subjects achieve weekly angioedema activity score (AAS7) = 0 between extension study baseline and Week 12

Objective(s)	Endpoint(s)
• To describe the efficacy of ligelizumab in achieving Dermatology Life Quality Index (DLQI) = 0-1 at Week 12 when used as re-treatment for all subjects receiving the same dose regimen as in the core studies, i.e. 72 mg or 120 mg q4w	• Percentage of subjects achieving DLQI = 0-1 at Week 12
For self-administration efficacy evaluation:	
• To describe the efficacy of ligelizumab in the treatment of CSU, 12 weeks after starting self-administration	• The proportion of subjects with well-controlled disease (UAS7 ≤ 6), 12 weeks after starting self-administration
For safety & tolerability evaluation:	
• To assess the safety and tolerability of ligelizumab in all subjects	In each dose group, and for each duration of treatment: • Occurrence of treatment emergent adverse events during the study • Occurrence of treatment emergent serious adverse events during the study • Vital signs • Lab assessments
• To assess the safety and tolerability of ligelizumab 120 mg q4w 1mL pre-filled syringe (PFS)	For the duration of treatment: • Occurrence of treatment emergent serious adverse events during study Week 12 onwards • Vital signs Week 12 onwards • Lab assessments Week 12 onwards
• To assess the safety and tolerability of ligelizumab 120 mg q4w in all subjects who self-administer	• Occurrence of treatment emergent adverse events • Occurrence of treatment emergent serious adverse events • Vital signs • Lab assessments

Objective(s)	Endpoint(s)
[redacted]	



On 06 April 2022, following extensive assessment of data from the Phase III studies (CQGE031C2302, CQGE031C2303) of ligelizumab in CSU, Novartis communicated a strategic decision to discontinue further clinical development of ligelizumab in chronic urticaria (CSU and chronic inducible urticaria (CINDU)). The decision to not proceed was not based on

any safety concerns with ligelizumab. As a result of this decision, this study CQGE031C2302E1 was terminated.

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed by the Novartis team internally following the protocol section 12, using SAS version 9.4 or above.

DMC analyses will be done by the independent statistician and programmers in a separate CRO. Statistical Analysis Plan for the DMC analyses will be prepared separately.

The first interim analysis is planned once all subjects from the CQGE031C2302 and CQGE031C2303 have completed Week 12 (Visit 204) in the first half of the treatment period to evaluate the primary endpoint of retreatment efficacy.

The second interim analysis will be performed at the end of the first half of the treatment period once all treated subjects completed the first half of the treatment period (see below for rules of cutoff) to evaluate endpoints up to the end of 1 year treatment:

- Subjects who enter the second half of the treatment period without going to the second observation period: data up to and including visit 214 (excluding the DAR page)
- Subjects who enter the second observation period: data up to and include visit 301
- Subjects who discontinue prior to visit 214: all data up to date of study discontinuation

Additional interim analyses may be performed to support health authority interactions as necessary.

All analyses (including safety, [redacted] and efficacy, except for some lab parameters and the DLQI/CDLQI questionnaire), will be provided for adolescents and the adults combined, unless stated otherwise. [redacted]

Adolescents (<18 years old) or adults (≥ 18 years old) will be determined based on the baseline age at the time of enrollment, unless it is specified otherwise.

The general descriptive statistical rules for summarizing the categorical data and continuous data are provided below:

All categorical data will be summarized by frequencies and percentages. The frequencies and percentages will also be presented for missing observations.

Continuous data will be summarized with either standard descriptive statistics (i.e. the number of non-missing data points, arithmetic mean, standard deviation, minimum, 25% percentiles(Q1), median, 75% percentiles (Q3) and maximum), or will be collapsed into categorical data and be summarized as categorical data.

2.1.1 General definitions

2.1.1.1 Study Treatment

Study treatment groups used for analysis are defined as below:

- ligelizumab 72 mg q4w liquid in vial – ligelizumab 120 mg q4w PFS
- ligelizumab 120 mg q4w liquid in vial – ligelizumab 120 mg q4w PFS

2.1.1.2 Study periods

The following study periods will be considered for analysis:

- Screening period (SCR): from the date of signing informed consent form (ICF) to, and not include the date of the first ligelizumab treatment (i.e. V201) in extension, or the first visit in the first observation period (i.e. V101), whichever comes first.
- First observation period (OBS1): from Visit 101 up to Visit 199. The duration of OBS1 period for each subject varies, as it depends on occurrence of relapse (UAS7 ≥ 16). Maximum duration of OBS1 is 36 weeks.
- First 12 weeks of the first half of the treatment period (TRT1A): from Visit 201 to Visit 204.
- Week 12 to Week 52 of the first half of the treatment period (TRT1B): from Visit 204 to Visit 214 or 301, whichever comes first.
- Entire first half treatment period (TRT1): from Visit 201 to Visit 214 or 301, whichever comes first.
- Second observation period (OBS2): from Visit 301 up to Visit 399. The duration of OBS2 period for each subject varies, as it depends on occurrence of relapse (UAS7 ≥ 16). Maximum duration of OBS2 is 52 weeks.
- Second half of the treatment period (TRT2): Visit 214 to Visit 9998 (excluding Visit 301 to Visit 399)
- Follow-up period:
    - Subjects who do not complete a continuous 104-week treatment will enter the follow-up period (FU12) for 12 weeks duration and will only perform Visit 9999.
    - Subjects who have completed the full 104-week treatment period without interruption will enter the follow-up period (FU52) of 52 weeks duration and will perform Visit 501 to Visit 9999 (Week 116 to Week 156).

2.1.1.3 Study Day and Study Week

2.1.1.3.1 Study Day

Study day is defined with respect to extension and will be used for all efficacy and safety analyses. The first day of administration of study treatment (first dose) of extension study is defined as 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. For the dates before Day 1, study day for an event date will be calculated as [Date of event] - [Date of first dose]. Hence, study days for the following critical dates are defined as follows:

- Signing ICF (Day *a*) : [Date of signing ICF] - [Date of first dose]
- Start of OBS1 (Day *b*): [Date of Visit 101] - [Date of first dose]
- Start of TRT1 (Day 1): defined as Day 1
- Start of TRT2 (Day *c*): [Date of Visit 214] - [Date of first dose] +1
- Start of OBS2 (Day *d*): [Date of Visit 301] - [Date of first dose] +1
- Start of 52-week FU (Day *e*): [Date of Visit 501] - [Date of first dose] +1

Duration of an event will be calculated as (Event end date – Event start date + 1).

The descriptor "Day 0" will not be used.

2.1.1.3.2 Study week in the treatment period

The *study week in the treatment period* defined in this section will be used for the primary and secondary efficacy analyses based on the eDiary. Other assessments collected on Rave CRF visit will be analyzed according to the CRF collected visit weeks. Note that the "baseline week" (Baseline) is comprised of the 7 days prior to Day 1 (Day -7 to Day -1).

For all subject in SAF, study weeks (Week *x*) in the first half of the treatment period (including 12 week-follow up in case of early discontinuation) are defined based on the study days as indicated in Table 2-1:

Table 2-1 Study Week definition based on Study Day, first half of the treatment period (including 12 week-follow up in case of early discontinuation)

Study Week (*x*)	Study Days
Baseline	Day (-7) ~ (-1)
Week 1	Day 1 ~ 7
...	...
Week *x*	Day [7×(*x*−1)+1] ~ [7×*x*]
...	...

Study Week (x)	Study Days
Week 52	Day 358 ~ 364

For subjects who **enter the second half of the treatment period without entering OBS2** (including subjects in the continuous long term treatment subpopulation), study weeks (Week x) in the second half of the treatment period (including 12 week-follow up in case of early discontinuation) are defined based on the study days as indicated in Table 2-2a:

Table 2-2a Study Week definition based on Study Day, second half of the treatment period (including 12 week-follow up in case of early discontinuation), for subjects who enter the second half of the treatment period without entering OBS2

Study Week (x)	Study Days
Week 52	Day 358 ~ 364
...	...
Week x	Day $[7\times(x-52)+358] \sim [7\times(x-51) + 357]$
...	...
Week 104	Day 722 ~ 728

For subjects who **enter the second half of the treatment period after entering OBS2** (i.e. subjects in the long-term treatment with a rest subpopulation), study weeks (Week x) in the second half of the treatment period (including 12 week-follow up in case of early discontinuation) are defined based on the study days and study day of Visit 214 (Day c) as indicated in Table 2-2b:

Table 2-2b Study Week definition based on Study Day, second half of the treatment period (including 12 week-follow up in case of early discontinuation) , for subjects who enter the second half of the treatment period after entering OBS2

Study Week (x)	Study Days
Week 52 (V214)	Day $c \sim 6+c$
...	...
Week x	Day $[7\times(x-52)+c] \sim [7\times(x-51) +c -1]$
...	...
Week 104	Day $364+c \sim 370+c$

2.1.1.3.3 Study week in observation periods

[redacted]

For subjects entered OBS1 prior to the treatment period, study weeks (OBS1 Week *x*) in the observation period are defined based on the study days and study day of start of OBS1 (Day *b*) as indicated in Table 2-3:

Table 2-3 OBS1 Study Week definition based on Study Day, first observation period (for subjects entering first observation period on Day b prior to the second treatment period)

OBS1 Study Week (*x*)	Study Days
OBS1 Week 1	Day $b \sim b+6$
...	...
OBS1 Week *x*	Day $[7\times(x-1)+ b] \sim [7\times x+ b-1]$
...	...
OBS1 Week 36	Day $[245+b] \sim [b+251]$

For subjects entered OBS2 prior to the second half of the treatment period, study weeks (OBS2 Week *x*) in the second observation period are defined based on the study days and study day of start of OBS2 (Day *d*) as indicated in Table 2-4:

Table 2-4 OBS2 Study Week definition based on Study Day, first observation period (for subjects entering second observation period on Day d prior to the second half of the treatment period)

OBS2 Study Week (*x*)	Study Days
OBS2 Week 1	Day $d \sim d+6$
...	...
OBS2 Week *x*	Day $[7\times(x-1)+ d] \sim [7\times x+ d-1]$
...	...
OBS2 Week 52	Day $[364+d] \sim [d+370]$

2.1.1.3.4 Study week in the 52-week follow-up period

[redacted] Duration of follow-up period is 52 weeks in subjects who have completed the full 104-week treatment period without interruption and 12 weeks for all other subjects.

Study weeks (FU Week *x*) in the follow-up period are defined based on the study days and study day of start of FU (Day *e*) as indicated in Table 2-5:

Table 2-5 FU Study Week definition based on Study Day, 52-week follow-up period

FU Study Week (*x*)	Study Days
FU Week 1	Day *e* ~ *e* +6
...	...
FU Week *x*	Day [7×(*x*−1)+ *e*] ~ [7×*x*+ *e*-1]
...	...
FU Week 52	Day [364+*e*] ~ [*e* +370]

For the by visit summary tables, they will include all the information collected at the scheduled visit. The unscheduled visit information will not be included in the by visit summary table.

2.1.1.4 Baseline

2.1.1.4.1 Baseline for efficacy analyses

The baseline eDiary score corresponding to a score in the 7 days prior to the first dosing visit assessment, the baseline will be defined as the baseline week (see Table 2-1).

For DLQI/CDLQI [redacted], baseline is the assessment obtained at Visit 201. For a subject who receives partial dose for the first dose day of study treatment, the baseline will be still defined according to the first dosing date of the partial dose. For a subject without any administration of study dose, the baseline assessment will be his last assessment in the Extension study. If a questionnaire was completed more than once on the same date, on the last date on or before treatment start date, then the worst outcome of the duplicate observations on that date will be used as baseline.

2.1.1.4.2 Baseline for safety analyses

In general, baseline is the last assessment (including unscheduled visits) obtained on or after signing ICF and on or before the first dose of study treatment in extension. All assessments obtained after the first dose of study treatment in extension are considered as post-baseline unless otherwise specified.

For CU Index, if no evaluable outcome is available at the extension study baseline, the first evaluable post-baseline outcome will be used for summary of baseline characteristics.

For ECG numeric measurements, baseline will be defined as the mean of scheduled measurements taken at screening (Visit 1). If there is additional screening (re-screening, Visit 2) and/or unscheduled assessment(s) taken before the first dosing date, the assessment taken at

the last date on or before the first treatment dosing data will be considered as baseline for ECG measurements.

For ECG overall interpretation, baseline will be the most common interpretation (normal/abnormal) taken at the last assessment date on or before the first treatment dose date. If the subject has the same number of normal and abnormal interpretations at the same last assessment date, then the overall interpretation will be set to abnormal.

[redacted]

2.2 Analysis sets

Enrolled set (ENR): The ENR will include all enrolled subjects, regardless of whether or not they receive a dose of study drug.

Full Analysis Set (FAS): The FAS will include all enrolled subjects who received at least one dose of study treatment. Subjects will be analyzed according to the treatment group they have been assigned to.

Safety Set (SAF): The SAF will include all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment they actually received. The safety set will be used in the analysis of all safety variables [redacted]. The actual treatment will be defined as the treatment received over the study. In case of error in dispensation, the actual treatment will correspond to the treatment which was given most often.

[redacted]

Table 2-6 Subject classification rules

Analysis set	PDevs that cause subject to be excluded	Non-PDev criteria that cause a subject to be excluded
ENR	NA	NA
FAS (Full Analysis Set)	NA	No study drug taken in the extension study
SAF (Safety Analysis Set)	NA	No study drug taken in the extension study
[redacted]		[redacted]
[redacted]	[redacted]	[redacted]

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

For each PDev, the number and percentage of subjects for whom the deviation applies will be tabulated based on SAF by treatment group for the entire study. Other PDevs in subjects who are in the ENR set but not in the SAF set will be listed only. COVID-19 related PDev will be summarized separately based on SAF by treatment group for the entire study.

No deviation will result in exclusion from FAS or SAF in this study.

2.2.1 Subgroup of interest

2.2.1.1 Subgroup of interest supporting efficacy analysis

- CU index (positive/negative): based on baseline CU index status. If a subject has a missing baseline CU index assessment, this patient will be excluded from the subgroup analysis.
- Preceding study (C2302/C2303, C2202, and C1301): based on subject's preceding study.
- Treatment group in preceding study:
  - C2302/C2303: ligelizumab 72 mg q4w liquid in vial, ligelizumab 120 mg q4w liquid in vial, omalizumab 300 mg q4w, Placebo - ligelizumab 120 mg q4w liquid in vial
  - C2202: ligelizumab 120 mg q4w liquid in vial, ligelizumab 24 mg q4w liquid in vial, Placebo - ligelizumab 120 mg q4w liquid in vial
  - C1301: ligelizumab 120 mg q4w liquid in vial

2.2.2 Subpopulations

The following subpopulations are defined for primary and key secondary efficacy analyses:

- **Ligelizumab retreatment subpopulation** (applicable to subjects whose preceding studies are C2302 and C2303): subjects who are treated with same dosage of ligelizumab in the two core studies (C2302 and C2303) and the extension study.
- **Ligelizumab responder retreatment subpopulation** (applicable to subjects whose preceding studies are C2302 and C2303): subjects who were treated by the same dosage of ligelizumab in the two core studies (C2302 and C2303) and the extension study and achieved UAS ≤ 6 at core study week 12.

Subjects who switched from placebo to ligelizumab in core studies are not included in ligelizumab retreatment subpopulation or ligelizumab responder retreatment subpopulation.

