NOVARTIS

Clinical Development

QGE031/Ligelizumab

CQGE031C2302 / NCT03580369

A multi-center, randomized, double-blind, active and placebo-controlled study to investigate the efficacy and safety of ligelizumab (QGE031) in the treatment of Chronic Spontaneous Urticaria (CSU) in adolescents and adults inadequately controlled with H1-antihistamines

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
[redacted]				

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List of abbreviations

[redacted]	[redacted]
AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
BMI	body mass index
CDLQI	Children's Dermatology Life Quality Index
CM	Concomitant Medication
COVID-19	Corona Virus Disease 2019
CRO	Contract Research Organization
CSR	Clinical Study report
CSU	Chronic Spontaneous Urticaria
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ENR	enrolled set
FAS	Full Analysis Set
H1-AH	H1-antihistamines
[redacted]	[redacted]
IVR	Interactive Voice Response
IWR	Interactive Web Response
LLN	lower limit of normal
LLOQ	Lower Level of Quantification
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	mixed-effects model repeated measures
NCI	National Cancer Institute
od	Once Daily
OS	Overall Survival
[redacted]	[redacted]
PFS	Progression-Free Survival
[redacted]	[redacted]
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAN	Randomized set
RAP	Report and Analysis Process
RDO	Retrieved drop-out
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

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 the protocol version 2.0, dated 07-Jan-2021. [redacted] his SAP amendment reflects all the changes accordingly.

1.1 Study design

This is a Phase III multi-center, randomized, double-blind, active- and placebo-controlled, parallel-group study. The study consists of 3 distinct periods:

- Screening period (Day - 28 to Day 1): Duration of up to 4 weeks in which subjects who have given informed consent are assessed for eligibility.
- Double-blind 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 3 visits (every 4 weeks) with the final visit occurring 16 weeks after the last dose at Week 48.

The study population will consist of approximately 1050 male and female subjects aged ≥ 12 years who have been diagnosed with CSU and who remain symptomatic despite the use of H1-AH at locally approved doses. Of these, approximately 1000 adults and 50 adolescents are planned for inclusion in the study. To avoid assigning an unnecessarily large number of subjects to placebo, subjects will be randomized in a 3:3:3:1 ratio to ligelizumab high dose (120 mg), ligelizumab low dose (72 mg), omalizumab and placebo, respectively administered subcutaneously, every 4 weeks (s.c. q4w) (see details in Figure 1-1).

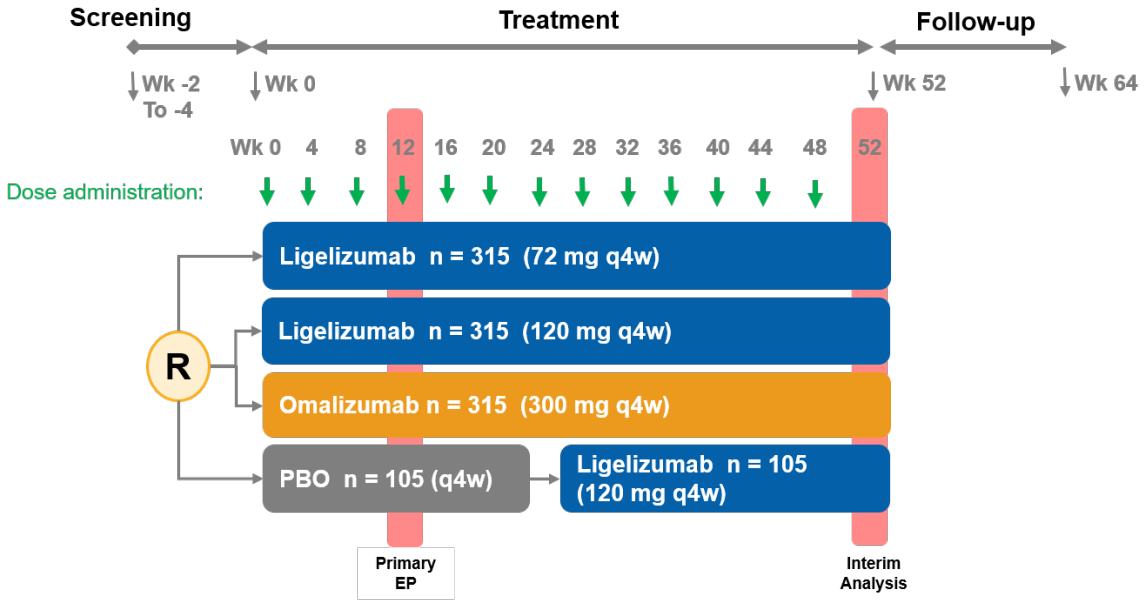
Since both adults and adolescent subjects will be enrolled into this study, randomization will be stratified by age group. In addition, randomization for adults will be stratified by region and/or country to ensure a balanced assignment to each treatment group. Considering the relatively small sample size of adolescent subjects, there will be no additional stratification by region for adolescent subjects.

The primary analysis time point is Week 12. Subjects who are assigned to the placebo group at the randomization visit will remain on placebo until Week 24, when they will be transitioned to ligelizumab 120 mg sc q4w. A primary efficacy analysis will be performed after all adult subjects have completed the treatment period (Week 52 visit). [redacted]

Analyses for the Data Monitoring Committee (DMC) will be conducted approximately [redacted] (for periodic safety review) by independent statistician and programmers from an

external CRO; which will be covered by a separate SAP. Additional analyses for the DMC may be conducted if needed for monitoring the safety of subjects enrolled in the study.

