NOVARTIS

Clinical Development

QGE031 / Ligelizumab

CQGE031C1301 / NCT03907878

A multi-center, open-label study to investigate the safety/tolerability and efficacy of ligelizumab (QGE031) in the treatment of adult Japanese patients with Chronic Spontaneous Urticaria (CSU) inadequately controlled with H1 antihistamines

Statistical Analysis Plan (SAP)

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Document type:	SAP Documentation
Document status:	Amendment 1
Release date:	22-Feb-2022
Number of pages:	38

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
09Apr2019	Prior to FPFV	Creation of final version	N/A - First version	NA
22Feb2022	Prior to DB lock	In general the SAP was amended to align with C2302 and C2303 studies	SAP Amendment 1	
		Added additional details for study day on eDiary and study week based on Rave X		2.1.1
		Added definition for some analysis sets		2.2
		Added additional details for the subgroup analysis		2.2.1
		Added section for Pre/During COVID-19 population		2.2.1.1
		Added variables for demographic and other baseline data		2.3
		Added additional details for the study treatments		2.4.1
		Added additional details for prior, concomitant and post therapies		2.4.2
		Added additional details for TEAE		2.5.2
		Added secondary endpoints to align		2.6

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		C2302 and C2303 studies		
		Added supportive analyses to mitigate impact of missing data due to device issues		2.6.4
		Exposure adjusted incidence rate calculation is added;		2.7.1.1
		Updated adverse events of special interest and added analyses for some specific adverse events (e.g. COVID-19 infection) as per C2302 and C2303 studies		2.7.1.2
		Added analyses to respond to requirements from CT.gov and EudraCT		2.7.1.3
		Added additional details for other safety items than adverse events		2.7.3 2.7.4
		[redacted]		2.7.4.3, 2.8, 2.9
		[redacted]		[redacted]
		[redacted]		[redacted]

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		Updated clinically notable or abnormalities criteria for laboratory test, vital signs, ECG, and liver-enzyme		Appendix
		Added SAS example code for efficacy analysis on MMRM		
		[redacted]		
		Additional reference papers are added.		Reference

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List of abbreviations

ADA	Anti-Drug Antibody
AE	Adverse event
ATC	Anatomical Therapeutic Classification
BMI	body mass index
CINDU	Chronic inducible urticaria
COVID-19	Corona Virus Disease 2019
CM	Concomitant Medication
CSR	Clinical Study report
CSU	Chronic Spontaneous Urticaria
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
eCRF	Electronic Case Report Form
eCRS	Case Retrieval Strategy
ENR	enrolled set
H1-AH	H1-antihistamines
[redacted]	[redacted]
IVR	Interactive Voice Response
LLN	lower limit of normal
LLOQ	Lower Level of Quantification
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	mixed-effects model repeated measures
[redacted]	[redacted]
[redacted]	[redacted]
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
SAE	serious adverse event
SAF	Safety set
SAP	Statistical Analysis Plan
SOC	System Organ Class
ULN	upper limit of normal
ULOQ	Upper Level of Quantification
UPDD	Urticaria patient daily device
[redacted]	[redacted]

1 Introduction

This document contains details of the statistical methods that will be used in the phase III clinical trial CQGE031C1301. This study is designed to provide long term safety data of Ligelizumab (QGE031) in Japanese patients with chronic Spontaneous Urticaria (CSU) for the registration of QGE031 in Japan.

Data will be analyzed according to Section 12 of the study protocol.

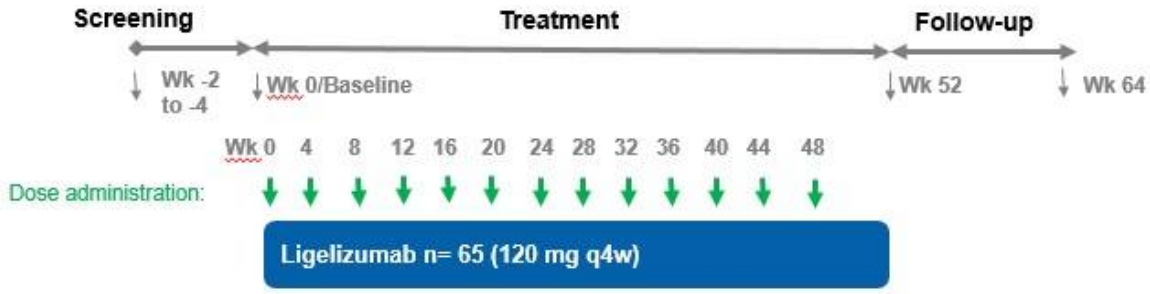
This SAP is based on the original protocol version 0.0, data 23-Oct-2018.