The following subpopulations are defined for relevant secondary [redacted]

- **PFS subpopulation** (applicable to all SAF subjects, irrespective of preceding studies): subjects who have at least one dose of ligelizumab 120 mg q4w PFS

- **Outside-of-clinic self-administration subpopulation** (applicable to SAF subjects, irrespective of preceding studies): subjects who receive ligelizumab via self-administration outside-of-clinic at least once.
- **Monotherapy subpopulation** (applicable to SAF subjects, irrespective of preceding studies): subjects who are qualified for ligelizumab monotherapy (i.e. discontinued H1-AH background medication) per investigators' decision at week 64.
- **Continuous long term treatment subpopulation** (applicable to SAF subjects, irrespective of preceding studies): subjects with an uninterrupted treatment period of 104 weeks.
- **Long term treatment subpopulation** (irrespective of preceding studies): subjects who receive ligelizumab treatment in the second half of treatment period without entering the second observation period.
- **Long term treatment with a rest subpopulation** (irrespective of preceding studies): subjects who received one-year ligelizumab treatment and move to the second observation period before moving to the second half of the treatment period.

2.3 Patient disposition, demographics and other baseline characteristics

Demographic and other baseline data including baseline disease characteristics will be summarized descriptively by treatment group and preceding study for all subjects in the ENR set and the subjects included in the FAS set. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Information from all enrolled subjects, including subjects who complete only first observation period and do not transition into the first half of the treatment period, will be provided in a listing. Information on screen-failed subjects will not be included in the summaries of demographics, disease characteristics at baseline, and medical history.

2.3.1 Demographics (collected at Screening Visit 1)

- Age
- Age group (adolescents (12-17 years), adults (18 - 65 years, ≥ 65 years))
- Sex
- Race
- Ethnicity
- Weight
- Height

- Body Mass Index (BMI) – calculated as weight (kg) / (height (m))2
- BMI group (< 25, 25 - < 30, >= 30 kg/m2)

2.3.2 Disease characteristics at baseline (baseline is defined in Section 2.1.1.4)

- CU Index category
- [redacted]
- Baseline UAS7 score
- Duration of CSU – collected at Visit 201
- Baseline AAS7 score
- Baseline proportion of AAS7 = 0
- Type of prior urticaria medication – collected at Visit 201

2.3.3 Medical History

Relevant medical histories and current medical conditions collected from preceding study baseline before patients received any study drug will be reported. Urticaria related medical history will be summarized by system organ class and preferred term, by treatment group and preceding study in the FAS set. Summaries for urticaria-specific medical history will be provided in a descriptive manner as well. Other medical history will be listed.

2.3.4 Patient disposition

The following will be presented based on the ENR set by overall and preceding study and preceding study treatment group:

- The number and percentage of subjects who complete the screening period will be presented. In addition, the reasons for screen failures will be provided.
- The number and percentage of subjects who enter and completed the first observation period (OBS1) will be presented. In addition, the reasons for discontinuation in OBS1 will be provided.

Patient disposition during treatment, observation, and follow-up periods will be listed. The following will be presented based on the FAS set by overall and treatment group defined in section 2.1.1.1:

- The number and percentage of subjects who entered, completed, and discontinued TRT1A (including the reason for discontinuation)
- The number and percentage of subjects who entered, completed, and discontinued TRT1B (including the reason for discontinuation)
- The number and percentage of subjects who entered, completed, and discontinued TRT2 (including the reason for discontinuation)

- The number and percentage of subjects who entered, completed, and discontinued OBS2 (including the reason for discontinuation)
- The number and percentage of subjects who entered, completed, and discontinued 52-week FU (including the reason for discontinuation)
- The number and percentage of subjects who entered, completed, and discontinued 12-week FU (including the reason for discontinuation)

In addition, duration of study periods TRT1, OBS2, TRT2, FU12 and FU52 will be summarized by treatment group for FAS; duration of study period OBS1 will be summarized for ENR. *Duration in weeks* will be calculated as (the date of the study period end date - the date of the study period start date + 1) / 7.

Note that the end date of each study period is defined as below:

- OBS1 (only applicable for subjects who enter OBS1): max (OBS1 disposition date, last visit end date) and (101<=last visit number <199)
- TRT1 (only applicable for subjects who enter TRT1): max (TRT1 disposition date, last visit end date) and (201<=last visit number <214)
- OBS2 (only applicable for subjects who enter OBS2): max (OBS2 disposition date, last visit end date) and (301<=last visit number <319)
- TRT2 (only applicable for subjects who enter TRT2): max (TRT2 disposition date, last visit end date) and (last visit number in (214, 401-412))
- FU12 (only applicable for subjects who enter FU12): study disposition date
- FU52 (only applicable for subjects who enter FU52): max (study disposition date, last visit end date) and (501<=last visit number <9999)

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

2.4.1 Study treatment / compliance

The analysis of treatment will be performed based on the SAF for relevant study periods and by treatment groups. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The number of patients and the duration of exposure to each treatment will be as indicated in Table 2-7. Duration of exposure is defined as the date of the last treatment minus the date of first treatment in the extension study plus 4 weeks (28 days). For example, duration of exposure of ligelizumab 120 mg q4w liquid in vial is defined as: the date of last injection of ligelizumab 120 mg q4w liquid in vial – the date of the first injection of ligelizumab 120 mg q4w liquid in vial +28 days. Likewise, duration of exposure of ligelizumab 120 mg q4w PFS is defined as:

the date of last injection of ligelizumab 120 mg q4w PFS – the date of the first injection of ligelizumab 120 mg q4w PFS +28 days.

In addition, the number of doses per patient that are correctly administered per protocol, and number of missed doses will be presented. A partial dose will be considered as if 100% of the dose of the assigned treatment has been administered.

At interim and final analyses, treatment exposures will be summarized as needed.

Table 2-7 Treatment exposures evaluated in relevant study periods

Treatment	Study period
ligelizumab 120 mg q4w (liquid in vial)	TRT1A
ligelizumab 72 mg q4w (liquid in vial)	TRT1A
ligelizumab 120 mg q4w (PFS)	TRT1B, TRT1B+TRT2
ligelizumab 120 mg q4w (PFS+ outside-of-clinic self-administration)	TRT1B, TRT2
ligelizumab 120 mg q4w (PFS+monotherapy)	TRT2
ligelizumab, SAF	TRT1A+ TRT1B+TRT2

2.4.2 Prior and concomitant therapies

2.4.2.1 Prior medications

Prior medications which were taken and stopped prior to first dose of study treatment in preceding studies will not be re-summarized for extension study, as they have been summarized in the preceding studies.

Prior medications for CSU which were taken after V1999 of preceding studies and stopped prior to first dose of study treatment in the extension study will be summarized based on SAF by treatment group. Prior medications for CSU will be summarized by type of therapy, preferred term, and treatment group.

2.4.2.2 Concomitant medications and non-drug therapies

Concomitant medications are defined as any medication given at least once between the first dose of the study treatment and the date of the last study visit in the extension study. Concomitant medications will be listed and summarized based on SAF by treatment group, separately for urticaria related background medications and non-urticaria related medications, by the Anatomical Therapeutic Chemical (ATC) code and preferred term (PT).

The concomitant medication tables will be provided for the treatment periods, observation periods, and the entire study period separately, by treatment group defined in section 2.1.1.

The summary tables will be provided for the following:

- TRT1A: the first 12 weeks of the first half of the treatment period (up to Visit 204)

- TRT1B: week 13 to week 52 in the first half of the treatment period (up to Visit 214 or 301, whichever comes first)
- OBS2: the second observation period
- TRT2: the second treatment period
- FU: the follow-up period

Similarly, significant non-drug therapies will be listed.

2.4.2.3 Concomitant use of rescue medication

If unbearable symptoms occur during the study, subjects will be instructed by investigators on the acceptable treatment (H1-AH and oral corticosteroid) for managing their disease with the use of rescue medication.

Fexofenadine, loratadine, desloratadine, cetirizine, levocetirizine and rupatadine H1-AHs, in addition to being allowed as background medication, will be allowed as rescue medication and used on an as-needed basis during all study periods (i.e. screening, observation, treatment and follow-up).

In addition, after the Week 12 (Visit 204) primary endpoint, subjects will be permitted to use oral corticosteroids such as prednisone and its equivalents as rescue medication if needed.

2.4.2.3.1 Concomitant use of rescue medication based on eCRF

Concomitant use of rescue medication (using eCRF information) will be summarized and listed by study period based on the starting date, by ATC code and preferred term as indicated in **Table 2-8** below.

Table 2-8 Study periods for rescue medications

	H1-AH	Oral Corticosteroid
SCR	×	
OBS1	×	
TRT1A	×	
TRT1B	×	×
OBS2	×	
TRT2	×	×
12-week FU	×	×
52-week FU	×	×

2.4.2.3.2 Concomitant use of rescue medication in eDiary

The number of tablets taken, and name of rescue medication (H1-AH and oral corticosteroids) used over the past 24 hours for controlling CSU 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 eDiary data will be summarized by study week. Median with quartiles will be displayed graphically over time to describe the score change during the study periods. 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.

2.4.2.4 Prohibited medication

The use of prohibited medication in study will be captured by PDs.

2.5 Analysis of the primary objective

This section will detail the statistical analysis of the primary endpoint. Details of the hypothesis testing strategy, including primary and secondary endpoints to handle multiplicity, are provided in Section 2.6.

2.5.1 Primary endpoint

The primary endpoint is the proportion of subjects with well-controlled urticaria, defined as Weekly Urticaria Activity Score (UAS7) ≤ 6, at Week 12 (Visit 204) in the first half of the treatment period.

The analysis of primary endpoint will be performed on the subjects whose preceding study is CQGE031C2302 or CQGE031C2303 (i.e. the two core studies) and received ligelizumab treatment with same dose regimen.

2.5.1.1 Primary estimand

Subjects who discontinue from study treatment early will be encouraged to stay in the study following the procedures described in the protocol Section 9.1.1. These are considered as retrieved drop-out (RDO) subjects. To be noted, if the patients take unplanned study treatment (e.g., Omalizumab) in the follow-up period after study treatment discontinuation, the efficacy data collected after that will not be considered as RDO data and will be excluded from analysis.

The definition of primary estimand is described by the following attributes.

- **Population**: Adult and adolescent participants receiving H1-antihistamines therapy at local-approved dose level as background medication suffering from chronic spontaneous urticaria and meeting study inclusion/exclusion criteria, who were rolled over from the previous pivotal studies (CQGE031C2302 and CQGE031C2303).
- **Variable**: the proportion of subjects with well-controlled urticaria (UAS7 ≤ 6) at Week 12

- **Treatment of interest**: ligelizumab retreatment after rolling over from the pivotal studies (CQGE031C2302 and CQGE031C2303) with stable H1-antihistamines (H1-AH) at local-approved doses as background medication + allowed rescue medication, if needed.
- **Handling of intercurrent events:**

1. Discontinuation of initially assigned study treatment prior to Week 12 due to adverse events (AE) or lack of efficacy (LoE) or any other reasons except for the reason of study early termination: Participants who discontinue from study treatment early will be encouraged to stay in the study. RDO data collected after study treatment discontinuation will be used for analysis. (*treatment policy strategy*).
2. Discontinuation of initially assigned study treatment prior to Week 12 due to study early termination: had participants not discontinued treatment prior to Week 12 study termination (*hypothetical strategy*)
3. Use of rescue medication prior to Week 12: ignore (*treatment policy strategy*).

- **The summary measure:** the proportion of subjects with well-controlled urticaria (UAS7≤6) at Week 12 for each treatment arm.

2.5.2 Statistical hypothesis, model, and method of analysis

No inferential statistical methods are planned. Descriptive statistics will be used to summarize data.

Retreatment efficacy of ligelizumab 120 mg q4w or 72 mg q4w in achieving well-controlled CSU at Week 12 in the first half of the treatment period will be evaluated in subjects transitioning from the core studies. The primary analysis will be performed for subjects receiving the same dose of ligelizumab they received in the core studies, i.e. 72 mg or 120 mg for one year.

For subjects rolling over from study CQGE031C2302 and CQGE031C2303 (i.e. two core studies) and treated with same ligelizumab dose regimen, summary statistics for the proportion of subjects achieving UAS7 ≤ 6 response will be provided by treatment group in core studies, and by visit starting from Visit 201 up to Visit 204 (i.e. Week 12 of the first half of the treatment period. The corresponding 95% confidence interval for response rate also will be derived based on the score method including continuity correction (Newcombe, 1998).

For the subgroup of subjects who achieved UAS7 ≤ 6 at Week 12 in the core studies, and who received either 72 mg or 120 mg ligelizumab, the proportion of subjects with the response of UAS7 ≤ 6 at Week 12 of the first half of the treatment period in this extension study will be provided together with a 95% confidence interval.

Subjects rolling over from study CQGE031C2302 and CQGE031C2303, who received different treatment or different ligelizumab dose regimen, will not be included in the primary analysis for re-treatment efficacy.

Subjects rolling over from study CQGE031C1301, who received ligelizumab 120 mg, will not be included in this primary analysis.

Subjects rolling over from the adolescent PK/PD study CQGE031C2202 will also not be included in this primary analysis, as they received treatment doses of ligelizumab of 24 mg or 120 mg for different treatment times.

2.5.3 Handling of missing values/censoring/discontinuations

The UAS7 score is derived from the sum of the HSS7 score and the ISS7 score, as noted above. The HSS7 and ISS7 score will be derived by adding up the daily HSS and ISS scores of the 7 days preceding the visit, respectively. The daily score (HSS and ISS) will be calculated by averaging the morning and evening HSS and ISS score, respectively. If one of the morning or evening scores is missing, the non-missing score for that day (morning or evening) will then be used as the daily score.

A minimum of 4 out of 7 daily scores are needed to reliably calculate a weekly HSS7, ISS7 or UAS7 score. For each weekly score from UPDD (i.e. HSS7, ISS7 and UAS7 score), if one or more of the daily scores are missing, the following principles will be applied to handle the missing data:

- If a subject has at least 4 “non-missing” daily scores within the 7 days prior to the study visit, 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 considered as missing for that week.

Subjects who discontinue from study treatment early will be encouraged to stay in the study following the procedures described in the study protocol Section 9.1.1. These are considered as retrieved dropout (RDO) subjects.

The primary analysis will account for different post-dosing events for missing data handling as follows:

- Discontinuation of initially assigned study treatment prior to Week 12 (Visit 204) due to AEs or lack of efficacy or any other reasons, except for the reason of study early termination: Retrieved dropout (RDO) data collected after study treatment discontinuation will be used for analysis. If no RDO data was collected after study treatment permanent discontinuation, non-responder imputation will be applied for missing data imputation.
- Discontinuation of initially assigned study treatment prior to Week 12 (Visit 204) due to study early termination: the efficacy data collected after the discontinued treatment will be censored. The missing data caused by this intercurrent event occurrance will be imputed based on the treatment arm (ligelizumab 72 mg or 120 mg q4w) data under the missing at random (MAR) assumption using multiple imputation separately.
- Use of protocol allowed rescue medication prior to Week 12 of the first half of the treatment period (V204): Efficacy data collected during intake of rescue medication will not be excluded from the analysis. H1-AH is being used as rescue medication in addition to background medication. Considering that, the patient population are refractory to H1-

AHs and that ligelizumab efficacy is being evaluated on top of H1-AH therapy, all data collected will be used for analysis.

For missing or censored UAS7/HSS7/ISS7 scores due to all other reasons, non-responder imputation will be applied for missing data imputation.