Figure 1-1 Study Design



R: Randomized

1.2 Study objectives and endpoints

Table 1-1 Study objectives and endpoints

Objectives	Endpoints
Primary Objective ● To demonstrate that ligelizumab (72 mg q4w and/or 120 mg q4w) is superior to placebo and superior to omalizumab 300 mg q4w in change from baseline in UAS7 at Week 12	**Endpoint for primary objective** ● Absolute change from baseline in UAS7 at Week 12
Secondary Objectives ● To demonstrate that a greater proportion of subjects achieve UAS7=0 at Week 12 who are treated with ligelizumab 72 mg q4w and/or 120 mg q4w compared to placebo-treated subjects and compared with omalizumab 300 mg q4w treated subjects	**Endpoints for secondary objectives** ● Percentage of subjects achieving UAS7=0 at Week 12
● To demonstrate the superiority of ligelizumab 72 mg q4w and/or 120 mg q4w treated subjects with respect to a reduction from baseline in the weekly itch severity score at Week 12 compared to placebo-treated subjects and omalizumab 300 mg q4w treated subjects	● Absolute change from baseline in ISS7 score at Week 12

Objectives	Endpoints
● To demonstrate that a greater proportion of subjects who are treated with ligelizumab 72 mg q4w and/or 120 mg q4w achieve DLQI = 0-1 at Week 12 compared to placebo-treated subjects and omalizumab 300 mg q4w treated subjects*	● Percentage of subjects achieving DLQI = 0-1 at Week 12*
● To demonstrate that the ligelizumab 72 mg q4w and/or 120 mg q4w treated subjects have a longer angioedema occurrence-free period compared with placebo-treated subjects and omalizumab 300 mg q4w treated subjects	● Cumulative number of weeks that subjects achieve AAS7=0 responses between baseline and Week 12
● To demonstrate the safety and tolerability of ligelizumab 72 mg q4w and 120 mg q4w	● Occurrence of treatment emergent adverse events during the study ● Occurrence of treatment emergent serious adverse events during the study

[redacted]

* For the adolescents subgroup analyses, CDLQI will be used for the objective/endpoints assessments.

The detailed definition and justification of the corresponding primary estimand, as well as the definition of supplementary estimands are provided in appendix 5.

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 .

DMC analyses will be done by the independent statistician and . Statistical Analysis Plan for the DMC analyses will be prepared separately.

All analyses (including safety, [redacted] and efficacy) will be provided for adolescents and adults separately. Due to the relatively low number of adolescent subjects for this study, the data collected for adolescent subjects will be analyzed in a descriptive manner. 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.

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 for efficacy analysis:

- QGE031 72 mg q4w
- QGE031 120 mg q4w
- Omalizumab 300 mg q4w
- Placebo – QGE120 mg q4w*

* In the efficacy analysis outputs, any analyses for time points prior to placebo switch will be labelled as placebo group.

Study treatment groups used for analysis are defined as below for safety analysis:

- For the placebo control period up to week 24
  - QGE031 72 mg q4w
  - QGE031 120 mg q4w
  - Omalizumab 300 mg q4w
  - Placebo
- For the entire study period
  - QGE031 72 mg q4w
  - QGE031 120 mg q4w
  - Omalizumab 300 mg q4w
  - Transitioned to QGE120 mg q4w

2.1.1.2 Study Day and Study Week based on eDiary

The first day of administration of study treatment (first dose) is defined as Day 1. The study day and study week defined in this section will be used for the efficacy analyses based on the eDiary data recorded in the study.

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].

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

The descriptor "Day 0" will not be used.

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.

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

Study Week	Study Days
Baseline	Day (-7)-(-1)
Week 1	Day 1-7
...	...
Week x	7×(x−1)+1 - 7×x
...	...
Week 64	Day 442 – 448

2.1.1.3 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.

2.1.1.4 Baseline

Baseline eDiary score is defined as the eDiary score in the 7 days prior to the first dosing visit assessment (see Table 2-1).

Otherwise for lab, vital sign assessments etc collected at a the scheduled visit, the last assessment (including unscheduled visits, if any) obtained on or before the first dose day of study treatment is considered as baseline. For a subject who receives partial dose for the first dose day of study treatment, the baseline will still be 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/her last assessment under the study. If multiple assessments are taken on the same date, then the pre-dosing assessment closest to the dosing time (i.e., the latest recorded time prior to the dosing time on that date) will be used for baseline. If the recorded time parts

of duplicated assessments are the same or missing, then the averaged outcome of the duplicated assessment on that date will be used for baseline.

For ECG measurements, baseline will be defined as the scheduled measurements taken at screening (Visit 1). If there is additional unscheduled assessment(s) taken before the first dosing date, the latest assessment taken on or before the first treatment dosing date will be considered as baseline for ECG measurements. If multiple assessments are taken on the same date, then the worst outcome of them will be used for baseline.

For DLQI/CDLQI, if the questionnaire was completed more than once on the same date, on the last date on or before treatment start date, then the first assessment of the duplicate assessments (i.e. the earliest recorded time on that date) will be used as the baseline assessment. If the recorded time parts of the duplicated assessments are the same or missing, then the worst outcome (i.e. the highest score) of the duplicate assessments on that date will be used for baseline.

2.2 Analysis sets

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

Randomized set (RAN): The RAN set will include all randomized subjects, regardless of whether or not they receive a dose of study drug. Subjects will be analyzed according to the treatment they are assigned to.
Full analysis set (FAS): The FAS set will include all randomized subjects who received at least one dose of study drug. Subjects will be analyzed according to the treatment to which they are assigned at randomization. Mis-randomized patients (mis-randomized in IRT) will be excluded. Mis-randomized patients are defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the patient's final randomization eligibility and no study medication was administered to the patient. FAS will be used for all efficacy variables, unless otherwise stated.