1.1 Study design

This is a Phase III multi-center, open-label, single arm study. The study consists of 3 distinct periods:

- Screening period (Day -28 to Day -14): Duration of up to 4 weeks in which subjects who have given informed consent are assessed for eligibility.
- Treatment period (52 weeks): The subjects will be seen in the clinic every 4 weeks.
- Post-treatment follow-up period (12 weeks): This period consists of a subject visit in the clinic every 4 weeks with the final visit (Visit 1999) occurring 16 weeks after the last treatment dose.

Figure 1-1 Study design



This study is designed to obtain safety data of QGE031 in 65 Japanese CSU patients. Details of sample size are described in Section 3 in this document.

The study population will consist of approximately 65 male and female subjects aged ≥ 18 years who have been diagnosed with CSU and who remain symptomatic despite the use of H1-AH.

It is anticipated that approximately 81 subjects will need to be screened (an estimated screening failure rate of 20%) in order to enroll approximately 65 subjects into the 52 week treatment period (see Figure 1-1).

No randomization is planned in this study.

The primary objective of this study is to investigate the safety and tolerability of ligelizumab 120 mg q4w for 12 months.

The primary variable is the number and percentage of patients who reported treatment emergent adverse events during the 64 week (treatment period+ follow-up period) study period.

No interim analysis is planned in this study.

1.2 Study objectives and endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• The primary objective of this study is to investigate the safety and tolerability of ligelizumab 120 mg q4w for 12 months	• Overall safety data, assessed as treatment emergent adverse events during the study
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**

• To evaluate the efficacy of ligelizumab 120 mg q4w by evaluation of:
  • UAS7, HSS7 and ISS7 change from baseline over time
  • Achievement of the complete UAS7 = 0, HSS7 = 0 and ISS7 = 0 response over time
  • Profile of change from baseline in the Dermatology Life Quality Index (DLQI)
  • Achievement of DLQI = 0/1 by visit up to end of study
	• Absolute change from baseline of UAS7, HSS7 and ISS7 by visit up to end of study
	• Proportion of subjects with UAS7 = 0, HSS7 = 0, and ISS7 = 0 response by visit up to the end of study
	• Absolute change from baseline of DLQI by visit up to end of study
	• Proportion of subjects with DLQI = 0/1 by visit up to end of study

[redacted]	[redacted]

2 Statistical methods

2.1 Data analysis general information

All data analysis will be performed by Novartis according to the data analysis section 12 of the study protocol using SAS version 9.4 or above.

General descriptive statistical rules to summarize quantitative or qualitative parameter are: continuous variables will be summarized using descriptive statistics (i.e. number of non-missing data, mean, median, standard deviation, 25th percentiles(Q1) and 75th percentiles(Q3), minimum, and maximum) and categorical variables will be summarized in terms of the number and percentage of patients in each category including a category for missing data if any.

The analysis will be conducted on all subject data at the time the trial ends.

2.1.1 General definitions

Study day and Study week based on eDiary

Study day is defined as the number of days since the date of first dose of study medication. The date of first dose of study medication is defined as Day 1 and the day before the first dose of study medication is defined as Day -1.

Therefore, for a particular date, study day will be calculated as follows:

- for dates on or after the first date of study medication,
  Study day = Assessment date – Date of first dose of study medication + 1;
- for dates prior to the first date of study medication,
  Study day = Assessment date – Date of first dose of study medication.

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].

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

The study weeks are defined based on the study days starting with Day 1 (see Table 2-1), which is the day the patient receives the first study treatment.

The study week defined in this section will be used for the efficacy analyses based on the eDiary.

Table 2-1 Study Week definition based on Study Day of eDiary

Study Week	Study Days
Baseline	(-7)-(-1)
1	1-7
2	8-14
x	7×(x−1)+1 - 7×x
64	442 – 448

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. No remapping visit will be provided.

Study Week based on RaveX collected visit information

For the by visit summary tables (lab results, ECGs, vital signs, PROs, [redacted] etc..) , all the information collected at the scheduled visit will be included for the analyses. Unscheduled visit information will not be included in the by visit summary descriptive statistics. The unscheduled visit information will be only included in the maximum or minimum post treatment assessment summaries.

Baseline

In general, baseline is defined as the last measurement (including unscheduled visits) prior to or on the first dose of study drug at Day 1. Refer to the baseline definitions for each analysis described in the later sections.

When change and percent change from baseline is of interest the following formula will be used for each scheduled visit and time-point where baseline and post-baseline values are both available:

Change from baseline = post-baseline value – baseline value

Percent change from baseline = (post-baseline value – baseline value) / baseline value * 100

2.2 Analysis sets

The following analysis sets will be used in this trial:

Enrolled set (ENR) will include all patients who had signed an informed consent form and had a screening visit.