Multiple imputation (MI)

Multiple imputation is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard methods. Rubin (1987) presented rules how to combine the multiple sets of estimates to produce overall estimates and confidence intervals that adequately incorporate missing data uncertainty. The multiple imputation analysis will be imputed based on the individual treatment arm information.

Missing values for the "change from baseline UAS7 score" will be imputed separately for each treatment group including region, CU index and baseline UAS7 score in the model.

Specifically, the missing data will be imputed following the steps below:

1. Impute the following missing data which will be used for primary analysis following the MAR assumption.
   - The intermittent missing data;
   - Missing data with intercurrent events handled through hypothetical strategy.

   The missing data not fit in to the categories above will not be imputed in this step.

   The imputed results will be transferred back for the imputed values on the primary endpoint "proportion of UAS7 ≤ 6 at week 12."
2. Impute the rest missing data of the primary efficacy endpoint with non-responder imputation.

Duplicate data handling of questionnaires

For HSS7, ISS7, 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.

2.6 Analysis of the key secondary objective

For retreatment efficacy evaluation (based on subjects who roll-over from C2302/C2303 and in the retreatment subpopulation):

- To describe the efficacy of ligelizumab 72 mg or 120 mg q4w in achieving complete control of chronic spontaneous urticaria (CSU) at Week 12 when used as retreatment
- To describe the efficacy of ligelizumab with respect to a reduction from extension study baseline in the UAS7 and its components (weekly itch severity score (ISS7) and weekly hives severity score (HSS7) at Week 12

- To describe the efficacy of ligelizumab in achieving an angioedema-free period at Week 12
- To describe the efficacy of ligelizumab in achieving Dermatology Life Quality Index (DLQI) = 0-1 at Week 12 when used as re-treatment

For self-administration efficacy evaluation (based on subjects who roll-over from all preceding studies and in the self-administration subpopulation):

- To describe the efficacy of ligelizumab in the treatment of CSU, 12 weeks after starting out-of-clinic self-administration

2.6.1 Key secondary endpoints

For all secondary efficacy analyses, the FAS (or subpopulations within FAS) will be used. All listings and tables will be presented by treatment group unless stated otherwise. All data will be included in the analysis regardless of rescue medication use.

All secondary analyses to be performed in this study are described and summarized in

Table 2-9.

Table 2-9 Overview of analyses on secondary efficacy endpoints

Analysis Population and Analysis Period/time point	**Endpoints and Analysis**
Objective: to assess the retreatment efficacy of ligelizumab	
population: Ligelizumab retreatment subpopulation period/time point: TRT1A/Visit204 (Week 12)	• The proportion of subjects with completely controlled urticaria (UAS7 = 0) at Week 12 • Absolute change from extension study baseline in the UAS7 and its components (ISS7 and HSS7) at Week 12 • Cumulative number of weeks that subjects achieve weekly angioedema activity score (AAS7) = 0 between extension study baseline and Week 12 • Percentage of subjects achieving DLQI = 0-1 at Week 12
Objective: to assess the self-administration efficacy	
Population: self-administer subpopulation, who have at least one self-administration in TRT1B Period/time point: 12 weeks after starting outside-clinic self-administration in TRT1B	• The proportion of subjects with well-controlled disease (UAS7 $\leq$ 6), 12 weeks after starting self-administration

- Percentage of subjects achieving UAS7 = 0 (complete control of urticaria) at week 12 after retreatment of ligelizumab for subjects receiving the same dose regimen as in the core studies.

The proportion of subjects with UAS7 = 0 at Week 12 will be summarized in a descriptive manner, it will be provided together with 95% Clopper-Pearson exact confidence interval.

Similar missing data imputation rules as the primary endpoint analysis will be applied in this secondary efficacy endpoint analysis. The missing data imputation will be based on the proportion of subject with UAS7 = 0 at week 12.

- Absolute change from extension study baseline in UAS7 at Week 12 after retreatment of ligelizumab for subjects receiving the same dose regimen as in the core studies.

The absolute change from extension study baseline in UAS7 score at Week 12 will be summarized descriptively, it will be provided together with 95% confidence interval. The change from extension study in UAS7 components (ISS7 and HSS7) will also be provided in descriptive manner at Week 12.

Similar missing data imputation rules as the primary endpoint analysis based on change from baseline in UAS7 score at week 12 will be used for this secondary endpoint analyses. The imputations for ISS7 and HSS7 will follow the same missing data imputation rules.

- Percentage of subjects achieving DLQI = 0-1 (no impact on subjects QoL) at Week 12 after retreatment of ligelizumab for subjects receiving the same dose regimen as in the core studies.

An overall score will be calculated according to the scoring manual. The proportion of subjects with overall DLQI scores ≤ 1 at Week 12 will be summarized in a descriptive manner, it will be provided together with a 95% Clopper-Pearson exact confidence intervall. Similar missing data imputation rules as the primary endpoint analysis will be applied in this secondary efficacy endpoint analysis. The missing data imputation will be based on the proportion of subject with UAS7 = 0 at week 12.

- Cumulative number of weeks that subjects achieve AAS7 = 0 between extension study baseline and Week 12

The cumulative number of weeks achieving AAS7 = 0 response between baseline and Week 12 will be derived based on the AAS eDiary. A weekly AAS7 score will be derived by adding up the daily scores of the 7 days preceding the visit, and ranges from 0 to 105. For a weekly AAS7 score, if one or more of the daily scores are missing, the same principles as handling the weekly score from UPDD will be applied to handle the missing data. If the AAS7 score is missing, similar missing imputation rules as the primary analysis will be applied on AAS7 = 0 proportion over the first 12 weeks. The imputed AAS7 = 0 will be used for the cumulative number of weeks that subjects achieve AAS7 = 0 response calculation. The cumulative frequency plot will be provided together with the summary statistics.

- Percentage of subjects achieving UAS7 ≤ 6 (well-controlled urticaria) at 12 weeks after starting self-administration in the first half of the treatment period.

The proportion of subjects with UAS7 ≤ 6, 12 weeks after starting self-administration will be summarized in a descriptive manner, and it will be provided together with 95% Clopper-Pearson exact confidence interval. Missing data will be considered as non-responder in the analysis.

2.6.2 Statistical hypothesis, model, and method of analysis

No inferential statistical methods are planned. Descriptive statistics will be used to summarize data.

2.6.3 Handling of missing values/censoring/discontinuations

Missing data handling for HSS7, ISS7, and UAS7 score

Refer to Section 2.5.3.

Missing data handling for AAS7 score

The weekly score AAS7 will be derived by adding up the daily scores of the 7 days preceding the visit. The weekly score will then range from 0 to 105.

For each weekly score from AAS, 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.

Missing data handling for DLQI score

There was a very high success rate of accurate completion of the DLQI. However, if responses were incomplete, the following rules were applied:

1. If one question was left unanswered, then the missing value was imputed to a 0 score and the overall DLQI/CDLQI score was summed up in the usual way out of 30.
2. If two or more questions were left unanswered, then the questionnaire was not scored (left to missing).
3. If question no. 7 was answered ‘yes’, then it was scored to a value of ‘3’. If question no. 7 was answered ‘not relevant’ then the score was 0. If question was answered ‘no’ (not being preventing to work or study) but the skin was a problem for working or studying, then the scores per possible response were either ‘a lot’ (2) or ‘a little’ (1) or not at all (0).

Missing data imputation for UAS7=0, UAS7≤ 6, DLQI=0-1, and AAS7=0 response

In analyses of above mentioned secondary efficacy endpoints, missing values with respect to response variables based on UAS7 score, DLQI/CDLQI score will be imputed as described in Section 2.6.1.

Multiple imputation methods refer to Section 2.5.3.

2.7 Analysis of secondary efficacy objective(s)

No other secondary efficacy objectives were analyzed.

2.8 Safety analyses

For all safety analyses, the safety set (or subpopulations within SAF) will be used. All subjects enrolled into the extension study, regardless of which preceding studies they came from will be included in the safety analysis. All listings and tables will be presented by treatment group. All data will be included in the analysis regardless of rescue medication use.

All safety analyses to be performed in this study are described and summarized in **Table 2-10**.

Table 2-10 Overview of analyses on secondary [redacted]

Analysis Population and Analysis Period	Endpoints and Analysis
Secondary Objective: to assess the safety and tolerability of ligelizumab in all subjects	
Population: SAF Period: entire study	• TEAE, TESAE, TEAESI (crude incidence), by study period • Related TEAE, TEAEs leading to discontinuation, death (crude incidence), by study period • Summary of vital signs, by visit, by study period • Summary of lab assessments, by visit, by study period
Population: Continuous long term treatment subpopulation Period: TRT1+TRT2	• TEAE, TESAE, TEAESI (crude incidence), by study period • Related TEAE, TEAEs leading to discontinuation, death (crude incidence), by study period • Summary of vital signs, by visit, by study period • Summary of lab assessments, by visit, by study period
Population: Long term treatment subpopulation Period: TRT1A; TRT1B; TRT2; TRT1+TRT2	• TEAE, TESAE, TEAESI (crude incidence and EAIR • TEAEs leading to discontinuation (crude incidence and EAIR) • Summary of clinical notable lab abnormality (only TRT1+TRT2) • Summary of newly occurring or worsening vital signs (hypertension, hypotension, bradycardia, tachycardia; only TRT1+TRT2)
Population: Long term treatment with a rest subpopulation Period: TRT1A; TRT1B; TRT2	• TEAE, TESAE (crude incidence and EAIR) • TEAEs leading to discontinuation (crude incidence and EAIR) • AESI of CCV and malignancy (crude incidence and EAIR; TRT1+OBS2+TRT2+FU) • Summary of clinical notable lab abnormality (only TRT1+OBS2+TRT2+FU) • Summary of newly occurring or worsening vital signs (hypertension, hypotension, bradycardia, tachycardia; only TRT1+OBS2+TRT2+FU)

Secondary Objective: to assess the safety and tolerability of ligelizumab 120 mg q4w 1mL pre-filled syringe (PFS)	
Population: PFS subpopulation (by treatment group + total) Period: week 12 onwards (TRT1B+TRT2)	• TEAE, TESAE, TEAESI (crude and exp.adjusted incidence) • Related TEAE, TEAEs leading to discontinuation, death (crude incidence), by study period • Summary of vital signs, by visit • Summary of lab assessments, by visit
Secondary Objective: to assess the safety and tolerability of ligelizumab 120 mg q4w in all subjects who self-administer	
Population: self-administer subpopulation (by treatment group + total) Period: during TRT1B+TRT2, after first dose of self-administer	• TEAE, TESAE, TEAESI (crude and exp.adjusted incidence) • Related TEAE, TEAEs leading to discontinuation, death(crude incidence), by study period • Summary of vital signs, by visit • Summary of lab assessments, by visit

[redacted]

2.8.1 Adverse events (AEs)

2.8.1.1 General information

All adverse events (AEs) reported will be coded using MedDRA and summarized by treatment group, primary System Organ Class (SOC) and Preferred Term (PT).

Summary tables and/or listings will be provided for non-treatment emergent AEs by study period on an as-needed basis.

Treatment emergent AEs will be summarized by actually received treatment, in relevant treatment periods (see **Table 2-10**).

Treatment emergent AEs (TEAE) are defined as:

- Events started after the first dose of study treatment (ligelizumab) in the extension study and within 16 weeks of last dose of study treatment
- Events present prior to the first dose of study treatment (ligelizumab) in the extension study but:
    - increased in severity based on preferred term (e.g. worsening of headache),
    - same PT but increased severity (e.g. from mild to moderate),
    - same PT but increase in seriousness (from non-serious AE to SAE; if already a SAE from medical significant to LT/fatal)

TEAEs which will be counted for a specific treatment period are those which are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but get worsen (increased in severity based on preferred term, or same PT but increased severity, or same PT but increase in seriousness) after the start of the treatment period. Within a specific treatment period, a subject with multiple AEs within a primary system organ class is only counted once with the greatest severity at the system organ class level, where applicable, towards the total of the primary system organ class.

Overview tables for the numbers and percentage of subjects with TEAE will be provided for:

- Any event (AE of special interest, related AE, SAE)
- Maximum intensity of events.
- Events with outcome of death.
- Other significant AEs leading to treatment discontinuation

2.8.1.2 Crude and Exposure-Adjusted Incidence Rate

The crude incidence rate is defined as the percentage of subjects with a specific adverse event divided by the total number of subjects in each study group.

In a long-term follow-up of the patients, the crude incidence rate might not be a correct measure because it does not include the individual subject's total exposure time in the calculation. As described in **Table 2-10**, the exposure-adjusted incidence rate (EAIR) will be provided for the safety analysis in certain study periods in addition to the crude rate.

The EAIR is defined as the number of subjects with a specific event divided by the total exposure-time among the subjects in the study group. That is, the EAIR is calculated as:

$EAIR = n / \Sigma\, t_i$, where n is the number of subjects having the i^{th} type event, and t_i is a subject's exposure time until having an i^{th} type event. If a subject has multiple events of the i^{th} type, the t_i is the time of the first event of that type. For a subject having no event of the i^{th} type, the t_i is the last follow-up time for that subject. The total exposure time of all subjects in a treatment group is $\Sigma\, t_i$. The EAIR is interpreted as the number of events occurring in a population per unit time. The exact Poisson 95% confidence interval for the EAIR will be provided as well, where

an exact 100*(1-α)% confidence interval will be derived as follows (Garwood 1936, Sahai and Khurshid 1993):

- Lower confidence limit $L = \frac{0.5C_{\alpha/2,2n}}{\sum t_i}$ for n>0, 0 otherwise,
- Upper confidence limit $U = \frac{0.5C_{1-\alpha/2,2n+2}}{\sum t_i}$,

where $C_{\alpha,k}$ is the αth quantile of the Chi-square distribution with k degrees of freedom.

Whenever applicable, exposure adjusted incidence rates will be provided for the type as below:

1. TEAE and TESAE: Primary SOC level and preferred term level
2. Treatment emergent AE of special interest: up to SMQ level 5

When calculating EAIR for AESI of cardiovascular and cerebrovascular (CCV) and malignancy, the adverse event and exposure time both consider the entire study period after the first study treatment.

2.8.1.3 AE summaries for Secondary Safety Endpoints

For safety and tolerability of ligelizumab for all subjects during the study, summaries will be provided by study period. For TRT1A and TRT1B, summaries of TEAE, treatment emergent SAE (TESAE), treatment emergent AESI (TEAESI), TEAEs leading to discontinuation, TEAEs leading to death, and TEAE by severity will be provided for SAF.

For the long term treatment subpopulation, TEAE, TESAE, TEAESI, and TEAEs leading to discontinuation will be summarized for TRT1A, TRT1B, TRT2 and TRT1+TRT2.

For the long term treatment with a rest subpopulation,TEAE, TESAE, TEAEs leading to discontinuation, AESI of CCV and malignancy will be summarized for TRT1A, TRT1B, and TRT2.

In addition, a summary table of TEAE during entire treatment period was planned to be provided for the continuous long term treatment subpopulation. However, this analysis will not be conducted in the final analysis due to study early termination due to study early termination.

To investigate the safety and tolerability of ligelizumab 120 mg PFS, summaries of TEAEs, TESAEs, and TEAESIs will be provided to include the AEs after the first dose of PFS use. Only the subjects who receive at least one dose of ligelizumab 120 mg PFS use will be included in this analysis.