Safety set (SAF): The SAF set will include all subjects who received at least one dose of study drug whether or not being randomized. Subjects will be analyzed according to the treatment they received. The safety set will be used in the analysis of all safety variables. The actual treatment will be defined as the treatment received over the study. In case of error in dispensation, the actual treatment group will correspond to the treatment which was given most often (i.e. the actual treatment received different from the planned randomized treatment more than 50% of the exposure period).

[redacted]

[redacted]

2.2.1 Subgroups of interest

[redacted]

2.2.1.2 Region

Subgroup analysis will be performed by status of region as pre-specified in the stratum and will be presented for the primary efficacy endpoint and additionally for the secondary efficacy endpoints related to UAS7 or ISS7. If any patients were mis-stratified at baseline, the right region classification will be derived based on the country information. The detailed classification of region by country will be provided in the Appendix.

2.2.1.3 Adolescent population

All the safety and efficacy information for the adolescent subgroup will be presented separately. The adolescent subgroup will be defined based on the subjects' age collected at screening.

[redacted]

[redacted]

[redacted]

2.2.1.6 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 is defined by region (see, Table 2-2).

Table 2-2 Start of the pandemic by different regions.

Region/Country	Start Date	End Date
South Korea	20-Feb-2020	End date has not yet been defined
Japan	21-Feb-2020	End date has not yet been defined
Italy	23-Feb-2020	End date has not yet been defined
Rest of the World	01-Mar-2020	End dates have not yet been defined

Subject disposition of the pre- and during-pandemic populations will be presented to assess the impact of the COVID-19 pandemic. 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 2-2 Subgroup analyses

Endpoint/analysis	[redacted]	Analyses by region	Analyses for adolescents population	Analyses for Japanese population	Analyses by pre-/during COVID-19 pandemic population	Pairwise comparison[2]
Disposition						
Baseline characteristics			X	X	X	
Patient disposition table			X	X	X	
Exposure						
duration of exposure, the number of doses and number of missed doses			X	X	X	
Efficacy						

Endpoint/analysis [redacted]	Analyses by region	Analyses for adolescents population	Analyses for Japanese population	Analyses by pre-/during COVID-19 pandemic population	Pairwise comparison[2]
Change from Baseline in UAS7 and ISS7	X	X – no pair wise comparison, only summary table	X – no pair wise comparison, only summary table		at Week 12, Week 24 and Week 52
urticaria activity response (UAS7=0)	X	X – no pair wise comparison, only summary table	X – no pair wise comparison, only summary table		at Week 12, Week 24 and Week 52
Safety					
TEAE/TESAE by SOC and PT		X	X		
TEAE of special interest		X	X		
[redacted]		X	X[1]		

Note: Only endpoints/analysis that need subgroup analyses are presented in this table.

[redacted]

[2] The pairwise comparison will be performed between different treatment arms for each subgroup.

In the inferential efficacy analysis, the subgroup estimates [redacted]/by region will be obtained using the treatment by subgroup interaction in the logistic modeling or the MMRM modeling.

The descriptive analysis of the scores in change from baseline for the adolescent population and Japanese population will be performed, as for this subgroup analysis, no multiplicity adjustment is needed.

2.3 Patient disposition, demographics and other baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristic variables for each treatment group and for all subjects in the randomized set (RAN). The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and all subjects.

Demographics (collected at Visit 1)

- Age
- Age group (adolescents (12-17 years), adults (18 - <65 years, ≥ 65 years))
- Sex
- Race
- Ethnicity
- Region
- Weight
- Height
- 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 2.2.2)

- [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; Severe: 28≤UAS7≤42)
- Duration of CSU – calculated as (first study treatment date – first diagnosis date +1)/365.25 years)
- Baseline AAS7 score
- Duration of a typical angioedema episode
- Type of prior urticaria medication
- Experienced angioedema within the past 4 weeks/within the past year
- Duration of the last episode of angioedema

Medical History

Any conditions entered as medical history or current medical condition at baseline will be coded using the MedDRA dictionary. They will be summarized by system organ class and preferred term of the MedDRA dictionary for RAN. Summaries for urticaria-specific medical history will be provided in a descriptive manner as well.

2.3.1 Patient disposition

The number of screened subjects who complete the screening period will be given and the reasons for not entering into the double-blind treatment period will be summarized based on the ENR set. The number and percentage of subjects in the RAN set who got mis-randomized, completed or discontinued the treatment period, and the reasons for discontinuation will be presented by treatment group and overall. The number and percentage of subjects in the RAN set who entered the follow-up period, and the reasons for discontinuation will also be presented by treatment group and overall; the number and percentage of subjects who completed the entire

study (i.e., completed both the treatment period and the follow-up period) will be presented by treatment group and overall as well.

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

2.4.1 Study treatment / compliance

The analysis of treatment will be performed by each treatment group based on the SAF.
The number of patients and the duration of exposure to each study drug and dose will be summarized by treatment. 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).

In addition, the number of doses, total cumulative dose, 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.

The exposure summary table will be provided for 24 weeks treatment period and the entire study separately. 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 and treatment groups.

2.4.2 Prior and concomitant therapies

Prior medications are defined as medications taken by trial subject and the use was stopped prior to first dose of study treatment. Prior medications will be summarized based on RAN set. Prior medications for CSU will be summarized by type of therapy, preferred term, and treatment group. Prior medications non-related to CSU will be summarized by ATC code and preferred term.