Safety Set (SAF) will include all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received. Safety Set will be used for all safety analyses and also for all efficacy analyses.

[redacted]

IG analysis set will include all subjects who have had at least one immunogenicity assessment and received at least one dose of study drug.

[redacted]

[redacted]

2.2.1.1 Pre-/During COVID-19 population

Pandemic-related subpopulations are defined based on the start date of the COVID-19 pandemic. All the participants enrolled prior to the start date of the pandemic will be considered as pre-pandemic population, while the participants enrolled on or after the start date of the pandemic will be considered as during-pandemic population. The start date of the pandemic in Japan is defined as "21-Feb-2020".

Subject disposition of the pre- and during-pandemic populations will be presented to assess the impact of the COVID-19 pandemic. Differences in demographics and background characteristics of the pre- and during-pandemic populations will be provided as well.

The analyses for the above subgroups are listed in Table 2-3.

Table 2-3 Subgroup analyses

Endpoint/analysis	[redacted]	**Analyses by pre-/during COVID-19 pandemic population**
Demographics/Baseline characteris		
Demographics		X
Baseline characteristics		X
Patient disposition table		X
Exposure		
duration of exposure, the number of doses, total cumulative dose, and number of missed doses		X
Efficacy		
Change from Baseline in UAS7		
Complete urticaria response (UAS7=0)		
Change from Baseline in HSS7		
Complete hives response (HSS7=0)		
Change from Baseline in ISS7		
Complete itch response (ISS7=0)		
Change from Baseline in DLQI		

2.3 Patient disposition, demographics and other baseline characteristics

Demographic and other baseline data

Demographic and other baseline data will be listed and summarized descriptively for the SAF.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum, and maximum will be presented.

Demographics (collected at Visit 1)

- Age
- Age group (18 - 65 years, ≥ 65 years)
- Sex (Male, Female, Unknown, Undifferentiated)
- Race
- Ethnicity
- Region
- Weight (kg)
- Height (cm)
- Body Mass Index (BMI) – calculated as weight (kg) / (height (m)) ^{2}
- BMI group (< 25, 25 - < 30, >= 30 kg/m^2)

Disease characteristics at baseline (baseline is defined as 2.1.1)

- [redacted]
- [redacted]
- Baseline UAS7 score
- Baseline weekly urticaria activity severity (Urticaria free: UAS7=0; Well controlled: 0<UAS7≤6; Mild: 6<UAS7<16; Moderate: 16≤UAS7<28; Severity: 28≤UAS7≤42)
- Baseline ISS7 score
- Baseline HSS7 score
- Duration of CSU – calculated as (inform consent date – first diagnosis date +1)/365.25 years)
- [redacted]
- Type of prior urticaria medication
- Experienced angioedema within the past 12 months (Yes, No)
- Experienced angioedema within the past 4 weeks (Yes, No)
- DLQI Score
- Medical history – Occurrence of CINDU (Yes, No)
- Medical history – Allergic rhinitis (Yes, No)
- Medical history – Anaphylaxis (Yes, No)
- Medical history – Angioedema (Yes, No)
- Medical history – Asthma (Yes, No)

- Medical history – Hives (Yes, No)
- Medical history – Parasitic infections (Yes, No)
- Medical history – Pruritus (Yes, No)
- Medical history – Serum sickness (Yes, No)

Medical History

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term. Summary for urticaria-specific medical history will also be provided.

2.3.1 Patient disposition

For each study epoch (i.e., screening period, treatment period, follow-up period), the overall number of patients who entered, completed, and discontinued that phase will be summarized including the reasons for discontinuation.

The number of patients included in each analysis set will be tabulated, as well as the reasons for exclusions from SAF. Patient exclusion from analysis sets will be listed for all patients with reasons for exclusion.

The number of patients with protocol deviations will be tabulated by category (e.g., selection criteria not met, prohibited concomitant medication, key procedures not performed as per protocol) and deviation for the SAF. Protocol deviations will be listed, deviation and analysis populations from which patients are excluded.

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.

The number of patients and the duration of exposure to QGE031 will be summarized by means of descriptive statistics. Duration of exposure is defined as the date of the last treatment minus the date of first study drug administration plus 4 weeks (28 days).

The number of injections per patient who are correctly administered as per protocol and number of missed injections will be summarized. A partial dose will be considered as if 100% of the dose of the assigned treatment has been administered.

The exposure summary table will be provided for the entire study. The exposure of the pre- and during-pandemic populations will be provided as well.

For protocol deviations (PDs) and COVID-19 related PDs, the number and percentage of subjects for whom the deviation applies will be summarized by PD category based on the ENR.