To investigate the safety and tolerability of ligelizumab 120 mg in all subjects who will be self-administered, summaries on TEAEs, TESAEs, and TEAESIs will be provided to include the information after the first dose using “out of clinic” self-administration. Subjects who move from self-administration back to in- clinic administration during the study, will be included in this analysis if majority (>50%) of drug use is based on “out of clinic” self-administration.

The safety and tolerability of ligelizumab 120 mg self-administration with PFS has been evaluated at the interim analysis. Those analyses will not be re-conducted in the final analysis.

[redacted]

2.8.2 Others

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables "Treatment emergent adverse events which are not serious adverse events with an incidence greater than 5%" and "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. These tables will not be included in the CSR.

2.8.2.1 Adverse events of special interest / grouping of AEs

2.8.2.1.1 Adverse Events of Special Interest

AESI for Ligelizumab treatment isspecified as compound-level risk factors defined in the Case Retrieval Strategy (eCRS).

In the final analysis, TEAESI will be summarized for SAF for TRT1A and TRT1B, by treatment group and study period; TEAESI will be summarized for the long term treatment subpopulation for TRT1A, TRT1B, and TRT2, by treatment group and study period; TEAESI will be summarized for the long term treatment with a rest subpopulation for TRT1A, TRT1B, TRT2, and TRT1+TRT2, by treatment group and study period. AESI of CCV and malignancy will be summarized for the long term with a rest subpopulation for TRT1+OBS2+TRT2+FU.

2.8.2.1.2 Adjudicated AEs

In addition to the AESI listed above, the following AEs will be adjudicated by the independent committee. The positively adjudicated events will be listed with treatment emergent flag applied.

- Anaphylactic events
- Major cardio-cerebrovascular events
- Neoplastic events

2.8.3 Deaths

No separate listing or table will be provided from the database. Death will be reported as part of SAE with a fatal outcome.

2.8.4 Laboratory data

The summary of laboratory evaluations will be presented for 2 groups of laboratory tests (hematology and serum chemistry). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline values. For categorical parameters, frequencies by categories at each visit will be summarized.

Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value in the first half of the treatment period separately.

The laboratory values below Lower Level of Quantification (LLQ) or above Upper Level of Quantification (ULQ) will be imputed as LLQ or ULQ in the summary tables, respectively. The numerical part of the reported result will be treated as the actual LLQ or ULQ. These laboratory values will be displayed in listings using the standard unit with the reported sign ("<" or ">")."

The number of patients with newly occurring or worsening abnormalities during the study will be listed by treatment and by study periods (as defined in section 2.1.1.2), based on the notable criteria specified in the Appendix 1 to 3 of the study protocol (See section 16.1 to 16.3 of the study protocol). A case is considered as a newly occurring abnormality if the value is not notable or missing at baseline but is notable thereafter during the study. A case is considered as a worsening abnormality if the value is notable at baseline and at least one post-baseline value during the study is worse than baseline.

If an adolescent subject turned to be an adult subject during the study, the normal range, notable criteria for analysis will be based on the age by the visit assessment.

To evaluate potential drug-induced liver injury, newly occurring liver enzyme abnormalities at any time post-baseline will also be summarized according to protocol Appendix 2.

Data from local laboratories will not be used in any of the summary analyses included in this session.

2.8.5 Other safety data

2.8.5.1 ECG and cardiac imaging data

All ECG data will be listed by treatment group, subject and visit/time, and by study period identified in Section 2.1.1.2. Newly occurring or worsening abnormalities will be flagged.

A listing of all notable abnormalities will be provided, as well as a by-subject listing of all quantitative ECG parameters.

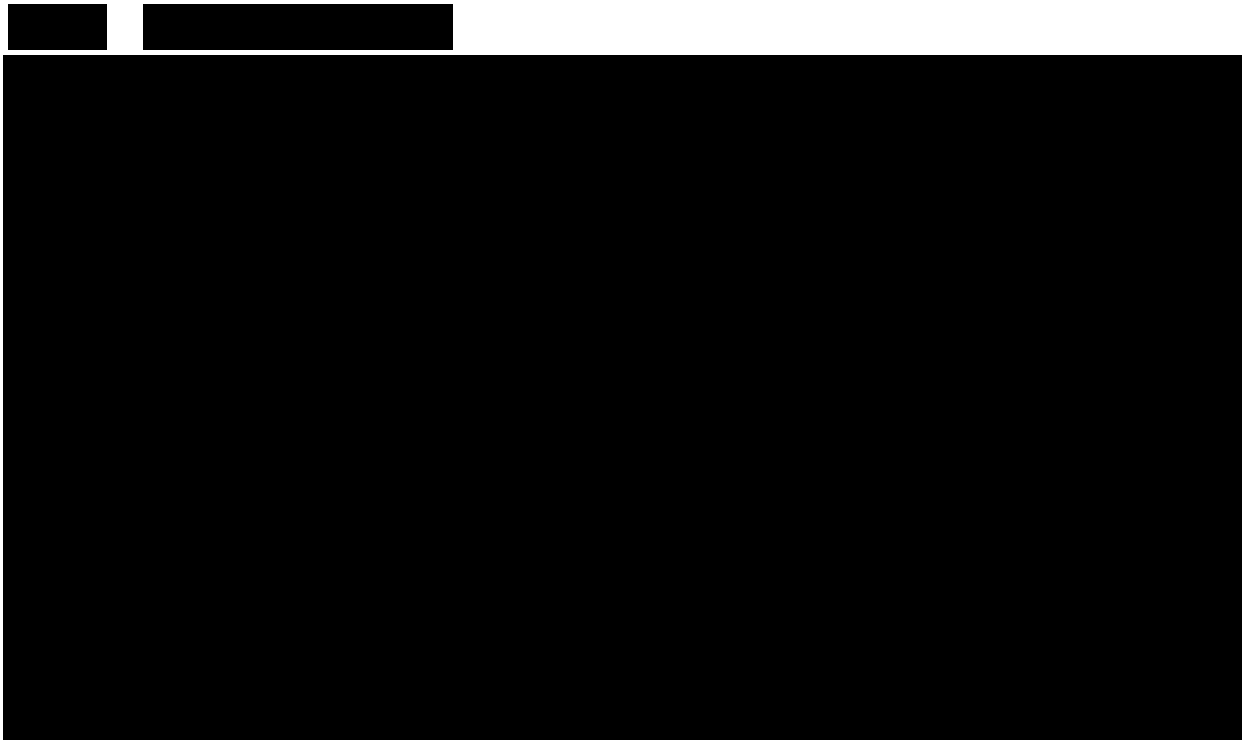
For ECGs a notable QTc value is defined as a QTcF interval of greater than 450 ms for males or greater than 460 ms for females – all such ECGs will be flagged by the Central CRO's cardiologist and require assessment for clinical relevance by the investigator. For adolescent subjects, the Central CRO will use age-and gender-specific reference values.

2.8.5.2 Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign and treatment group and separately in adults and adolescents. Change from baseline will only be summarized for subjects with both baseline and post-baseline values. Subjects with notable vital signs will be listed by study periods defined in Section 2.1.1.2. Newly occurring or worsening vital sign values outside of notable ranges will be summarized as needed. A case is considered as a newly occurring abnormality if the value is not notable or missing at baseline but is notable thereafter during the study. A case is considered as a worsening abnormality if the value is notable at baseline and at least one post-baseline value during the study is worse than baseline.

Notable values for adults and adolescents are defined as follows:

- heart rate of < 60 and > 100 bpm
- systolic blood pressure of < 90 and ≥ 140 mmHg
- diastolic blood pressure of < 60 and ≥ 90 mmHg



[redacted]

2.8.5.4 Resource utilization

Data relating to resource utilization will be used for the purpose of economic evaluation and will be carried out and reported as a separate activity.

[redacted]

[redacted]

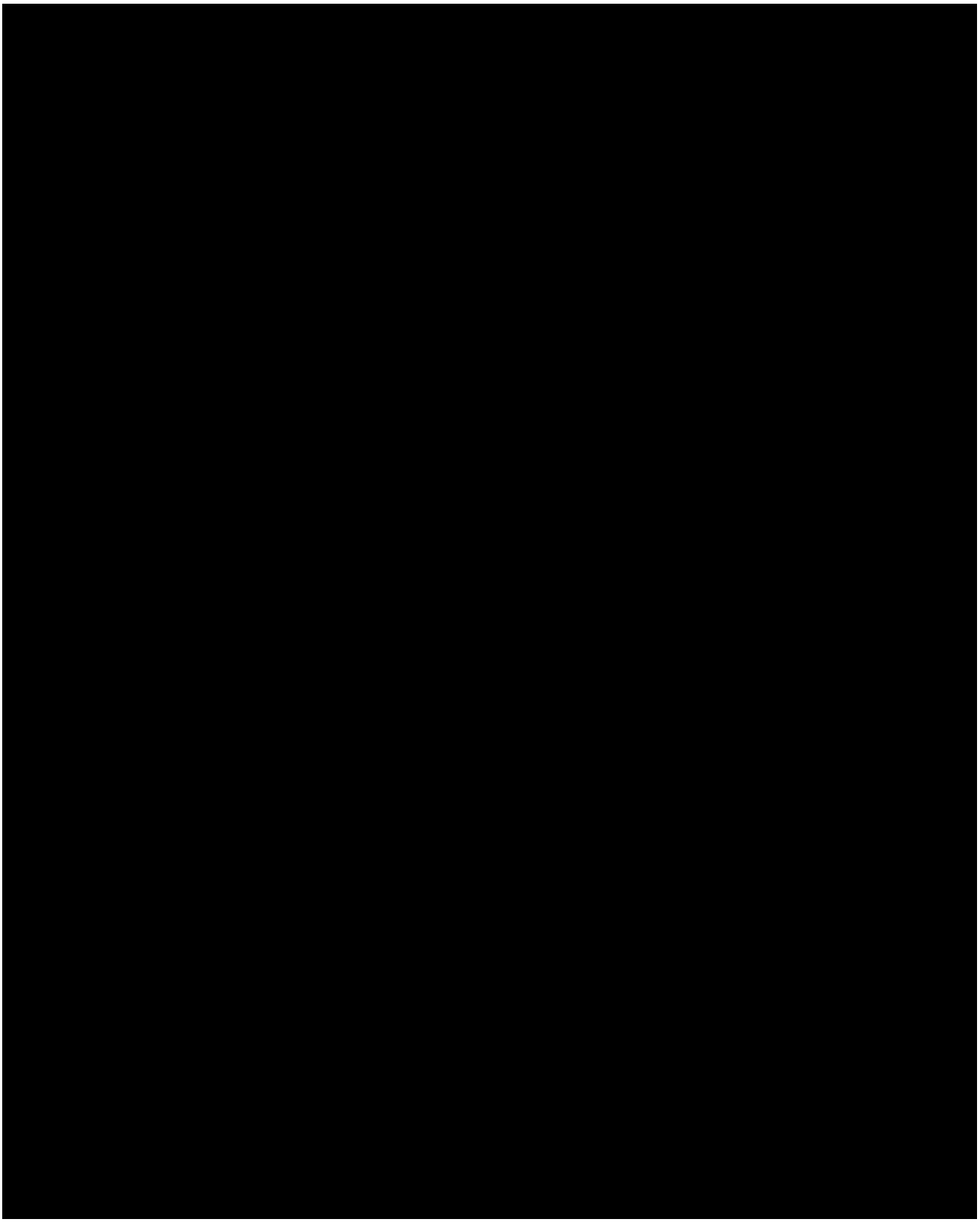
2.11 Biomarkers

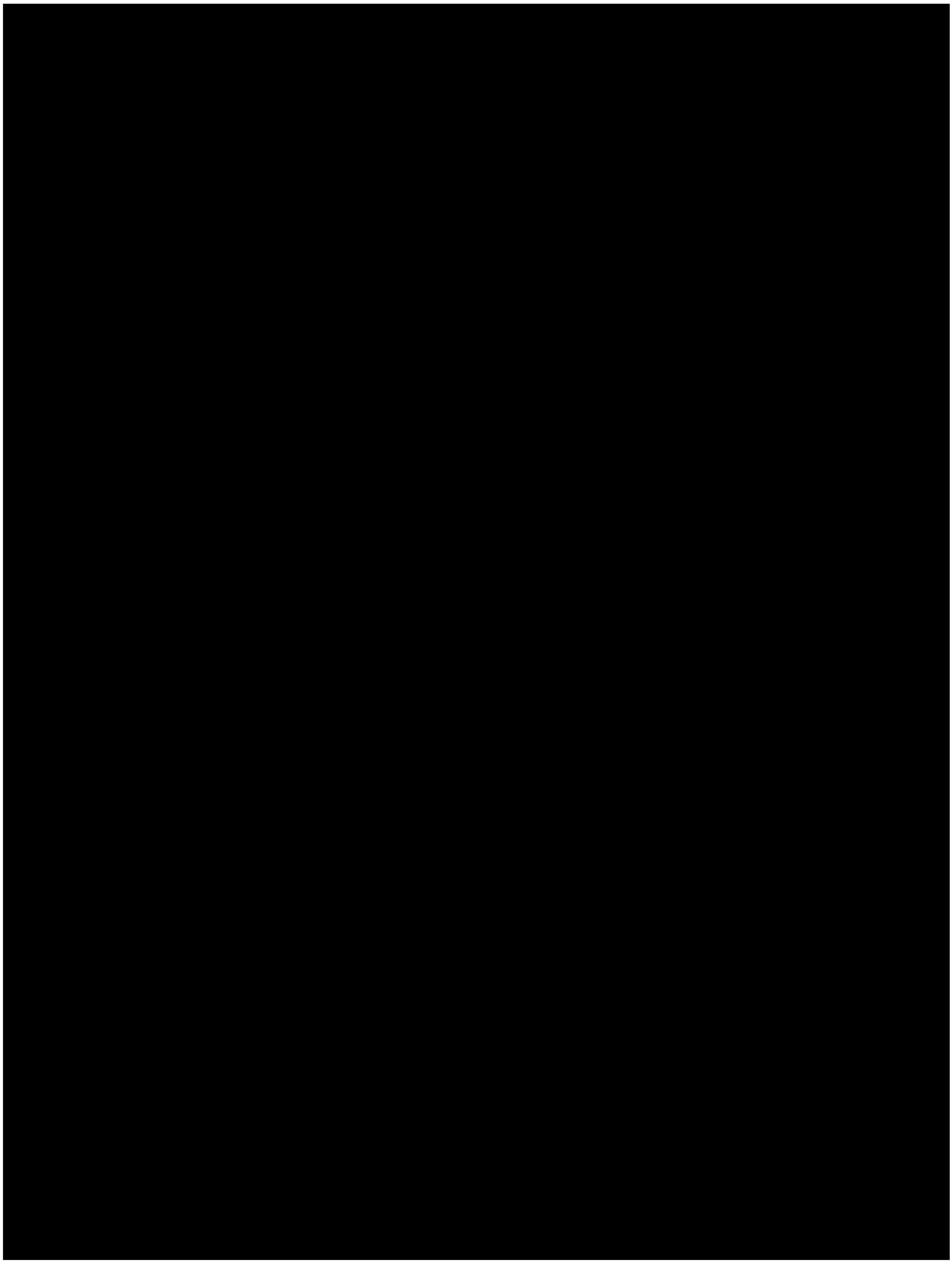
2.11.1 Chronic Urticaria (CU) index panel