Concomitant medications are defined as any medication given at least once between the day of first dose of study treatment and the date of the last study visit. The medications started taking prior to the first dosing and still be used on or after the first dosing date will be also counted as concomitant medications. Concomitant medications will be summarized by ATC code, preferred term and treatment group for SAF set, separately for urticaria-related background medications, urticaria related concomitant medication and non-urticaria related medications.

Concomitant medication tables by treatment groups will be provided for the 24 weeks treatment period and entire study period separately. Summary tables will evaluate the treatment in two separate periods: one period covering information up to 24 weeks for all treatment groups including the placebo arm before transition to active treatment (placebo only group); another period will cover the information up to end of study covering all the treatment groups and will include data from the placebo arm after transition to active treatment (transitioned to ligelizumab 120mg group). If the concomitant medication start date is before the 24 week treatment period cut off definition, it will be counted in the summary table for the 24 weeks treatment period.

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 absolute change from baseline in UAS7 score at Week 12, which is the UAS7 score at Week 12 minus the UAS7 score at baseline.

The UAS7 score is the sum of the HSS7 score and the ISS7 score, and ranges from 0-42. Weekly scores (HSS7 and ISS7 scores) will be derived by adding up the average daily scores of the 7 days preceding the visit.

The primary estimand will account for two categories of intercurrent events which will be treated in different ways. We will distinguish between intercurrent events unrelated to the COVID-19 pandemic and intercurrent events that happened due to operational complications caused by the COVID-19 pandemic, e.g., patients missed their dose as they were not able to receive their study medication due to regional lockdowns. Intercurrent events due to non-operational reasons during the COVID-19 pandemic will be considered as unrelated to the COVID-19 pandemic and will therefore be classified as intercurrent events unrelated to the COVID-19 pandemic for the primary efficacy analysis. In order to distinguish between these two categories, protocol deviations arising due to the COVID-19 pandemic will be collected in addition to the original list of protocol deviations defined prior to the pandemic. Hence, the COVID-19 pandemic related protocol deviations supplement the set of protocol deviations already in place. The COVID-19 pandemic related protocol deviations will identify intercurrent events due to COVID-19, which will then be split into operational due to COVID-19 (e.g., a missed dose because the patient was not able to reach the site because of a local lockdown due to COVID-19, etc.) and non-operational complications due to COVID-19 (e.g., lack of efficacy and adverse events).

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 participants receiving H1-antihistamines therapy at local-approved dose level as background medication suffering from chronic spontaneous urticaria and meeting study inclusion/exclusion criteria.
- **Variable**: absolute change from baseline in UAS7 score at Week 12
- **Treatment of interest**: ligelizumab or the placebo or omalizumab treatment with stable H1-antihistamines (H1-AH) at local-approved doses as background medication + allowed rescue medication if needed.

- **Handling of remaining intercurrent events**:

Intercurrent events unrelated to the COVID-19 pandemic:

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 unrelated to the COVID-19 pandemic: 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. Use of rescue medication prior to Week 12 unrelated to the COVID-19 pandemic: ignore (*treatment policy strategy*).

Intercurrent events related to the operational complications caused by the COVID-19 pandemic:

1. Discontinuation of study treatment prior to Week 12 due to the COVID-19 pandemic: had participants not discontinued study treatment prior to Week 12 due to the COVID-19 pandemic (*hypothetical strategy*).
2. Missed treatment prior to Week 12 due to the COVID-19 pandemic: had participants not missed treatment prior to Week 12 due to the COVID-19 pandemic (*hypothetical strategy*)

- **The summary measure**: difference in mean absolute change from baseline in UAS7 score at Week 12 between treatments (ligelizumab 72 mg q4w vs placebo/omalizumab and ligelizumab 120 mg q4w vs placebo/omalizumab).

All other intercurrent events occurring during the COVID-19 pandemic period that are not due to pandemic related operational complications will be classified as intercurrent events unrelated to COVID-19 pandemic and handled by the treatment policy strategy.

2.5.2 Statistical hypothesis, model, and method of analysis

The analysis of primary and secondary endpoints included in the hierarchical testing strategy will focus on adult subjects.

The statistical hypotheses test for the primary endpoint being tested is that the absolute change from baseline in UAS7 score at Week 12 in any of the ligelizumab groups (low or high dose) is not superior to the omalizumab group and placebo group, i.e.,

$H_{01}: \mu_{ligelizumab} \geq \mu_{Placebo}$ versus $H_{A1}: \mu_{ligelizumab} < \mu_{Placebo}$

$H_{01}': \mu_{ligelizumab} \geq \mu_{omalizumab}$ versus $H_{A1}': \mu_{ligelizumab} < \mu_{omalizumab}$

where μ is the mean change from baseline of UAS7 at Week 12.

Stating these formulae in another way gives the following:

H_{1l}, H_{1h}: Ligelizumab low or high dose is not superior to placebo with respect to change from baseline at Week 12;

H_{1l}', H_{1h}': Ligelizumab low or high dose is not superior to omalizumab with respect to absolute UAS7 change from baseline at Week 12.

A linear mixed model with repeated measures (MMRM) will be used to estimate treatment differences for change from baseline in UAS7 score at Week 12, based on the FAS. [redacted] Repeated measures within subject are modeled using an unstructured covariance of the error terms. For the primary analysis, data up to Week 12 will be used in the model. [redacted]

[redacted]

Multiple intercurrent events occurring prior to Week 12

If there are multiple intercurrent events occurring prior to Week 12, use of rescue medication prior to Week 12 will be ignored. Besides that, in general, if other intercurrent events occur prior to Week 12 with different relations to the COVID-19 pandemic, i.e., at least one of the intercurrent event is classified as being unrelated to COVID-19 and others are classified as being related to COVID-19 operational complications, the treatment policy strategy will be applied. Therefore, multiple intercurrent events (except for use of rescue medication) occurring prior to Week 12 will be handled by the hypothetical strategy only if all of them are classified as being due to COVID-19 operational complications.