2.4.2 Prior, concomitant and post therapies

Prior medications are defined as medications taken by trial subject and the use was stopped prior to first dose of study treatment. Prior and concomitant medications, and post therapies will be summarized and listed based on SAF set.

Prior medications for CSU will be summarized separately by type of therapy (i.e. Sedating H1-antihistamines, Non-sedating H1-antihistamines at licensed dose, Non-sedating H1-antihistamines at up to 4x licensed dose, H2-Antihistamines, Omalizumab, Leukotriene receptor antagonist, Cyclosporine, Other immunosuppressants, Oral corticosteroids, Dapsone, Anti-inflammatory drugs, Anti-depressants (doxepin)) and preferred term. Prior medications non-related to CSU will be summarized by Anatomical Therapeutic Chemical (ATC) code and preferred term.

Concomitant medications categorized as "General (Non-CSU related)" and "CSU related", and significant non-drug therapies prior to and after the start of the study treatment will be listed. Concomitant medication for CSU categorized as "Background Medication" will be summarized by preferred term. Concomitant medication for CSU categorized as "Rescue" will be summarized by medication type (H1-antihistamin, Oral corticosteroids), ATC and preferred term. Furthermore, concomitant medication for Non-CSU will also be summarized according to the ATC classification.

2.5 Analysis of the primary objective

The primary objective of this study is to investigate the safety and tolerability of ligelizumab 120 mg q4w for 12 months.

2.5.1 Primary endpoint

The primary variable is the number and percentage of patients who reported treatment emergent adverse events during the 64 week study period.

All adverse events which start after the first dose of study medication and within 16 weeks of the last dose will be considered as a treatment emergent adverse event.

2.5.2 Statistical hypothesis, model, and method of analysis

The number of subjects who had a treatment emergent adverse event (events which started on or after the first dose of study treatment and within 16 weeks after the last study treatment, or events present prior to the first dose of study treatment but increased in severity based on preferred term within 16 weeks after the last study treatment) will be summarized overall, by system organ class (SOC) and preferred term descriptively. No statistical model will be applied for the primary endpoints.

All information obtained on adverse events will be displayed by subject.

All treatment emergent adverse events (TEAEs) during treatment period will also be summarized separately.

In addition to what is described in the primary endpoints section, treatment emergent adverse events with the number and percentage of patients having any adverse event overall, by system organ class and preferred term will be provided for:

- Serious treatment emergent adverse events (TESAEs)
- TEAEs by maximum severity
- TEAEs suspected by the investigator as study drug related
- TEAEs leading to permanent discontinuation of study drug

The number of subjects with TEAEs of special interest will be listed and summarized.

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Unless otherwise specified, primary system organ classes will be sorted alphabetically and, within each primary system organ class, the preferred terms will be sorted in descending order of frequency. If a patient reported more than one adverse event with the same preferred term, the adverse event will be counted only once. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once at the system organ class level.

In addition, the most frequent TEAEs will be presented by preferred term in descending order of frequency.

For TEAEs by maximum severity, missing severity will be assumed to be severe in the summary table.

2.5.3 Handling of missing values/censoring/discontinuations

For the subject who discontinued treatment or study, no imputation or adjustment will be considered for counting the number of subjects who have a treatment emergent AE/SAE. All subjects will be treated equally when the data is summarized, regardless of the treatment duration and/or study duration of each subject.

2.5.4 Supportive analyses

No supportive analyses are planned.

2.6 Analysis of secondary efficacy objective(s)

All efficacy variables (UAS7, HSS7, ISS7 and DLQI) will be analyzed in the SAF.

2.6.1 Secondary endpoints

Each endpoint of efficacy variables (UAS7, HSS7, ISS7 and DLQI) are as follows.

- Absolute change from baseline of UAS7, ISS7 and HSS7
- Proportion of subjects with HSS7 = 0, ISS7 =0 and UAS7=0 response
- Time to achievement of complete UAS7 response (UAS7 = 0), time to achievement of UAS7 $\leq$ 6 response

- Time to loss of complete UAS7 response (UAS7 = 0) from Week 52 for patients have achieved complete UAS7 = 0 response at Week 52
- Time to UAS7 ≥ 16 for patients having achieved UAS7 ≤ 6 at week 52
- Absolute change from baseline of DLQI
- Proportion of subjects with DLQI = 0/1

2.6.2 Statistical hypothesis, model, and method of analysis

No formal statistical analysis will be provided.