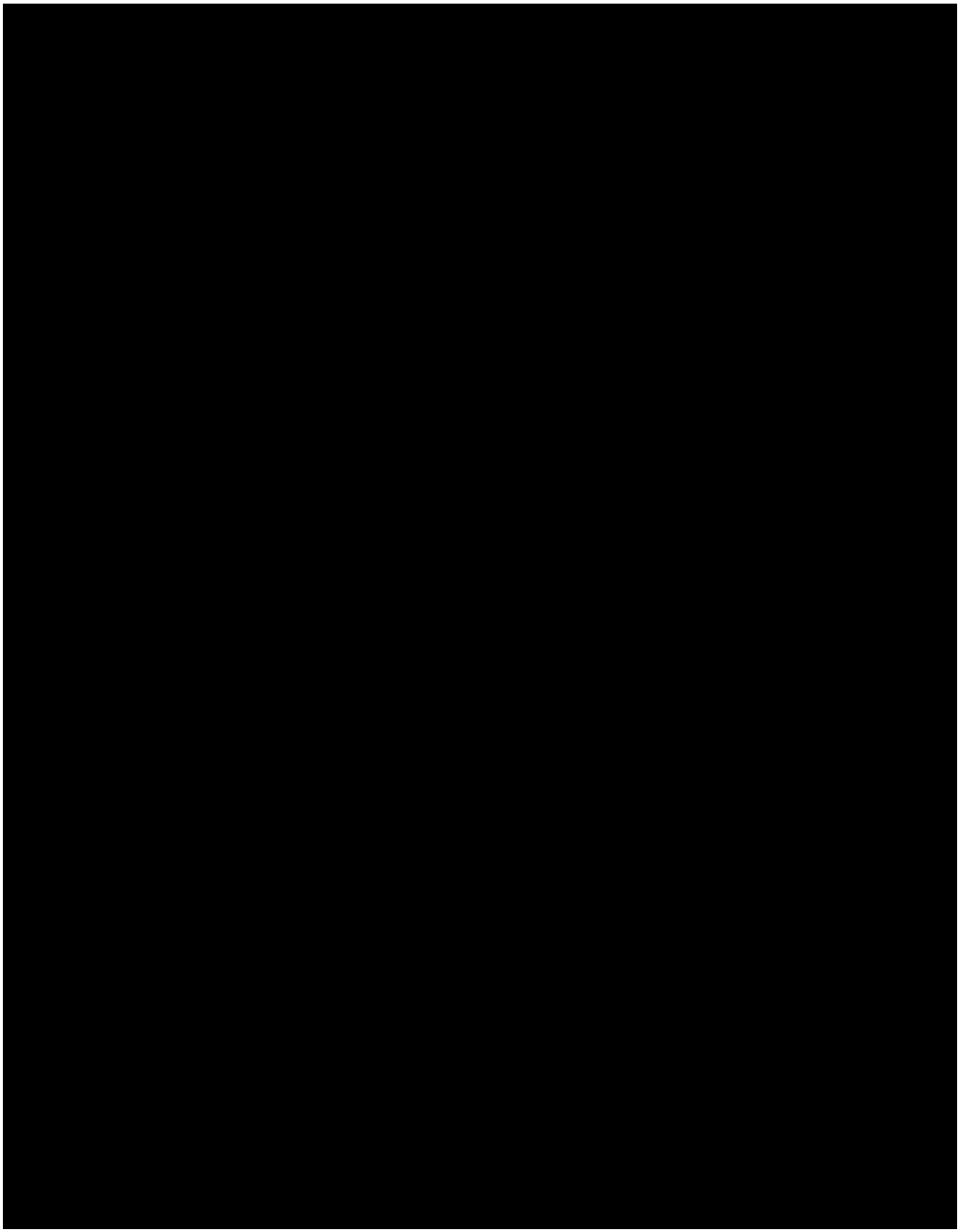
The CU index panel consists of the CU Index®, thyroid peroxidase IgG and thyroglobulin IgG assays. CU index assessed at V201 will be summarized as part of baseline characteristics (see section 2.3). Thyroid peroxidase IgG and thyroglobulin IgG will be listed and summarized by visit and treatment group. The unscheduled visit information will not be included in the summary table.

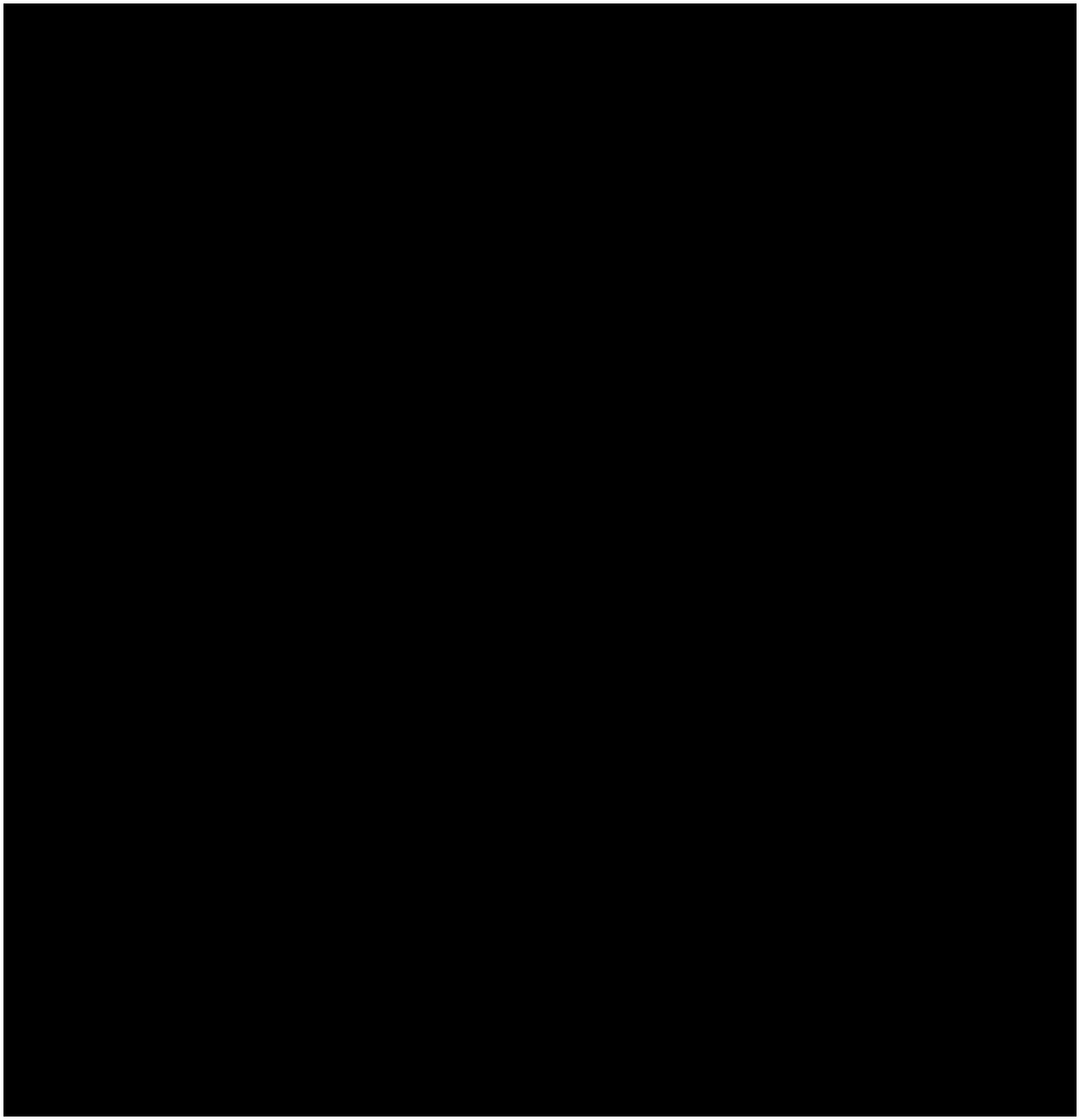
2.11.2 Total Tryptase

Total tryptase levels and sampling time will be listed by subject and sampling time point. Post-baseline measurements (i.e. those taken at the time of a suspect hypersensitivity event) will be flagged. A summary table will be provided for baseline values by treatment group. The unscheduled visit information will not be included in the summary table.









2.13 Interim analysis

2.13.1 Planned interim analysis

The first interim analysis (IA1) is planned once all subjects of the CQGE031C2302 and CQGE031C2303 have completed Week 12 (Visit 204) in the first half of the treatment period to evaluate the primary endpoint of retreatment efficacy. Details will be provided by the separate SAP for IA1.

The second interim analysis (IA2) will be performed at the end of the first half of the treatment period at Week 52 (i.e. once all subjects have complete visit 214 or 301, whichever comes first) to evaluate endpoints up to the end of 1 year treatment. Details will be provided by the separate SAP for IA2.

Scopes of IA1 and IA2 are described and summarized in **Table 2-12**. [redacted]

For the purpose of periodical safety review, independent analyses will be performed for DMC meetings, which will be held at least once for every 6 months. To maintain the treatment blinding until all subjects in this study have completed Week 12 (Visit 204), the outputs for the DMC will be conducted in a semi-blinded manner (using dummy treatment code) prior to the first interim analysis, by the independent statistician and programmer in the separate CRO who are not involved in CSR reporting. Details will be provided by the DMC charter. Outputs to be provided to the DMC will be specified in the separate document.

Additional analyses may be performed to support health authority interactions as necessary.

Due to the early termination of study CQGE031C2302E1, the planned interim analysis IA1 and IA2 will not be performed. A final analysis of all data collected up to last study visit will be performed when all subjects have completed the last study visit.

Table 2-12 Overview of Scope of Interim Analyses 1 & 2

Population/ Analysis /Study Period	**Endpoints**
Interim analysis I (week 12)	
Analysis: Efficacy Population: ligelizumab retreatment subpopulation Period/time point: TRT1A/Visit204 (Week 12)	• proportion of subjects with well-controlled urticaria (UAS7≤ 6) at Week 12 • The proportion of subjects with completely controlled disease (UAS7 = 0) at Week 12 • Absolute change from extension study baseline in the UAS7 and its components (ISS7 and HSS7) at Week 12 • Cumulative number of weeks that subjects achieve weekly angioedema activity score (AAS7) = 0 between extension study baseline and Week 12 • Percentage of subjects achieving DLQI = 0-1 at Week 12

Analysis: Safety Population: SAF Period: TRT1A	• TEAE (crude incidence) in TRT1A • TEAE, TESAE, TEAESI (crude incidence) in TRT1A • Related TEAE, TEAEs leading to discontinuation, death,(crude incidence), in TRT1A • Summary of vital signs, by visit, in TRT1A • Summary of lab assessments, by visit, in TRT1A
Interim analysis II (week 52)	
Analysis: Efficacy Population: self-administer subpopulation, who has at least one self-administration in TRT1B Period/time point: 12 weeks after starting outside-clinic self-admisitration in TRT1B	• The proportion of subjects with well-controlled disease (UAS7 ≤ 6), 12 weeks after starting self-administration
Analysis: Efficacy Population: 1) FAS whose preceding study is C2302/2303 (in two subpopulations, by preceding treatment group) 2) FAS Period: TRT1	• Proportion of subjects with UAS7 ≤ 6 response by visit • Proportion of subjects with UAS7 = 0 response by visit • Proportion of subjects with HSS7 = 0, ISS7 = 0 and UAS7 = 0 response by visit • Absolute and percent change from extension study baseline in HSS7, ISS7 and UAS7 by visit [redacted]
Analysis: Safety population: 1) SAF 2) PFS subpopulation (by treatment group + total) 3) Self-administer subpopulation period: TRT1	• TEAE, TESAE, TEAESI (crude incidence) • Related TEAE, TEAEs leading to discontinuation, death,(crude incidence) • Summary of vital signs, by visit • Summary of lab assessments, by visit

2.13.2 Unplanned interim analysis

An unplanned interim analysis will be performed to support CSU BLA submission and health authority interactions regarding outside-of-clinic self-administration of ligelizumab with PFS. The safety, efficacy [redacted] data available from this study at the time of CSU BLA submission will be provided in a separate abbreviated report. The Outputs shell will be provided in CSR outputs TFL shell.

The pivotal studies (CQGE031C2302/CQGE031C2303) and the extension study will still be ongoing at the time of the unplanned interim analysis, so all outputs will be provided in a blinded fashion. Any team members who are unblinded to the pivotal study treatment group will not participate in the CTT of the extension study.

2.13.2.1 Interim analysis set(s)

The Safety analysis set (SAF), as defined in Section 2.2, including all subjects who received at least one dose of study treatment will be used for all the analyses of this interim analysis.

Three types of administration defined in Table 2-13 are of interest in this interim analysis. The following subpopulations according to those types of administration will be considered in the safety and efficacy analyses for this interim analysis:

- **Outside-of-clinic self-administration:** participants who have at least one outside-of-clinic injection with PFS administered by either the participant herself/himself or a caregiver.
- **Self-administration:** participants who have at least one injection with PFS administered by the participant herself/himself or a caregiver either in clinic or outside of clinic.
- **In-clinic staff-administration:** participants who have all injections with PFS administered in clinic and by the site staff.

Definition of the above three subpopulations only depends on data in the first half of the treatment period. For example, participants who have all injections done in-clinic and by site staff in the first half of the treatment period, and start self-administration in the second half of the treatment period would belong to the in-clinic staff-administration subpopulation for the purpose of this interim analysis.

Table 2-13 Definition of type of administration

Type of administration	Definition
Outside-of-clinic self-administration	Outside-of-clinic injections with PFS administered by either the participant herself/himself or a caregiver
Self-administration	Injections with PFS administered by the participant herself/himself or a caregiver either in clinic or outside of clinic

In-clinic staff-administration	Injections with PFS administered in clinic and by the site staff

2.13.2.2 Treatment groups to be included at interim analysis

At the interim analysis, efficacy and safety outputs will be provided in blinded fashion, in other words, the study treatment group of interest in this interim analysis is defined as "Any ligelizumab treatment" since all subjects will be receiving same treatment (ligelizumab 120mg) starting from Week 12.

Additional listings maybe prepared and reported elsewhere in separate documents (e.g., SCE, SCS) by the QGE031C2302 and QGE031C2303 unblinded team to link unique subject identification numbers and treatment groups between the proceeding studies and the extension study, if needed.

2.13.2.3 Patient disposition, demographics, and other baseline characteristics for interim analysis

Demographic (defined in Section 2.3) and other baseline data including disease characteristics (listed below) will be summarized descriptively for all participants in the Safety Set (SAF), and the participants included in the subpopulations defined in Section 2.13.2.1. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Preceding study baseline is defined as the baseline in study CQGE031C2302, CQGE031C2303, CQGE031C2202 and CQGE031C1301. Extension study baseline is defined in study CQGE031C2302E1 Section 2.1.1.4.

2.13.2.3.1 Disease characteristics at baseline (defined in study Section 2.1.1.4)

- CU Index category
- [redacted]
- UAS7 score
- Duration of CSU – collected at Visit 201
- AAS7 score
- Angioedema occurrence (Yes/No) based on medical history

2.13.2.3.2 Patient disposition

The following will be presented based on the Safety Set (SAF) in overall and the subpopulations defined in section 2.13.2.1 (whenever applicable):

- First 12 weeks of the first half of the treatment period (from Visit 201 to Visit 204, denoted as TRT1A): the number and percentage of participants who entered, completed,

and discontinued treatment prior to the Week 12 visit (including the reason for discontinuation)

- Week 12 to Week 24 of the first half of the treatment period (from Visit 204 to Visit 207, denoted as TRT1B-a): The number and percentage of participants who entered, completed, and discontinued from Week 12 up to Week 24 in the first half of the treatment period (including the reason for discontinuation)
- Week 24 to Week 52 of the first half of the treatment period (from Visit 207 to Visit 214 or 301, whichever comes first, denoted as TRT1B-b): The number and percentage of participants who entered, completed, and discontinued from Week 24 onwards in the first half of the treatment period (including the reason for discontinuation)

Duration of each study periods mentioned above will be summarized in overall and the subpopulations defined in Section 2.13.2.1 (whenever applicable). Duration in weeks will be calculated as (the date of the study period end date - the date of the study period start date + 1) / 7.