[redacted]

[redacted]

[redacted]

2.5.3 Handling of missing values

The UAS7 score is derived from the sum of the HSS7 score and the ISS7 score, previously defined (Section 2.5.1). 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 daily 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.

Multiple imputation (MI)

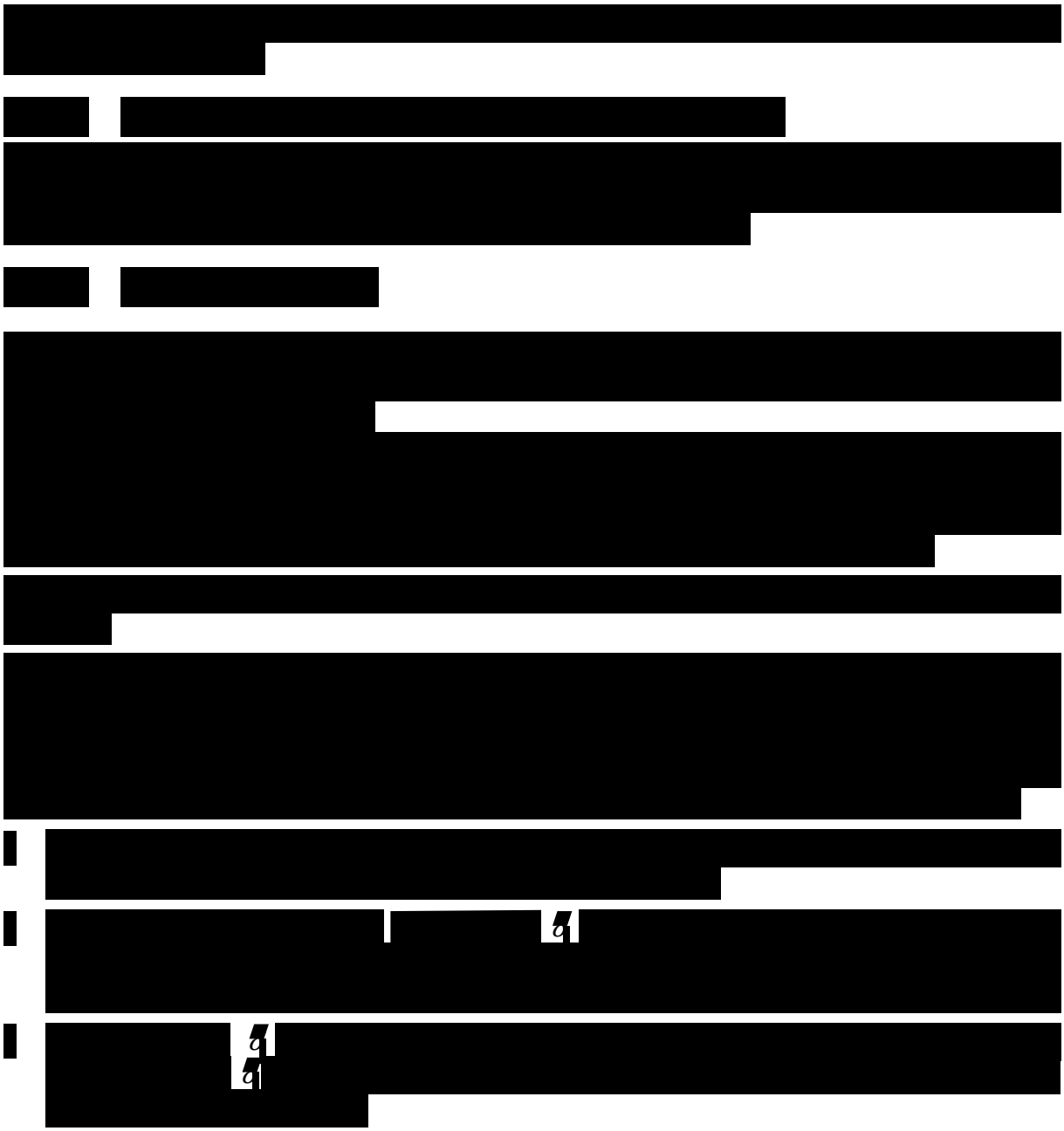
Multiple imputation is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard 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.

[redacted]

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.

[redacted]



2.6 Analysis of the secondary objectives

2.6.1 Secondary endpoints

The COVID-19 pandemic related intercurrent events will be handled the same way for the primary estimand. The definition of secondary estimand and the corresponding handling of intercurrent events are provided below for each of the secondary endpoints.

- **Percentage of subjects achieving UAS7=0 at Week 12**

The percentage of subjects with UAS7=0 at Week 12 will be analyzed using a logistic regression model
Odds ratios will be computed for comparisons of ligelizumab versus placebo or omalizumab

utilizing the logistic regression model fitted. Group comparisons will be summarized using odd ratios and 95% confidence intervals. [redacted] The odds ratios and their 95% CIs will be generated by the exponentiated of the model estimate.

[redacted]

- **Absolute change from baseline in ISS7 score at Week 12.**

The definition of the five attributes (expect for the endpoint) for the primary estimand would be applied for this secondary endpoint. The absolute change from baseline in ISS7 score at Week 12 will be analyzed analogously to absolute change from baseline in UAS7 score at Week 12, i.e. using MMRM modeling as the primary analysis. The missing data handling will follow the descriptions in Section 2.6.3.