Summary tables will be presented by visit or week using descriptive statistics. Categorical variables will be presented as frequencies and percentages. For continuous variables, mean, standard deviation, median, minimum, and maximum will be presented. Mean the change from baseline (UAS7, HSS7, ISS7 and DLQI) will be shown descriptively with 95% confidence interval based on one-sample t-test. Proportion of subjects (UAS7=0, HSS7=0, ISS7=0 and DLQI=0/1) will also be shown with 95% confidence interval based on the Clopper-Pearson (exact) method. All analyses will be provided descriptively and no formal statistical testing will be applied. Figures will also be provided. The UAS7=0 response status will be defined based on the weekly UAS7 score by week. For instance, if the observed UAS7=0 at week 12, it will be considered as response, otherwise it is considered as a non-response unless UAS7 is missing. No non-responder imputation is planned in this study.

For time to achievement of complete UAS7 response, Kaplan-Meier estimator will be used to estimate the cumulative incidence function and the results will be plotted. Only the treatment period will be included in this time to first response analysis. Time to first complete UAS7 = 0 response achievement will be considered censored at the date of the last non-missing weekly score for any patient who is a non-responder. For the time to achievement of UAS7≤ 6 response analysis, the patients with baseline UAS7≤ 6 response will be excluded from the analysis as well.

For subjects who completed 52 week treatment period, time to loss of complete UAS7 response from Week 52 will be analyzed using Kaplan-Meier estimator similarly as the time to achievement of complete UAS7 response analysis. Time to first loss of complete UAS7 response from Week 52 for patients having achieved complete UAS7=0 response at Week 52 will be considered censored at the date of the last non-missing weekly score for any patient who remains as a responder. Time to loss of response analyses will be based on post-treatment follow-up period.

Time to UAS7 ≥ 16 for patients having achieved UAS7 ≤ 6 at week 52 will be performed in a similar way as the time to loss of complete UAS7 response analysis.

2.6.3 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. If ISS7 or HSS7 is missing, UAS7 will also be missing. 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.

For each weekly score from the UPDD (i.e. HSS7, ISS7), if one or more of the daily scores are missing, the following principles will be applied to handle the missing data:

- If a patient has at least 4 non-missing daily (morning or evening) 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.

Duplicate data handling of questionnaires

For HSS7, ISS7, the daily score is derived from the average of morning and evening scores (e.g. in case HSS is entered twice in the morning at different times).

All other questionnaires (i.e. other than HSS and ISS) 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.

2.6.4 Supportive analyses

In order to mitigate the impact of missing data of UPDD (HSS, ISS), model based approach will be applied if applicable. A linear mixed model with repeated measures (MMRM) will be used to estimate treatment differences for change from baseline in UAS7 score up to the end of study, based on the SAF. The MMRM model will include [redacted], visit week, baseline UAS7 score and interaction of baseline UAS7 score by visit week as fixed effects. Repeated measures within subject are modeled using an unstructured covariance of the error terms. If the model does not converge, the compound symmetry covariance structure will be used. For details, please see the Appendix.

For HSS7 and ISS7, same analyses will be performed.

[redacted]

The SAS program code and is described in section 5.5.2.

2.7 Safety analyses

For all safety analyses, the SAF will be used.

2.7.1 Adverse events (AEs)

Refer to the AEs analyses described in Section 2.5 in this document.

2.7.1.1 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.

Due to expected differences in exposure and follow-up due to varied duration of study participation between participants, adverse event incidence rates will be provided as "exposure adjusted AE incidence rates (EAIRs)" in addition to the crude incidence.

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 and defined as the shortest of the following:

1) time to the first episode of the i^{th} type event (if the event occurs),
2) duration of study treatment plus the 16-week washout period (approximately corresponding to five half-lives) after last treatment dose, or
3) end of the analysis period (week 64 for all safety follow-up).

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

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, PT level
2. TEAE of special interest

2.7.1.2 Adverse events of special interest / grouping of AEs

Refer to the AEs analyses described in Section 2.5 in this document.

Adverse events of special interest

The following adverse events of special interest (AESI) will be summarized separately by each category and SOC/PT.

Details will be provided in the separate document (eCRS). The search criteria in the latest eCRS corresponding the MedDRA version at the database lock will be used and reported in the CSR.

- Hypersensitivity reactions (including anaphylaxis)
- Cardiovascular and Cerebrovascular (CCV) events
- Neoplastic conditions
- Injection site reactions
- Serum Sickness
- Eosinophilic Conditions / Churg-Strauss Syndrome

- Parasitic (Helminthic) infections
- Thrombocytopenia

Injection site reactions

For injection site reactions (ISR), besides the overall summary table for AESI, ISR will be summarized by events and subject separately in each treatment group for the following categorical variables.