In addition, the following will be summarized:

- Number and proportion of participants in each subpopulation defined in Section 572.13.2.1.
- Number and proportion of each type of administration (listed in **Table 2-13**) at each visit, from Visit 204 (Week 12) to Visit 207 (Week 24) in the self-administration subpopulation only.
- Number and proportion of participants who receive at least 50% injections with PFS by participants herself/himself or a caregiver after Visit 207 (Week 24). This summary will be provided in the self-administration subpopulation only.

2.13.2.3.3 Study treatment / compliance

The analysis of treatment received will be performed based on the SAF for relevant study periods in overall and the subpopulations defined in Section 572.13.2.1. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The number of participants and the duration of exposure to each treatment will be as indicated in **Table 2-14**. Duration of exposure is defined as the date of the last treatment minus the date of first treatment in the extension study plus 4 weeks (28 days), specified as below.

- Duration of exposure of ligelizumab 72/120 mg q4w liquid in vial is defined as: the date of last injection of ligelizumab 72/120 mg q4w liquid in vial minus the date of the first injection of ligelizumab 72/120 mg q4w liquid in vial plus 28 days.
- Duration of exposure of ligelizumab 120 mg q4w (PFS, administered by site-staff/self/caregiver **in clinic**) between Week 12 and Week 24 is defined as: the date of last injection of ligelizumab 120 mg q4w PFS before Week 24 visit date minus the date of the first injection of ligelizumab 120 mg q4w PFS plus 28 days.

- Duration of exposure of ligelizumab 120 mg q4w (PFS, administered by site-staff/self/caregiver **in clinic or outside of clinic**) from Week 24 onwards up to data cut is defined as: the date of last injection of ligelizumab 120 mg q4w PFS by the cut-off date of this interim minus the date of the first injection of ligelizumab 120 mg q4w PFS since Week 24 visit date plus 28 days.
- Duration of exposure of ligelizumab (any ligelizumab treatment) up to data cut is defined as: the date of last injection of ligelizumab 72/120 mg q4w PFS by the cut-off date of this interim minus the date of the first injection of ligelizumab 72/120 mg q4w liquid in vial plus 28 days.

Visit on the cut-off date is included in the next study period. For example, Week 12 visit is included in the study period of Week 12 – Week 24. Missing visit on the cut-off date will be handled in different scenarios. The study period with missing visit on the cut-off date will be adjusted according to the missing reasons as specified below.

- Missing visit at Week 12:

Reason of missing visit at Week 12	Adjusted study period of "Up to Week 12"
Early discontinued during Week 0-12	From Week 0 to the day of discontinuation
Missed Week 12 visit and completed the next visit	From Week 0 to the day before PFS injection
Have not reached Week 12 visit yet	From Week 0 to the cut-off date of this interim

- Missing visit at Week 24:

Reason of missing visit at Week 24	Adjusted study period of "Week 12 – Week 24"
Early discontinued during Week 12-24	From Week 12 to the day of discontinuation
Missed Week 24 visit and completed the next visit	From Week 12 to the day before next injection
Have not reached Week 24 visit yet	From Week 12 to the cut-off date of this interim

In addition, the number of doses per patient that are correctly administered per protocol, and number of missed doses will be presented. A partial dose will be considered as if 100% of the dose of the assigned treatment has been administered.

Table 2-14 Treatment exposures evaluated in relevant study periods

Treatment	Study period
ligelizumab 72/120 mg q4w (LIVI)	Up to Week 12
ligelizumab 120 mg q4w (PFS, administered by site-staff/self/caregiver in clinic)	Week 12 – Week 24
ligelizumab 120 mg q4w (PFS, administered by site-staff/self/caregiver in clinic or outside of clinic)	Week 24 onwards (up to data cut off)
ligelizumab (any ligelizumab treatment)	entire study (up to data cut off)

2.13.2.4 Efficacy analyses at interim analysis: variables and type of analysis

No inferential statistical methods are planned for this interim analysis. Descriptive statistics will be used to summarize the following efficacy endpoints in the subpopulations defined in Section 2.13.2.1 at baseline, Week 4, 8, 12, 16, 20, 24, 28, 32, 36, 42, 44, 48, and 52:

- Change from extension study baseline and 95% confidence intervals in UAS7/ISS7/HSS7 score, based on the observed data.
- Number and proportion of participants who achieve UAS7=0/UAS7≤6/HSS7=0/ISS7=0 response, based on the observed data.
- [redacted]

Separate tables will be provide for LIVI (baseline, Week 4, 8, 12) and PFS (Week 12 onwards).

2.13.2.5 Safety analyses at interim analysis: variables and type of analysis

To assess the safety and tolerability of ligelizumab, adverse events (AEs) will be summarized in the safety set.

2.13.2.5.1 General information

Only treatment emergent adverse events (TEAEs) will be considered. All TEAEs reported will coded using MedDRA terminology and summarized by primary System Organ Class (SOC) and Preferred Term (PT) in the overall population and the subpopulations defined in Section 2.13.2.1.

Non-treatment emergent AEs by study period (including observation period 1) will only be listed and not further summarized.

TEAEs will be summarized by actual received treatment, in relevant treatment periods (see Table 2-15) for each subpopulation defined in Section 2.13.2.1.

TEAEs are defined as:

- Events starting after the first dose of study treatment (ligelizumab) in the extension study and within 16 weeks of last dose of study treatment
- Events present prior to the first dose of study treatment (ligelizumab) in the extension study but:
    - increase in severity based on preferred term (e.g. worsening of headache),
    - same PT but increased severity (e.g. from mild to moderate),
    - same PT but increase in seriousness (from non-serious AE to SAE; if already a SAE from medically significant to life-threatening/fatal)

Within a specific treatment period, a subject with multiple AEs within a primary system organ class will be counted only once for the primary SOC, with the greatest severity at the system organ class level displayed.

The following Treatment emergent AEs of special interest (TEAESIs) defined in the compound-level electronic Case Retrieval Strategy (eCRS) will be presented up to SMQ level 5. The search criteria in the latest eCRS and the corresponding MedDRA version at the database lock will be used for reporting:

- Hypersensitivity reactions (including anaphylaxis)
- Injection site reactions
- Serum sickness

For AESIs with adjudication, separate listing(s) will be provided based on the adjudicated results.

2.13.2.5.2 Crude and Exposure-Adjusted Incidence Rate

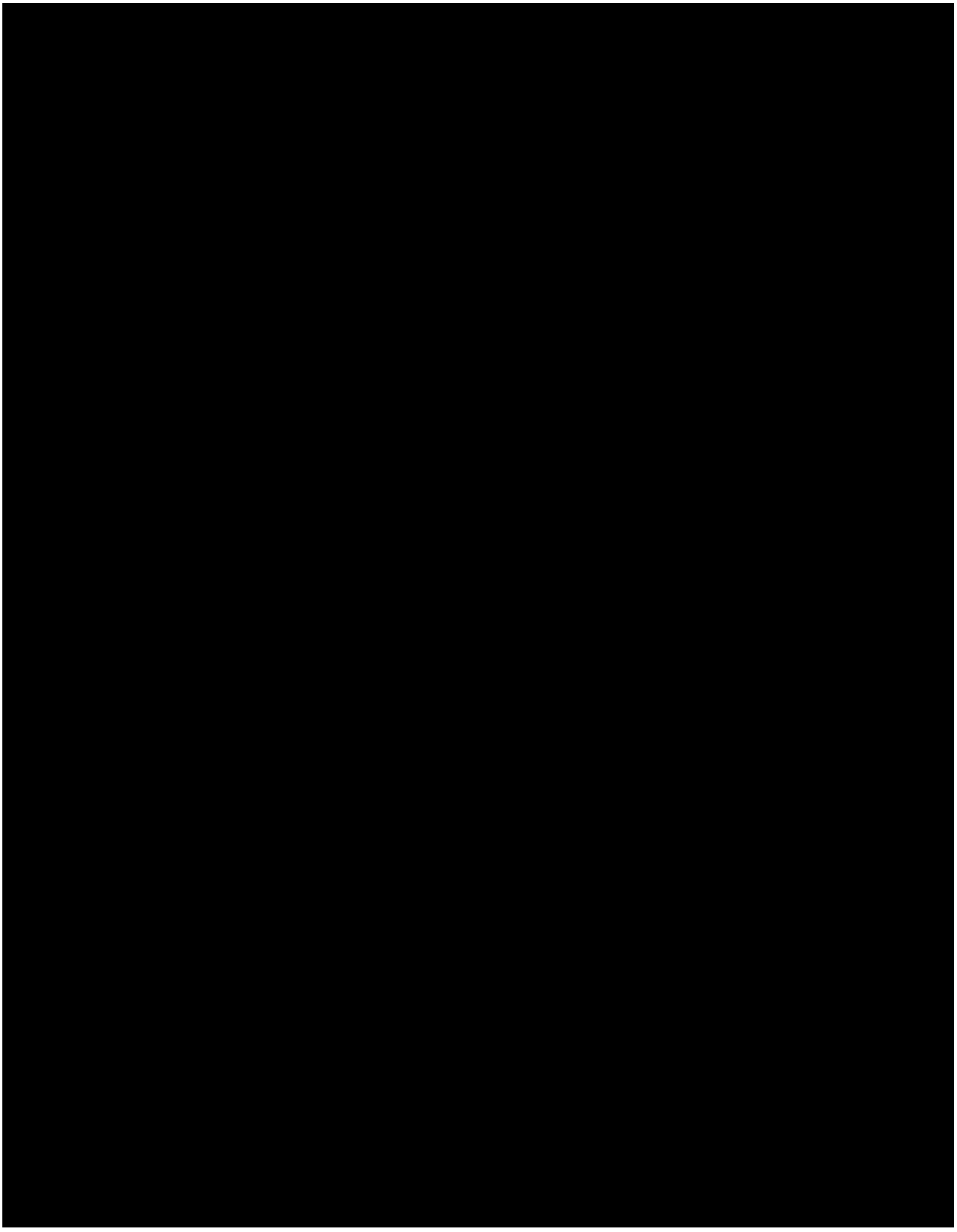
The crude incidence rate and EAIR are defined in Section 2.8.1.2, with formula $EAIR = n / \Sigma t_i$, where n is the number of subjects having the i^{th} type event in the corresponding study period (defined in Table 2-14), and t_i is a subject's exposure time until having an i^{th} type event. For TEAE possibly related to study treatment, n is the number of subjects having the i^{th} type event possibly related to study treatment in the corresponding study period (defined in Table 2-14), and t_i is a subject's exposure time until having an i^{th} type event possibly related to study treatment. As described in Table 2-15, the exposure-adjusted incidence rate (EAIR) will be provided for the safety analysis in certain study periods in addition to the crude rate.

In this interim analysis, whenever applicable, exposure adjusted incidence rates will be provided for the type as below:

1. TEAE: Primary SOC level and preferred term level
2. Treatment emergent AE of special interest: up to SMQ level 5

2.13.2.5.3 AE summaries

Table 2-15 in Section 2.13.2.8 lists the summaries tables and listings that will be provided for TEAE, treatment emergent SAE, treatment emergent AESI in the study periods defined in Table 2-14.



2.13.2.8 Overview of unplanned interim analysis

Table 2-15 Overview of unplanned interim analysis

Population/ Analysis /Study Period	Endpoints
Analysis: Efficacy Population: SAF Outside-of-clinic self-administration subpopulation Self-administration subpopulation In-clinic staff-administration subpopulation Study period: TRT1	• Proportion of subjects with well-controlled urticaria (UAS7≤ 6) by visit • The proportion of subjects with completely controlled disease (UAS7 = 0) by visit • The proportion of subjects with ISS7 = 0 by visit • The proportion of subjects with HSS7 = 0 by visit • Absolute change from extension study baseline in the UAS7 and its components (ISS7 and HSS7) by visit [redacted]
Analysis: Safety Population: SAF Outside-of-clinic self-administration subpopulation Self-administration subpopulation In-clinic staff-administration subpopulation Study period: Week 0—12 in TRT1 Week 12—24 in TRT1 Week 24 onwards up to interim data cut off Entire study up to interim data cut off	The crude incidence and exposure adjusted incidence will be provided for: • TEAE • Study treatment related TEAE • TESAE • TEAESI • TEAEs leading to discontinuation Other: • Listing of TEAEs leading to drug interruption • Crude incidence of TEAE by severity • Listing of adjudicated AE

2.14 Final analysis

Due to the early termination of study CQGE031C2302E1, a final analysis of all data collected up to last study visit will be performed when all subjects have completed the last study visit. Scope of the final analysis is described and summarized in Table 2-16. The outputs shell will be provided in CSR outputs TFL shells.

2.14.1 Final analysis sets

The enrolled set (ENR), the full analysis set (FAS), and the safety analysis set (SAF) as defined in Section 2.2, will be used for this final analysis. The following subpopulations will be considered in the safety and efficacy analyses for this final analysis:

- **Ligelizumab retreatment subpopulation** (as defined in Section 2.2.2): subjects in SAF who are treated with same dosage of ligelizumab in the extension study as in the core studies (C2302 and C2303).
- **Ligelizumab responder retreatment subpopulation** (as defined in Section 2.2.2): subjects in SAF who are treated with same dosage of ligelizumab in the extension study as in the core studies (C2302 and C2303) and achieved UAS7 $\leq$ 6 at week 12 in the core studies.

- **Long term treatment subpopulation** (as defined in Section 2.2.2)**:** subjects in SAF who receive ligelizumab treatment in the second half of treatment period without entering the second observation period. Due to study early termination, the definition of "continuous long term treatment subpopulation" will not be used for the final analysis.
- **Long term treatment with a rest subpopulation** (as defined in Section 2.2.2): subjects in SAF who received one-year ligelizumab treatment and moved to the second observation period before moving to the second half of the treatment period.
- **Self-administration subpopulation** (as defined in Section 2.13.2.1): subjects who have at least one injection with PFS administered by the participant herself/himself or a caregiver either in clinic or outside of clinic.

2.14.2 Patient disposition, demographics, and other baseline characteristics

In the final analysis, patient disposition, demographics, medical history and other baseline data including disease characteristics will be analyzed as described in Section 2.3.

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

In the final analysis, treatment exposure, and prior and concomitant therapies will be analyzed as described in Section 2.4.

2.14.4 Efficacy analyses at final analysis

Primary and some of the key secondary endpoints will be analyzed at the final analysis, as described in Section 2.5 and Section 2.6. [redacted]

2.14.5 Safety analyses at final analysis

In the final analysis, analyses for AEs will be conducted as described in Section 2.8.1 and 2.8.2.

Laboratory data will be analyzed as described in Section 2.8.4. Lab assessments will be summarized by visit for TRT1 for SAF. For the long term treatment subpopulation, summaries of clinical notable lab abnormality will be provided for TRT1+TRT2. For the long term treatment with a rest subpopulation, summaries of clinical notable lab abnormality will be provided for TRT1+OBS2+TRT2+FU.