- **Percentage of subjects achieving DLQI = 0-1 at Week 12.**

[redacted]

An overall score will be calculated according to the scoring manual. The DLQI=0-1 response status will be defined based on the total DLQI score at week 12 and whether or not the subject discontinued from study treatment prior to week 12. That is, only if DLQI ≤ 1 at week 12 and the subject has not discontinued treatment prior to week 12, it will be considered as response, otherwise it is considered as a non-response.

[redacted]

The DLQI =0-1 response at Week 12 will be analyzed using a logistic regression model [redacted] The same analysis as UAS7=0 will be performed. [redacted]

- **Cumulative number of weeks that subjects achieve AAS7=0 responses between 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 AAS scores of the 7 days preceding the visit, and ranges from 0 to 105.

[redacted]

[redacted]

The cumulative number of weeks achieving AAS7=0 response between baseline and Week 12 will be modelled using a negative binomial regression [redacted]

In the negative binomial regression model, the response variable is the number of AAS7=0 weeks during the treatment period for each patient. The patient's time in the treatment period up to Week 12 (natural log of proportion of time in treatment period, i.e., natural log of [days in treatment period/84 days]) is used as an offset variable to obtain the AAS7=0 rate, adjusted for the varying lengths of patient's time in the randomized treatment period.

Treatment comparisons of Ligelizumab 72 mg and 120 mg doses versus Omalizumab 300mg or placebo will be performed using the ratio of the AAS7-free rates until Week 12, derived from the negative binomial model.

2.6.2 Statistical hypothesis, model, and method of analysis

Testing strategy

The efficacy analysis of secondary variables listed in the testing strategy will focus on adult subjects. The efficacy information for adolescent subjects will be provided in a descriptive manner over time.

The following null hypotheses (H_0) will be tested against the respective alternative hypotheses (H_A) in a closed testing procedure (Bretz et al 2009), thus controlling the family-wise type I error which is set to 0.025 (one-sided) at the level of the individual studies, and for the pooled dataset of both studies as listed in [redacted]:

Primary endpoint

UAS7 score change from baseline at Week 12

H_{01}: $\mu_{ligelizumab} \geq \mu_{Placebo}$ versus H_{A1}: $\mu_{ligelizumab} < \mu_{Placebo}$

H_{01}': $\mu_{ligelizumab} \geq \mu_{omalizumab}$ versus H_{A1}': $\mu_{ligelizumab} < \mu_{omalizumab}$

where μ is the mean change from baseline in UAS7 at Week 12, as described in Section 2.5.1.

Secondary endpoints

Percentage of subjects achieving UAS7=0 at Week 12

H_{02}: $\pi_{ligelizumab} \leq \pi_{Placebo}$ versus H_{A2}: $\pi_{ligelizumab} > \pi_{Placebo}$

H_{02}': $\pi_{ligelizumab} \leq \pi_{omalizumab}$ versus H_{A2}': $\pi_{ligelizumab} > \pi_{omalizumab}$

where π is the percentage of subjects achieving UAS7=0 at Week 12.

Stating these formulae in another way gives the following:

H_{2l}, H_{2h}: Ligelizumab low or high dose is not superior to placebo with respect to UAS7 = 0 response at Week 12;

H_{2l}', H_{2h}': Ligelizumab low or high dose is not superior to omalizumab with respect to UAS7 = 0 response at Week 12.

ISS7 score change from baseline at Week 12

H_{03}: $\mu_{ligelizumab} \geq \mu_{Placebo}$ versus H_{A3}: $\mu_{ligelizumab} < \mu_{Placebo}$

H_{03}': $\mu_{ligelizumab} \geq \mu_{omalizumab}$ versus H_{A3}': $\mu_{ligelizumab} < \mu_{omalizumab}$

where μ is the mean change from baseline in ISS7 to Week 12.

Stating these formulae in another way gives the following:

H_{3l}, H_{3h}: Ligelizumab low or high dose is not superior to placebo with respect to the absolute change from baseline to Week 12 of ISS7;

H_{3l}', H_{3h}': Ligelizumab low or high dose is not superior to omalizumab with respect to the absolute change from baseline to Week 12 of ISS7.

Percentage of subjects achieving DLQI=0-1 at Week 12

H_{04}: $\pi_{ligelizumab} \leq \pi_{Placebo}$ versus H_{A04}: $\pi_{ligelizumab} > \pi_{Placebo}$

H_{04}': $\pi_{ligelizumab} \leq \pi_{omalizumab}$ versus H_{A4}': $\pi_{ligelizumab} > \pi_{omalizumab}$

where π is the proportion of subjects achieving DLQI = 0 or 1 at Week 12.

Stating these formulae in another way gives the following:

H_{4l}, H_{4h}: Ligelizumab low or high dose is not superior to placebo with respect to the DLQI = 0 or 1 response at Week 12;

H_{4l}', H_{4h}': Ligelizumab low or high dose is not superior to omalizumab with respect to the DLQI = 0 or 1 response at Week 12.

Cumulative number of weeks that subjects achieve AAS7=0 responses between baseline and Week 12

H_{05}: $\mu_{ligelizumab} \leq \mu_{Placebo}$ versus H_{A5}: $\mu_{ligelizumab} > \mu_{Placebo}$

H_{05}': $\mu_{ligelizumab} \leq \mu_{omalizumab}$ versus $_{HA5}'$: $\mu_{ligelizumab} > \mu_{omalizumab}$

where μ is the mean cumulative number of weeks achieving AAS7 = 0 during 12 weeks.