The ISR selected by eCRS as ISR will be mapped to the exposure dosing window. The PTs (possible more than 1 records) happened during the same dosing window (on or after the drug injection administration date and before the next injection administration), they will be considered as one ISR event. If there is any missing dose injection occurred, any selected event will be all considered related to the last drug administration happened. For example, if a dose administration scheduled dose at Week 4 happened, and the next dose administration happened at Week 12 with Week 8 dose administration missing, all injection site reaction happened on or after Week 4 drug administration date before Week 12 drug administration date will be considered related to Week 4 drug administration.

If there were multiple PTs occurred during one dosing window, the worst case will be used for the summary and analysis of ISR. If there is any PT record detailed information (e.g. severity, resolution time, action or outcome etc..) missing or unknown, this PT record will not be included for the particular category summary of ISR. If all PT records for one ISR are with unknown/missing information for the summary category, the ISR will be summarized in the unknown category in the table.

- Recurrence of ISR (single ISR, 2-3 ISRs, > 3 ISRs)
- Severity of ISR (best to worst cases: mild, moderate, severe)
- Timing of ISR (during first administration, Week 4-Week 8, Week 8-Week 24, After Week 24)
- Time to resolution (best to worst cases: 24 hours, 24-48 hours, 48-72 hours, > 72 hours)
- Action taken (best to worst cases: Dose not changed, drug interrupted, drug withdrawn)
- Outcome (best to worst cases: Recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, Fatal)

Furthermore, for time to first treatment emergent injection site reaction, the Kaplan-Meier estimator will be used to estimate the cumulative incidence function for the entire study.

Adjudicated AEs

From the AESIs listed above, the following AEs will be adjudicated by the independent committee. The adjudicated events will be listed, and a summary table will be provided following the adjudication.

- Anaphylaxis
- Cardiovascular and Cerebrovascular (CCV) events

- Neoplastic conditions (Malignancy)

COVID-19 infection related analyses

A listing and summary of all TEAE COVID infections will be presented. All suspected and confirmed infection will be provided. The COVID-19 infection will be filtered based on eCRS.

Liver toxicity

Separate summary table and listing will be provided for the liver toxicity related adverse event.

2.7.1.3 Legal requirements of ClinicalTrials.gov and EudraCT

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables with treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and with treatment emergent serious adverse events and SAEs 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.

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

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

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

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

2.7.2 Deaths

No separate listing or table will be provided from the database. Death will be reported as part of SAE which cause death.

2.7.3 Laboratory data

All laboratory data will be listed by test group, subject, visit and laboratory test with abnormalities flag based on normal ranges. Shift tables for 2 groups of laboratory tests (hematology and serum chemistry) using the low/normal/high classification will be used to compare baseline to the worst on-treatment value. For the parameters with clinically notable abnormal criteria, newly occurred or worsening abnormality will also be summarized. 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.

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

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

The notable criteria and abnormalities are described in section 5.3.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

All ECG data will be listed by subject and visit with abnormalities flag based on the notable criteria. A shift table from baseline to the worst pot-baseline value will be presented on the overall ECG interpretation. The number of patients with notable abnormal ECG parameters after baseline will be summarized.

The notable criteria and abnormalities are described in section 5.3.

2.7.4.2 Vital signs

All vital signs data will be listed by subject and visit with the abnormalities flag based on the notable criteria. The number of patients with newly occurring or worsening vital sign abnormalities during the study vital signs will be summarized.

The notable criteria and abnormalities are described in section 5.3.

2.7.4.3 Anti-ligelizumab

IG analysis will be performed using the IG analysis set.

The incidence of pre-existing ADAs will be provided, indicating i) the number and percentage of subjects with confirmed positive ADAs at baseline and ii) the number and percentage of subjects with neutralizing ADAs at baseline. The percentage of subjects with neutralizing ADAs is determined based on all subjects with pre-existing ADAs.

Results for ADA (Anti-Drug Antibody) to ligelizumab will be listed by patient, visit/timepoint with the results of the confirmatory assay and the titer values determined. The summary of ADA incidence will be provided for overall population. The listing will also provide annotation with regards to the neutralizing nature of the positive ADA samples. The percentage of subjects with neutralizing ADAs is determined based on all subjects with treatment-emergent ADAs.

Treatment emergent ADAs are defined as ADAs developed on or after the treatment with ligelizumab (Rup et al, 2015, Shankar et al, 2014). Subjects with treatment emergent ADAs may also be sometimes denoted as "ADA-positive subjects".

[Treatment-emergent ADAs] = [Treatment-induced ADAs] + [Treatment boosted ADAs]

- In a treatment-induced ADA-positive subject, ADAs are developed de novo following biopharmaceutical administration. The pre-dose sample is ADA negative.

- In a treatment-boosted ADA-positive subject, following biopharmaceutical administration a subject with pre-existing antibodies develops an increased level of ADAs which is manifested by a ≥ four-fold increase in titer. The pre-dose sample is ADA positive and has a titer.