ECG and cardiac imaging data will be analyzed as described in Section 2.8.5.1.

Vital signs will be analyzed as described in Section 2.8.5.2. Vital signs will be summarized by visit for TRT1 for SAF. For the long term treatment subpopulation and the long term treatment with a rest subpopulation, newly occurring or worsening vital signs outside notable ranges for the following parameters will be summarized for TRT1+TRT2, and TRT1+OBS2+TRT2+FU, respectively.

- Hypertension (systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg).
- Hypotension (systolic blood pressure of < 90 mmHg and/or diastolic blood pressure of < 60 mmHg).
- Bradycardia (pulse rate below 60 bpm).
- Tachycardi (pulse rate above 100 bpm).

[redacted]

2.14.7 Biomarkers

In the final analysis, biomarkers analyses will be conducted as described in Section 2.11.

2.14.8 Handling of missing values/censoring/discontinuations

The missing data handling and imputation rules as described in Section 2.5.3 and Section 2.6.3 will be applied on the primary and some key secondary endpoints, respectively. All the other analyses in the final analysis will be based on the observed data.

Table 2-16 Overview of final analysis

Population/ Analysis /Study Period	Endpoints
First treatment period (TRT1)	
Analysis: Efficacy Populations: 1) FAS 2) Ligelizumab retreatment subpopulation 3) Ligelizumab responder retreatment subpopulation Period/time point: TRT1/up to week 52	• Proportion of subjects with well-controlled urticaria (UAS7≤ 6) at Week 12

Analysis: Efficacy Populations: 1) FAS 2) Ligelizumab retreatment subpopulation Period/time point: TRT1/up to week 52	• Proportion of subjects with completely controlled disease (UAS7 = 0) at Week 12
Analysis: Efficacy Populations: 1) FAS 2) Ligelizumab retreatment subpopulation Period/time point: TRT1/up to week 52	• Absolute and percent change from extension study baseline in the UAS7 and its components (ISS7 and HSS7) at Week 12 • Percentage of subjects achieving DLQI = 0-1 at Week 12
Analysis: Efficacy Populations: 1) FAS 2) Ligelizumab retreatment subpopulation Period/time point: TRT1A/up to week 12	• Cumulative number of weeks that subjects achieve weekly angioedema activity score (AAS7) = 0 between extension study baseline and Week 12
Analysis: Efficacy Population: Self-administration subpopulation Period/time point: 12 weeks after starting self-administration in TRT1	• The proportion of subjects with well-controlled disease (UAS7 ≤ 6), 12 weeks after starting self-administration
[redacted]	

Analysis: Safety Population: SAF Period: TRT1A; TRT1B	• TEAE, TESAE, TEAESI (crude incidence and EAIR) • TEAEs leading to discontinuation, death, (crude incidence and EAIR) • TEAE by severity (crude incidence) • Summary of vital signs, by visit • Summary of lab assessments, by visit
Entire treatment period (TRT1 + TRT2)	
[redacted]	
Analysis: Safety Population: 1) Long term treatment subpopulation Period: TRT1A; TRT1B; TRT2; TRT1+TRT2	• TEAE, TESAE (crude incidence and EAIR), TEAESI (crude incidence and EAIR) • TEAEs leading to discontinuation (crude incidence and EAIR) • Summary of clinical notable lab abnormality (only TRT1+TRT2) • Summary of newly occurring or worsening vital signs (hypertension, hypotension, bradycardia, tachycardia; only TRT1+TRT2)
Analysis: Safety Population: 1) Long term treatment with a rest subpopulation Period: TRT1A; TRT1B; TRT2	• TEAE, TESAE (crude incidence and EAIR) • TEAEs leading to discontinuation (crude incidence and EAIR) • AESI of CCV and malignancy (crude incidence and EAIR; only TRT1+OBS2+TRT2+FU) • Summary of clinical notable lab abnormality (only TRT1+OBS2+TRT2+FU)

	• Summary of newly occurring or worsening vital signs (hypertension, hypotension, bradycardia, tachycardia; only TRT1+OBS2+TRT2+FU)
Entire study period (for the legal requirements of ClinicalTrials.gov and EudraCT)	
Analysis: Safety Population: SAF Period: Entire study	• TEAE which are not serious adverse events with an incidence greater than 5% • TESAE and SAE suspected to be related to study treatment

3 Sample size calculation

3.1 Primary endpoint(s)

The total number of subjects enrolled will be determined by the drop-out rate prior to the Phase 3 extension study from studies CQGE031C2302, CQGE031C2303, CQGE031C2202 and CQGE031C1301.

Based on interim results from CQGE031C2201, it is assumed that the proportion of subjects achieving UAS7 ≤ 6 at Week 12 is around 55% for ligelizumab 72 mg q4w. It is assumed that the well-controlled response for ligelizumab 120 mg q4w will be similar. The corresponding 95% confidence interval is listed based on different assumptions of number of subjects who will be enrolled for each treatment arm.

Table 3-1 95% confidence interval based on number of subjects enrolled from the core studies (CQGE031C2302/2303)

Number of subjects enrolled	Number of subjects for each treatment group	Drop out rate at Week 12	Assumed proportion of subjects achieving UAS7 ≤ 6 at Week 12	Corresponding 95% confidence interval
500	250	10%	55%	(48.6% - 61.6%)
900	450	10%	55%	(50.2% - 59.9%)
1200	600	10%	55%	(50.8% - 59.2%)

To evaluate the retreatment efficacy in the subgroup of subjects who achieved UAS7 ≤ 6 at Week 12 after the retreatment on the same ligelizumab dose, the 95% confidence interval of the

response rate will be provided for each treatment group. It is assumed that 50% of subjects enrolled into this extension study were well-controlled responders during the core studies for each ligelizumab treatment group. A 15% drop out rate is assumed for each treatment group before Week 12. The number of subjects required at the baseline of re-treatment for each treatment arm is listed in Table 3-2 below, based on different assumptions of the retreatment response rates and the corresponding precision levels (width of the 95% confidence interval).

Table 3-2 Number of subjects required at the baseline of re-treatment for each treatment arm enrolled from the core studies (CQGE031C2302/2303)

	Precision		
Response rate after retreatment	10%	12%	15%
70%	191	135	85
80%	146	102	66
90%	83	59	38

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Patient-reported outcomes

All PRO endpoints will be summarized using FAS.

5.1.1 Urticaria Patient Daily Diary (UPDD)

Urticaria Patient Daily Diary (UPDD) includes UAS which assesses twice daily the severity of itch and number of hives, and once-daily the use of rescue medication, sleep and activity interference, angioedema occurrence and its management and records the calls to a health care practitioner (refer to Appendix 4 of the protocol, Patient Diary - Urticaria Patient Daily Diary (UPDD)). The components are presented in Table 5-1 and the relevant weekly scores are described in the following sections.

Table 5-1 Urticaria Patient Daily Diary (UPDD)

Diary component	When assessed
Urticaria Activity Score (UAS)	Morning & evening
• Itch severity	
• Number of hives	
Sleep interference	Morning
Daily activity interference	Evening

Diary component	When assessed
Rescue medication use	Evening
Angioedema	Evening
• Whether patient had an episode	
• If patient had an episode, how did they manage it	
Contact health care provider	Evening

5.1.1.1 Weekly Hives Severity Score (HSS7)

The HSS, defined by number of hives (wheals), will be recorded by the subject twice daily in their eDiary, on a scale of 0 (none) to 3 (see Table 5-2). A weekly score (HSS7) is derived by adding up the average daily scores of the 7 preceding days. The possible range of the weekly score is therefore 0 – 21.

Complete hives response is defined as HSS7 = 0.

Table 5-2 Hives Severity Score (HSS)

Score	Hives (Wheals) (every 12 hours)
0	None
1	1-6 hives/12 hours
2	7-12/12 hours
3	> 12 hives/12 hours

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 1 or more of the daily scores are missing, the following principles will be applied to handle the missing data:

The HSS7 score will be derived based on the sum of the available eDiary score during that week. It will be considered calculable with at least 4 daily scores provided in that week, otherwise, the weekly score will be left missing.

5.1.1.2 Weekly Itch Severity Score (ISS7)

The severity of the itch will be recorded by the subject twice daily in their eDiary, on a scale of 0 (none) to 3 (intense/severe) (see Table 5-3) A weekly score (ISS7) is derived by adding up the average daily scores of the 7 preceding days. The possible range of the weekly score is therefore 0-21 (maximum itch). Partially missing diary entries will be handled in the same way as described for the HSS7.

Complete itch response is defined as ISS7 = 0.

Table 5-3 Itch Severity Score (ISS)

Score	Pruritus (Itch) (every 12 hours)
0	None

Score	Pruritus (Itch) (every 12 hours)
1	Mild (minimal awareness, easily tolerated)
2	Moderate (definite awareness, bothersome but tolerable)
3	Severe (difficult to tolerate)

5.1.1.3 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 (highest activity).

5.1.1.4 Weekly Sleep interference score

Sleep interference will be assessed by the subject, once daily in the morning in the eDiary. It is scored on a scale from 0 to 3 (see Table 5-4). The weekly sleep interference score ranges from 0 to 21 (Table 5-4).

Table 5-4 Sleep interference score

Score	Sleep interference
0	No interference
1	Mild, little interference with sleep
2	Moderate, awoke occasionally, some interference with sleep
3	Substantial, woke up often, severe interference with sleep

5.1.1.5 Weekly Activity interference score

Activity interference will be assessed by the subjects on a scale of 0 to 3 (Table 5-5), once daily in the evening in the eDiary. Daily activities could include, school, sports, hobbies and activities with friends and family. The weekly activity interference score ranges from 0-21 (Table 5-5).

Table 5-5 Activity interference score

Score	Activity interference
0	No interference
1	Mild, little interference with daily activities
2	Moderate, some interference with daily activities
3	Substantial, severe interference with daily activities

5.1.1.6 H1-AH rescue medication use

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 subject. The dose per day of rescue medication will be calculated as the daily number of tablets times the dose of each tablet and then the dose per week of rescue medication will be calculated as the sum of the dose per day, over 7 days.

5.1.1.7 Angioedema occurrence

Angioedema occurrence is recorded once daily in the evening in the eDiary by the subject. Angioedema will be reported as number of days with angioedema. Actions and/or treatments related to those angioedema occurrences will be also recorded in the eDiary (Table 5-6).

Table 5-6 Actions/treatments for Angioedema

Actions/treatments
Did nothing
Took some prescription or non-prescription medication
Called my doctor, nurse or nurse practitioner
Went to see my doctor, nurse or nurse practitioner
Went to the emergency room at the hospital
Was hospitalized

5.1.1.8 Number of calls to doctor or nurse

The number of calls to doctor, nurse or nurse practitioner because of the subject's skin condition will be recorded once daily in the eDiary by the subject.

5.1.2 Dermatology Life Quality Index (DLQI/CDLQI)

The data will be analyzed separately for adults (for DLQI) and adolescents (for CDLQI).

The Dermatology Life Quality Index (DLQI) is a 10-item dermatology-specific health-related quality of life instrument measures functional disability of subjects with dermatological disorders that are greater than 18 years of age.

The instrument contains six functional scales and 10 items. Each item (question) will be answered with the following response: "not at all," "a little," "a lot," or "very much". Seven scores will be derived from the DLQI: the total score of each of the six dimensions as well as the total score over all items.

For DLQI, the domain scores are calculated for:

Symptoms and Feelings (0-6), Daily Activities (0-6), Leisure (0-6), Work and School (0-3), Personal Relationships (0-6) and Treatment (0-3) (see detail definitions in Table 5-7).

Table 5-7 DLQI domains

Domain	Relevant Question	Maximum score
Symptoms and feelings	Questions 1 and 2	6
Daily activities	Questions 3 and 4	6
Leisure	Questions 5 and 6	6
Work and school	Question 7	3
Personal relationships	Questions 8 and 9	6
Treatment	Question 10	3

For CDLQI, the domain scores are calculated for: Symptoms and Feelings (0-6), Leisure (0-9), School and holidays (0-3), Personal Relationships (0-6), Sleep (0-3) and Treatment (0-3) (see detail definitions in Table 5-8).

Table 5-8 CDLQI domains

Domain	Relevant Question	Maximum score
Symptoms and feelings	Questions 1 and 2	6
Leisure	Questions 4, 5 and 6	9
School or holidays	Questions 7	3
Personal relationships	Question 3 and 8	6
Sleep	Questions 9	3
Treatment	Question 10	3

The DLQI/CDLQI total score will be calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired.

There was a very high success rate of accurate completion of the DLQI. However, if responses were incomplete, the following rules were applied:

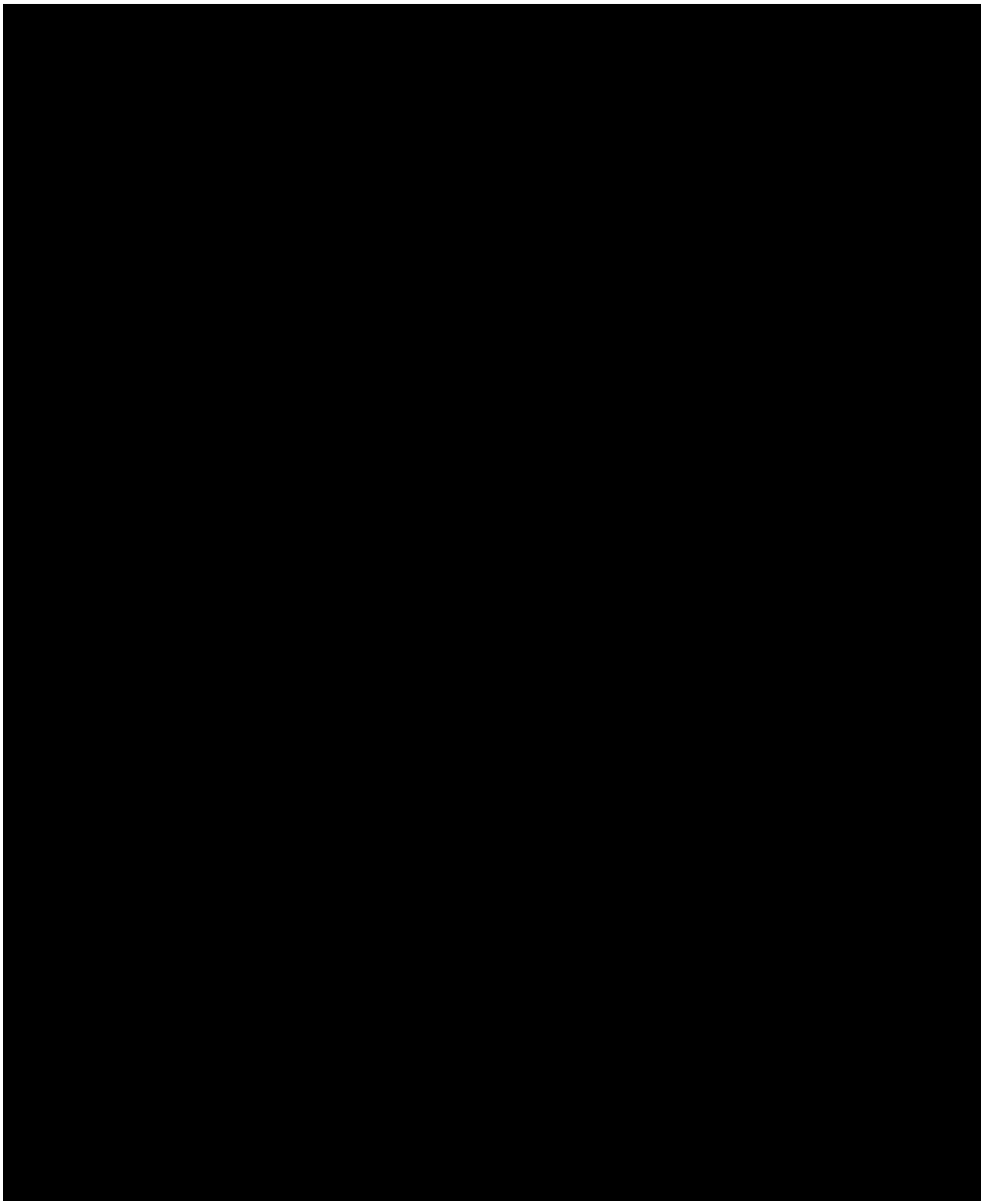
4. If one question was left unanswered, then the missing value was imputed to a 0 score and the overall DLQI/CDLQI score was summed up in the usual way out of 30.
5. If two or more questions were left unanswered, then the questionnaire was not scored (left to missing).
6. If question no. 7 was answered ‘yes’, then it was scored to a value of ‘3’. If question no. 7 was answered ‘not relevant’ then the score was 0. If question was answered ‘no’ (not being preventing to work or study) but the skin was a problem for working or studying then the scores per possible response were either ‘a lot’ (2) or ‘a little’ (1) or not at all (0).