Stating these formulae in another way gives the following:

H_{5l}, H_{5h}: Ligelizumab low or high dose is not superior to placebo with respect to the cumulative number of weeks achieving AAS7 = 0 during 12 weeks;

H_{5l}', H_{5h}': Ligelizumab low or high dose is not superior to omalizumab with respect to the cumulative number of weeks achieving AAS7 = 0 during 12 weeks.

[redacted]

A testing procedure is proposed with type-I-error control in the planned submission package which consists of studies C2302 and C2303 (both with identical design). Hypotheses can only be tested in the order as indicated by the arrows for alpha propagation for each individual study as listed in Figure 2-1. If the primary endpoint has demonstrated the superiority versus placebo and versus omalizumab, the alpha could be passed to the tests for all of the secondary endpoints. For the secondary endpoints, if an endpoint demonstrates superiority versus placebo based on each of the individual studies, the same endpoint can be tested based on the pooled dataset as pre-specified.

For the comparison versus placebo based on each individual study, the initial alpha level for each branch is set to $\alpha/2 = 0.0125$ (one-sided). The first hypothesis (H_{1h} and H_{1l}) is tested with $\alpha/2 = 0.0125$ (one-sided) of high/low dose ligelizumab versus placebo regarding the primary endpoint. If either of the hypotheses is rejected, the corresponding second hypothesis (H_{1h}' and/or H_{2l}') of high/low dose ligelizumab versus omalizumab is tested with $\alpha/2$. The same principle applies for moving from the second to the third hypothesis. If either H_{3h} and/or H_{3l} is rejected, $\alpha/4$ is passed to the other dose on primary endpoint testing together with the initial $\alpha/2$. The rest $\alpha/4$ is passed to test H_{4h} and/or H_{4l} for the same ligelizumab dose versus placebo. The testing within each sequence is strictly hierarchical, so that null hypotheses can be tested along the pre-defined order at the level assigned to the respective sequence until a null hypothesis cannot be rejected, at which point the testing in that sequence stops. If all null hypotheses in either of the sequence can be rejected, the “unused” type I error is transferred to the other

sequence, so that the initial level in the other sequence is increased. Thus, the family-wise type I is controlled at $\alpha = 0.025$ (one-sided).

[redacted]

2.6.3 Handling of missing values

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

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]

2.7 Safety analyses

All safety endpoints (i.e. adverse events, laboratory data, vital signs, and ECG) will be summarized by treatment for all subjects of the safety set. All data will be included in the analysis regardless of rescue medication use. In addition safety endpoints for adults and adolescents will be presented separately.

Treatment groups for evaluation of treatment period

The summaries for evaluation of the treatment periods will allow for comparisons of treatment groups with placebo, before treatment switching is initiated. Therefore, the safety data for the placebo-ligelizumab 120mg group will be provided in two separate periods. As concomitant medication and adverse event tables will be provided for the treatment period up to week 24 separately, the Week 24 treatment period definition is the treatment period up to Week 24 dosing date (excluding the Week 24 dosing date). For the Placebo-QGE120mg q4w group, if the first dosing date transitioning to QGE happened earlier or later than the Week 24 dosing date (e.g. Week 20 or Week 28) due to a dosing error, the placebo treatment period will be cut-off by all the information prior to the first QGE dosing date. The detailed description of the Week 24 cutoff date definition is provided in the statistical analysis plan appendix.

Treatment groups for evaluation of entire study

The summaries for evaluation of entire study will include all the information following the study design treatment groups.

Table 2-4 Treatment groups for safety analysis

	Ligelizumab 72mg	Ligelizumab 120mg	Omalizumab 300mg	Placebo only period	Transitioned to Ligelizumab 120mg period	Placebo-Ligelizumab 120 mg
Treatment Period up to 24 weeks	Yes	Yes	Yes	Yes[1]	No	No
Entire Study	Yes	Yes	Yes	No	Yes[2]	Yes[3]

[1] The information before the treatment switching is initiated will be included. It means only the safety information from the period when patients receive placebo will be included in the analysis.

[2] The information after the treatment transitioned is initiated will be included. It means only the safety information from the period when patients receive ligelizumab 120 mg will be included in the analysis.

[3] The Placebo-Ligelizumab 120 mg group will only be included in the baseline/screening patients summary table.

2.7.1 Adverse events (AEs)

Treatment emergent adverse events (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. Treatment emergent adverse events will be summarized by the actually received treatment group.

TEAEs will be summarized by presenting, for each treatment group, the number and percentage of subjects having any TEAE, having a TEAE in each primary system organ class and having each individual TEAE (preferred term). For the patients in the placebo arm, adverse events after switching to ligelizumab (on or after Week 24) will be summarized separately for the treatment phase. The summary of the TEAEs up to Week 24 will include all the TEAEs up to Week 24 for all the treatment groups, including the placebo only group. The summary of the TEAEs for the entire study will be provided for all the treatment groups listed in Table 2-4.

Summaries will also be presented for TEAEs by severity and for study treatment related TEAEs. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

Separate summaries will be provided for serious treatment emergent adverse events (TESAEs), related TESAEs and other significant adverse events – TEAEs leading to discontinuation and TEAE adverse events of special interest (AESIs). The summary of TESAEs and other significant adverse events will be provided in the same manner as the TEAE summary tables. For AESIs with adjudication (anaphylaxis, malignancy, CCV), separate listings will be provided based on the adjudicated results.

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.

2.7.1.1 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 in each study group.

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" 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 24 for the placebo 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 $L = \frac{0.5 C_{\alpha/2,2n}}{\sum t_i}$ 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, PT level
2. Most frequent (at least 2% in any treatment group) TEAE: Primary SOC level, PT level
3. Treatment emergent AE of special interest.