The ADA incidence summary table will be provided by overall population, indicating i) the number and percentage of subjects with treatment-induced, treatment-boosted and treatment emergent ADAs at anytime and ii) the number and percentage of subjects with neutralizing ADAs at any time, both compared with the total number of subjects in the analysis set who received ≥ 1 QGE031 dose.

The following is generated, including all subjects with treatment emergent ADAs: i) a box plot showing the titer distribution per time point, also including for each time point the number of ADA+ samples per total number of ADA samples at that time point (n/m (%)) and ii) the tabulated values of i), e.g. median, Q1, Q3, min, max.

The ADA and neutralizing ADA incidence is determined.

For ADA-positive subjects, provision will be made for a listing of typical immunogenicity-related AEs (generated based on Standardized MedDRA Queries (SMQ) narrow of Hypersensitivity, Anaphylactic reaction, Anaphylactic/anaphylactoid shock conditions and Angioedema, and serum sickness) and the timing of their occurrence along with time course of the occurrence of positive ADAs in those subjects. The safety profile for the ADA positive subjects will be assessed to determine the correlation between occurrence of immunogenicity related AE and ADA positive, i.e., AEs will be summarized in tabular format in the presence or absence of treatment-emergent ADA.

[redacted]

2.10 Patient-reported outcomes

All PRO endpoints will be summarized using SAF. The data will be analyzed.

Refer to the UAS7, HSS7, ISS7 and DLQI analyses described in Section 2.6 in this document.

2.10.1 Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) is a 10-item dermatology-specific health-related quality of life measure presented to each subject, from baseline (Visit 110, Day 1) up to the study end. The DLQI total score will be calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0.

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 2-2 DLQI domains).

Table 2-2 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

Missing data handling for DLQI

For the DLQI subscale and total score derivation, if there is only one missing score per visit, then it will be imputed to 0 and then the subscale including this item and the total score will be calculated accordingly. If there are two or more missing scores per visit, then the score will be missing.

[redacted]

[redacted]

[redacted]

2.13 Interim analysis

Not Applicable.

3 Sample size calculation

3.1 Primary endpoint(s)

No formal statistical power calculations to determine sample size were performed for this study. The sample size is determined based on the regulatory requirement by Pharmaceuticals and Medical Devices Agency (PMDA) to fulfill the long term safety data for Japanese patients. Considering 10% drop out rate based in the QGE031C2201 study, the planned sample size (N=65) in this study will have 58 patients with 1 year exposure, and it is expected to have 100 Japanese patients exposed to ligelizumab with 1 year in the total ligelizumab CSU program, together with QGE031C2201/E1 and QGE031C2303 studies. With the total sample size (N=100) exposed to ligelizumab in Japanese patients, one can expect to see at least one patient with a specific AE with 95% probability, assuming the occurrence rate of an AE is 3%, aligned with ICH E1 guideline. Safety data from the study will also be evaluated together with Japanese patients from other ligelizumab studies in the submission dossier.

3.2 Secondary endpoints(s)

The expected half-width of 95% confidence interval for the change from baseline in UAS7 would be 3.3, assuming 58 patients (10% missing) are available of post-baseline UAS7 data and SD=13. If the mean change from baseline in UAS7 for ligelizumab group is -22.0 (based on C2201 study at Week 12), 95% confidence interval of the mean change from baseline in UAS7 will be (-25.3, -18.7).

4 Change to protocol specified analyses

No change from protocol specified analysis is made.

5 Appendix

5.1 Derivation rules for end of treatment date

The end of treatment date up to Week 52 treatment period is defined as below.

1. If patients complete treatment period, the end date is the first non-missing date of the following dates: Week 52 dosing date, Week 52 visit date, PD date of missing visit at Week 52, first dosing date + 52 weeks.
2. If patients early discontinue treatment before Week 52, the end date is the first non-missing date of the following dates: last dosing date + 4 weeks, last visit date, PD date of missing visit at Week 52, first dosing date + 52 weeks.

5.2 Imputation rules

5.2.1 Study drug

No imputation of missing/partial start or study end date drug. If missing, the time of study 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, then 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	(a) Before Treatment Start	(b) Before Treatment Start	(b) Before Treatment Start	(b) Before Treatment Start
YYYY = TRTY	(a) Uncertain	(b) Before Treatment Start	(c) Uncertain	(c) After Treatment Start
YYYY > TRTY	(a) After Treatment Start	(b) After Treatment Start	(b) After Treatment Start	(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, then the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, then 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, then 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. Otherwise, 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, then the AE started after treatment. Therefore:
    a. If the AE month is missing, then the imputed AE start date is set to the year start point (01JanYYYY).
    b. Otherwise, if the AE month is not missing, then the imputed AE start date is set to the later of month start point (01MONYYYY) or 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. If the AE month is less than the treatment start month, then the imputed AE start date is set to the mid-month point (15MONYYYY).
    c. Otherwise, if the AE month is equal to the treatment start date month or greater than the treatment start date month, then 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

Rules for imputing the 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 ongoing at the end of the study, no numeric end date is derived.
- If the end date is completely missing no numeric end date is derived.
    a. If CM end day is missing and CM month/year are non-missing, then impute CM date as the minimum of study end date and the last day of the month.
    b. If CM end day/month are missing and CM year is non-missing, then impute CM date as the minimum of study end date and the end of the year (31DECYYYY).