5.1.3 Angioedema Activity Score (AAS)

The AAS consists of 5 questions and an opening question. A score between 0 and 3 is assigned to every answer field. The question scores are summed up to an AAS day sum score, 7 AAS day sum scores to an AAS week sum score (AAS7). Accordingly, the minimum and maximum possible AAS scores are 0 and 15 (AAS day sum score) and so AAS7 ranges from 0 to 105.

5.1.4 Rescue medication use

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 dose of rescue medication will be calculated as the sum of the dose per day, over 7 days. If rescue medication use was not recorded on one or more days over the week, then the total weekly dose will be missing.



5.2 Imputation rules

5.2.1 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 00:00:00.

5.2.2 AE date imputation

Rules for imputing the AE end date:

- If the AE end date month is missing, then the imputed end date should be set to the earliest of the study end date, 31DECYYYY or date of death.
- If the AE end date day is missing, then the imputed end date should be set to the earliest of the study end date, last day of the month or date of death.
- If AE year is missing or AE is ongoing, then 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. Otherwise, AE start reference date = treatment start date.

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, then the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if AE month is not missing, then 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. If the AE month is missing, then 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.

5.2.3 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, then no numeric end date is derived.

- For partial missing CM end date:
  a) If CM end day is missing and CM month/year are non-missing, then impute CM date as the earlier of (study end date, the last day of the month).
  b) If CM end month is missing and CM year is non-missing, then impute CM date as the earlier of (study end date, 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	**(2.a))** Uncertain	**(2.a))** Uncertain	**(2.a))** Uncertain	**(2.a))** 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	**(33.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.

5.2.3.1 Prior therapies date imputation

All therapies on the Prior urticaria therapy CRF page will be considered as prior. No additional imputation will be performed.

5.2.3.2 Post therapies date imputation

Not applicable

5.2.3.3 Other imputations

Not applicable

5.3 AEs coding/grading

Not applicable

5.4 Laboratory parameters derivations

Clinically notable criteria

The following notable criteria will be used in the study:

Table 5-10 Clinically notable criteria

Variable	Notable criterion
Creatinine (umol/L), Plasma/Serum	>ULN – 1.5 x ULN >1.5 - 3.0 x ULN; >1.5 - 3.0 x baseline >3.0 - 6.0 x ULN; >3.0 x baseline

Blood urea nitrogen* (mmol/L)	1.25 – 2.5 x ULN >2.5 – 5.0 x ULN >5.0 – 10.0 x ULN >10.0 x ULN	
Albumin (g/L)	<LLN - 30 g/L <30 - 20 g/L <20 g/L	
Alanine aminotransferase, ALT (U/L)	Normal baseline >ULN - 3.0 x ULN >3.0 – 5.0 x ULN >5.0 – 20.0 x ULN >20.0 x ULN	Baseline abnormal 1.5 – 3.0 x baseline >3.0 – 5.0 x baseline >5.0 – 20.0 x baseline >20.0 x baseline
Aspartate aminotransferase, AST (U/L)	Normal baseline >ULN - 3.0 x ULN >3.0 – 5.0 x ULN >5.0 – 20.0 x ULN >20.0 x ULN	Baseline abnormal 1.5 – 3.0 x baseline >3.0 – 5.0 x baseline >5.0 – 20.0 x baseline >20.0 x baseline
Alkaline phosphatase, ALP (U/L)	Normal baseline >ULN – 2.5 x ULN >2.5 – 5.0 x ULN >5.0 – 20.0 x ULN >20.0 x ULN	Baseline abnormal 2.0 – 2.5 x baseline >2.5 – 5.0 x baseline >5.0 – 20.0 x baseline >20.0 x baseline
Gamma glutamyl transferase, GGT (U/L)	Normal baseline >ULN – 2.5 x ULN >2.5 – 5.0 x ULN >5.0 – 20.0 x ULN >20.0 x ULN	Baseline abnormal 2.0 – 2.5 x baseline >2.5 – 5.0 x baseline >5.0 – 20.0 x baseline >20.0 x baseline
Bilirubin (umol/L)	Normal baseline >ULN – 1.5 x ULN >1.5 – 3.0 x ULN >3.0 – 10.0 x ULN >10.0 x ULN	Baseline abnormal >1.0 – 1.5 x baseline >1.5 – 3.0 x baseline >3.0 – 10.0 x baseline >10.0 x baseline
Platelets (10E9/L), Blood	<LLN # to 75 x10E9/L <75 - 50 x10E9/L < 50- 25 x10E9/L < 25 x10E9/L	
Leukocytes, WBC (10E9/L)	<LLN - 3.0 x 10E9/L <3.0 - 2.0 x 10E9/L <2.0 - 1.0 x 10E9/L <1.0 x 10E9/L	
	>100 x 10E9/L (leukocytosis, grade 3)	

Hemoglobin (g/L)	<LLN - 100 g/L <100 - 80g/L <80 g/L
Lymphocytes (10E9/L)	<LLN - 0.8 x 10E9/L <0.8 - 0.5 x 10E9/L <0.5 - 0.2 x 10E9/L <0.2 x 10E9/L
	>4.0 - 20 x 10E9/L (grade 2 lymphocytosis) >20 x 10E9/L (grade 3 lymphocytosis)
Neutrophils (10E9/L)	<LLN - 1.5 x10E9/L <1.5 - 1.0 x 10E9/L <1.0 - 0.5 x 10E9/L <0.5 x 10E9/L
# LLN = 140 x10E9/L * No CTCAE grades provided for BUN. Values derived from Division of Microbiology and Infectious Diseases (DMID) grading system When the parameters have different criteria for different baseline status (e.g., ATL, AST), the patients with normal baseline will follow the criteria on the left side, and the patients with abnormal baseline will follow the criteria on the right side.	

Liver-enzyme abnormalities

Table 5-11 Liver- enzyme abnormalities

Parameter	Notable criterion
ALT	>3xULN; >5xULN; >10xULN; >20xULN
ALT or AST	>3xULN; >5xULN; >8 xULN;>10xULN; >20xULN
(ALT or AST) & TBL	>3xULN & (TBL >1.5xULN; >2xULN)
(ALT or AST) & INR	>3xULN & INR>1.5
TBL	1 xULN; 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)

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

5.5 Statistical models and SAS sample code

5.5.1 Primary analysis

The primary analysis will be performed based on the data after the missing data imputation for the intercurrent events has been performed.

Step 1:

The SAS procedure proc mi will be used for multiple imputation for change from baseline in UAS7 score with the following sample code:

```
proc mi data=... out=... nimpute=... seed=123;
by group;
class ige cuind group;
fcs reg(/details);
var ige cuind group baseline wk12cfb;
run;
```

where group = treatment group
ige = baseline IgE
cuind = baseline CU index
baseline = baseline UAS7 score
wk12cfb = change from baseline UAS7 score at Week 12 in TRT1.

If the imputation model does not converge, remove the covariates as needed until it converges.

The following SAS sample code will be used to transfer the continuous variable change from baseline in UAS7 score to a binary response of UAS7 $\leq$ 6, and conduct non-responder imputation for subjects who discontinued due to study early termination:

```
data ...;
set ...;
resp = (baseline + wk12cfb) <= 6;
if flag = 0 then resp = 0;
run;
```

where resp = binary response of UAS7≤6
baseline = baseline UAS7 score
wk12cfb = change from baseline UAS7 score at Week 12 in TRT1
flag = flag of missingness
(1 = missing due to study early termination, 0 = missing not due to study early termination, . = data is observed).

Note that the order of multiple imputation and non-responder imputation could be reversed as needed.

Step 2:

The SAS procedure proc freq will be performed to calculate the primary endpoint (binary response of UAS7 $\leq$ 6 at Week 12) for each imputed dataset with the following sample code:

```
proc freq data = ...;
by _imputation_ group;
tables resp /nopercent nocol norow nocum binomial(level = "1" cl =
wilson(correct));
output out = sumstat binomial;
run;
```

where _imputation_ = the index for imputation times

group = treatment group
resp = binary response of UAS7≤6
sumstat is the dataset which includes the response rate estimate and the standard error in each group

Here "cl = wilson(correct)" is used to calculate the 95% confidence intervals by Wilson score method with continuity correction.

Step 3:

Rubin's Rule:

Rubin's Rule will be applied to combine the multiple sets of estimates to produce the overall estimates, standard error, confidence interval and p-values.

The SAS procedure proc mianalyze will be used for this analysis with the following code:

```
ods output ParameterEstimates = pe_comb VarianceInfo = var_comb;
proc mianalyze data = sumstat;
by group;
ModelEffects _BIN_;
stderr E_BIN;
run;
```

where pe_comb includes the estimates results, and var_comb includes the variance information.

If the datasets between imputations are identical after multiple imputation step, which will cause the SAS procedure proc mianalyze not runnable, the dataset with _imputation_=1 will be used to create the results.

95% confidence limits by Wilson score method with continuity correction:

For primary analysis, 95% confidence limits will be calculated by Wilson score method with continuity correction using the following formula:

$$\frac{\left(2\bar{Q}_m+\frac{1}{n}+\frac{t^2}{n}+\frac{t^2 r_m}{n}\right)}{2\left(1+\frac{t^2}{n}+\frac{t^2 r_m}{n}\right)} \pm \sqrt{\frac{\left(2\bar{Q}_m+\frac{1}{n}+\frac{t^2}{n}+\frac{t^2 r_m}{n}\right)^2}{4\left(1+\frac{t^2}{n}+\frac{t^2 r_m}{n}\right)^2} - \frac{\left(\bar{Q}_m{}^2+\frac{1}{4n^2}+\frac{\bar{Q}_m}{n}\right)}{\left(1+\frac{t^2}{n}+\frac{t^2 r_m}{n}\right)}}$$

where
$\bar{Q}_m$ is "Estimate" in pe_comb;
$r_m = \left(1+\frac{1}{m}\right) B_m/\bar{U}_m$;
B_m and $\bar{U}_m$ are "BetVar" and "WinVar" in var_comb, respectively;
n is the subgroup sample size;
t is the 95% quantile of t_v-distribution, with $v = (m-1)(1+1/r_m)^2$ degrees of freedom;
m is the number of imputed datasets.

5.5.2 Key secondary analysis

5.5.2.1 Secondary analysis for continuous endpoints

For continuous endpoints of change from extension study baseline in UAS7/HSS7/ISS7 score at Week 12, the secondary analysis will be performed based on the data after the missing data imputation for the intercurrent events have been performed.

The SAS procedure proc mi will be used for multiple imputation. Sample code refer to Section 5.5.1.

The SAS procedure proc means will be used to calculate the group means for each imputed dataset with the following sample code:

```
proc means data = ...;
by _imputation_ group notsorted;
var wk12cfb;
Output out = sumstat mean = meancfb std = stdcfb;
run;
```

where _imputation_ = the index for imputation times
group = treatment group
wk12cfb = change from baseline UAS7/HSS7/ISS7 score at Week 12 in TRT1
sumstat is the dataset which includes the mean estimate (meancfb) and the standard error (stdcfb) in each group.

The SAS procedure proc mianalyze will be used to combine the parameter estimates across imputed datasets with the following sample code:

```
ods output ParameterEstimates = pe_comb;
proc mianalyze data = sumstat;
by group;
ModelEffects meancfb;
stderr stdcfb;
run;
```

5.5.2.2 Secondary analysis for binary endpoints

For binary endpoints of UAS7=0/DLQI 0-1 at Week 12, the secondary analysis will be performed based on the data after the missing data imputation for the intercurrent events has been performed.

The SAS procedure proc mi will be used for multiple imputation with the following sample code:

```
proc mi data=... out=... nimpute=... seed=123;
by group;cuin
class ige cuind group week12;
fcs logistic (week12 = ige cuind group baseline / details);
var ige cuind group baseline week12;
run;
```

where group = treatment group
ige = baseline IgE

cuind = baseline CU index
baseline = baseline UAS7 score
week12 = binary response of UAS7=0/DLQI 0-1 at Week 12 in TRT1.

If the imputation model does not converge, remove the covariates as needed until it converges.

The SAS procedure proc freq, and proc mianalyze will be used for the analysis. Sample code refer to Section 5.5.1. Wilson score method is not necessary for 95% confidence limits calculation in secondary analysis. Other methods could be performed as needed.

5.5.2.3 Secondary analysis for count endpoint

For count endpoint of cumulative weeks with AAS7=0 up to Week 12, the secondary analysis will be performed based on the data after the missing data imputation for the intercurrent events have been performed.

The SAS procedure proc mi will be used for multiple imputation with the following sample code:

```
proc mi data=... out=... nimpute=... seed=123;
by group;cuin
class ige cuind group week1-week12;
fcs logistic (week1-week12 = ige cuind group baseline / details);
var ige cuind group baseline week1-week12;
run;
```

where group = treatment group
ige = baseline IgE
cuind = baseline CU index
baseline = baseline UAS7 score
week1-week12 = binary response of AAS7=0 at Week 1-12 in TRT1.

If the imputation model does not converge, remove the covariates as needed until it converges.

The SAS procedure proc genmod will be used to calculate the group means for each imputed dataset with the following sample code:

```
ods output LSMeans = sumstat;
proc genmode data = ... order = internal;
by _imputation_;
class group / param = glm;
model cum = group / noint dist = negbin link = log;
lsmeans group / cl ilink e;
run;
```

where _imputation_ = the index for imputation times
group = treatment group
cum = the cumulative weeks of AAS7=0 up to week 12
sumstat is the dataset which includes the mean estimate and the standard error in each group.

The SAS procedure proc mianalyze will be used to combine the parameter estimates across imputed datasets with the following sample code:

```
ods output ParameterEstimates = pe_comb;
proc mianalyze data = sumstat;
by group;
ModelEffects Mu;
stderr StdErrMu;
run;
```

5.6 Rule of exclusion criteria of analysis sets

No PD will be used for excluding from any analysis set.

Table 5-12 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
ENR	NA	NA
FAS	NA	No study drug taken in the extension study
SAF	NA	No study drug taken in the extension study
[redacted]	[redacted]	[redacted]

6 Reference

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