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

Rules for imputing the CM start date:

- If imputing end dates, then 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	**(a)** Uncertain	**(a)** Uncertain	**(a)** Uncertain	**(a)** Uncertain
YYYY < TRTY	**(a)** Before Treatment Start	**(a)** Before Treatment Start	**(a)** Before Treatment Start	**(a)** Before Treatment Start
YYYY = TRTY	**(a)** Uncertain	**(b)** Before Treatment Start	**(a)** Uncertain	**(c)** After Treatment Start
YYYY > TRTY	**(a)** After Treatment Start	**(b)** After Treatment Start	**(b)** After Treatment Start	**(b)** After Treatment Start

1. If the CM start date year value is missing, then 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, then the CM started before treatment. Therefore;
   a. If the CM month is missing, then the imputed CM start date is set to the mid-year point (01JulYYYY).
   b. Else if the CM month is not missing, then the imputed CM start date is set to the mid-month point (15MONYYYY).

1. 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, then the imputed CM start date is set to the year start point (01JanYYYY).
   b. Else if the CM month is not missing, then the imputed CM start date is set to the month start point (01MONYYYY).

1. 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, then 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, then 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.

If there is no end date and ongoing check is not ticked, the CM will be considered as ongoing and included in the summary table.

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

AEs will be coded using the MedDRA version at the database lock.

AE grading is not applied in this study.

5.4 Clinically notable criteria and abnormalities

5.4.1 Clinically notable criteria

The following notable criteria will be used in the study

Laboratory value

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.	

Vital sign

- Heart rate < 60 beats per minute (bpm) (bradycardia)
- Heart rate > 100 beats per minute (bpm) (tachycardia)
- Systolic blood pressure < 90 and ≥ 140 mmHg (hypertension)
- Diastolic blood pressure of < 60 and ≥ 90 mmHg (hypotension)

ECG

- QT interval - >500 msec
- QTcF (Fridericia's) interval - males > 450 msec
- QTcF (Fridericia's) interval - females > 460 msec
- QTcF change from baseline >30 msec, >60 msec
- PR >250 msec

5.4.2 Abnormalities

Liver-enzyme abnormalities

Table 5-1 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)
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, ALP = Alkaline phosphatase, TBL = Total bilirubin	

Renal abnormalities

Table 5-2 Renal abnormalities

Parameter	Notable criterion
Serum creatinine	Increase 25% – 49%
Serum creatinine	Increase ≥ 50% +

Parameter	Notable criterion
New onset dipstick proteinuria	≥1+

5.5 Statistical models

5.5.1 Primary analysis

Not applicable.

5.5.2 Key Secondary analysis

Mixed model with repeated measures (MMRM):

The supportive analyses for UAS7, HSS7 and ISS7 will be performed.

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

proc mixed data=…… order=internal covtest;

class subject week cuind;

model change = baseline week cuind baseline*week / s ddfm=kr;

repeated week / type=un subject=subject;

lsmeans week / cl e OM;

ods output LSmeans=mean ConvergenceStatus=convtest;

run;

where change = change from baseline UAS7 score

baseline = baseline UAS7 score

week = study week

[redacted]

subject = subject

If the computation of the MMRM model takes extreme amount of time, the ddfm=bw option could be considered. If the model with an unstructured covariance matrix does not converge, SAS will give a warning as "Unable to make hessian positive definite" or "Unable to Converge" or "stopped because of infinite likelihood". Meanwhile, the Status variable in the convtest dataset created will take on the value 0 or 1. In this case, the compound-symmetry structure should be used, by replacing type=un in the above codes with type=cs.

If after this step the model still does not converge, remove the covariates in the following order until it converges: baseline*week, [redacted]

5.6 Rule of exclusion criteria of analysis sets

Protocol deviations that cause subjects to be excluded

[redacted]

Table 5-3 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
SAF	NA	No study drug taken
[redacted]	[redacted]	[redacted]
IG	NA	Not in SAF; No immunogenicity assessments
[redacted]	[redacted]	[redacted]

6 Reference

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