2.7.1.2 Adverse events of special interest / grouping of AEs

Adverse events of special interest for ligelizumab treatment will also be summarized. AEs of special interest for QGE031 treatment include the following, specified as compound-level risk factors defined in the Case Retrieval Strategy (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 treatment emergent 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.

[redacted]

Furthermore, for time to first treatment emergent injection site reaction, the Kaplan-Meier estimator will be used to estimate the cumulative incidence function in each treatment group for 24 weeks treatment period and the entire study separately. Log-rank test will be performed between the treatment groups. Of note, for Placebo - QGE031 120mg group, the injection site reaction occurred during placebo only period will be excluded from the analysis for the entire study, and log-rank test will not be performed against this transitioned to QGE study for the entire study analysis.

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.

2.7.2 Deaths

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

2.7.3 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 and maximum/minimum value will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline values for quantitative parameters, and the maximum/minimum value could come from post-baseline scheduled, unscheduled or premature discontinuation visits. For categorical parameters, frequencies by categories at each visit will be summarized. A shift table from baseline to the most extreme post-baseline value will be presented based on normal range as well. Data from local laboratories will not be included in the summary tables.

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 ">").

The number of patients with newly occurring or worsening abnormalities during the study will be listed by treatment based on the notable criteria specified in the protocol (See Appendix 1). 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.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

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

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

The following will be considered as notable values for adults: QT > 500 msec; QTcF > 450 msec (males), QTcF > 460 msec (females); QTcF change from baseline > 30 msec, >60 msec; PR > 250 msec. The following were considered as notable ECG values for adolescents: QTcF

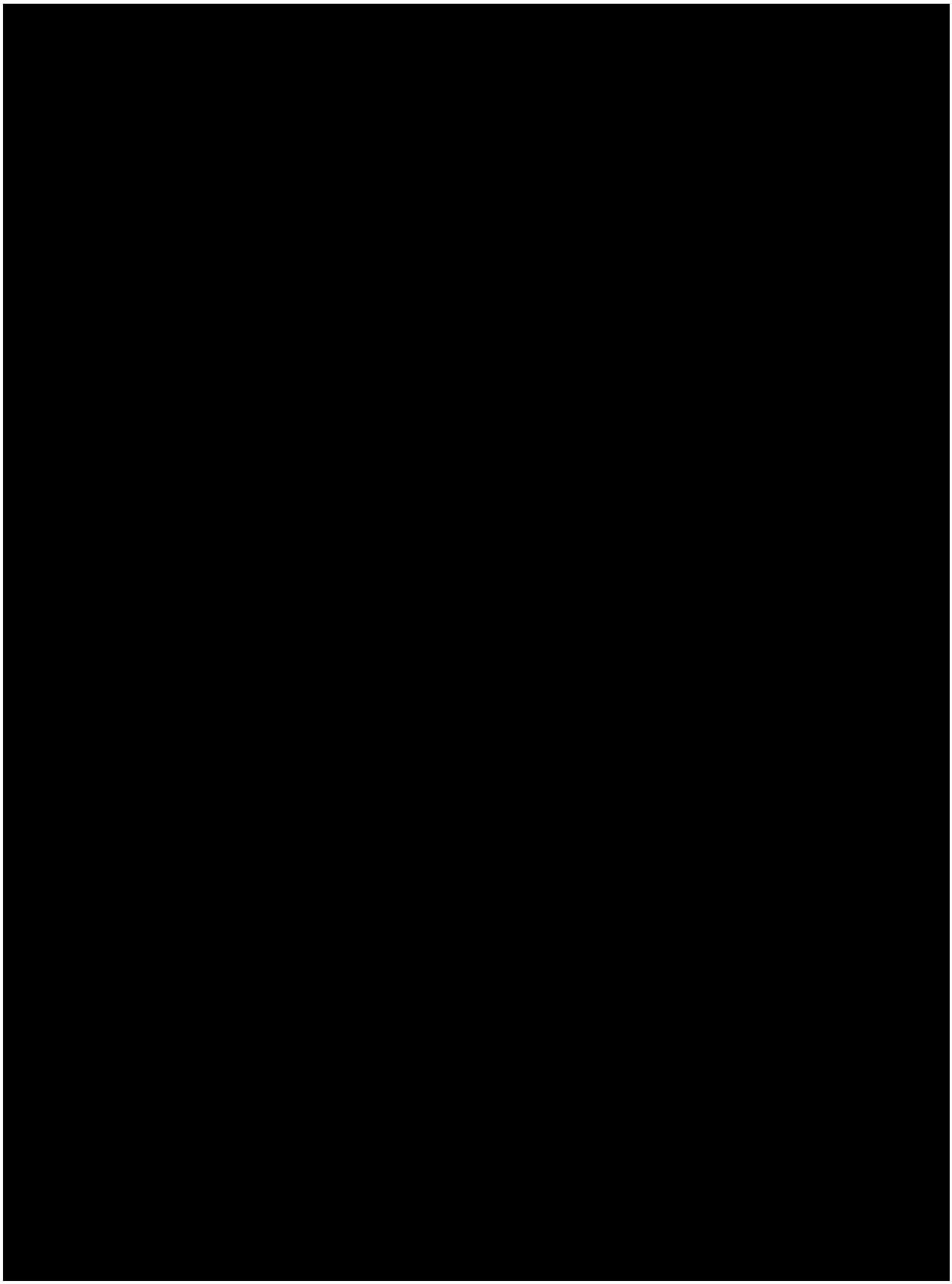
>450 msec (males), QTcF >460 msec (females); QTcF change from baseline >30 msec, >60 msec; PR >250 msec.

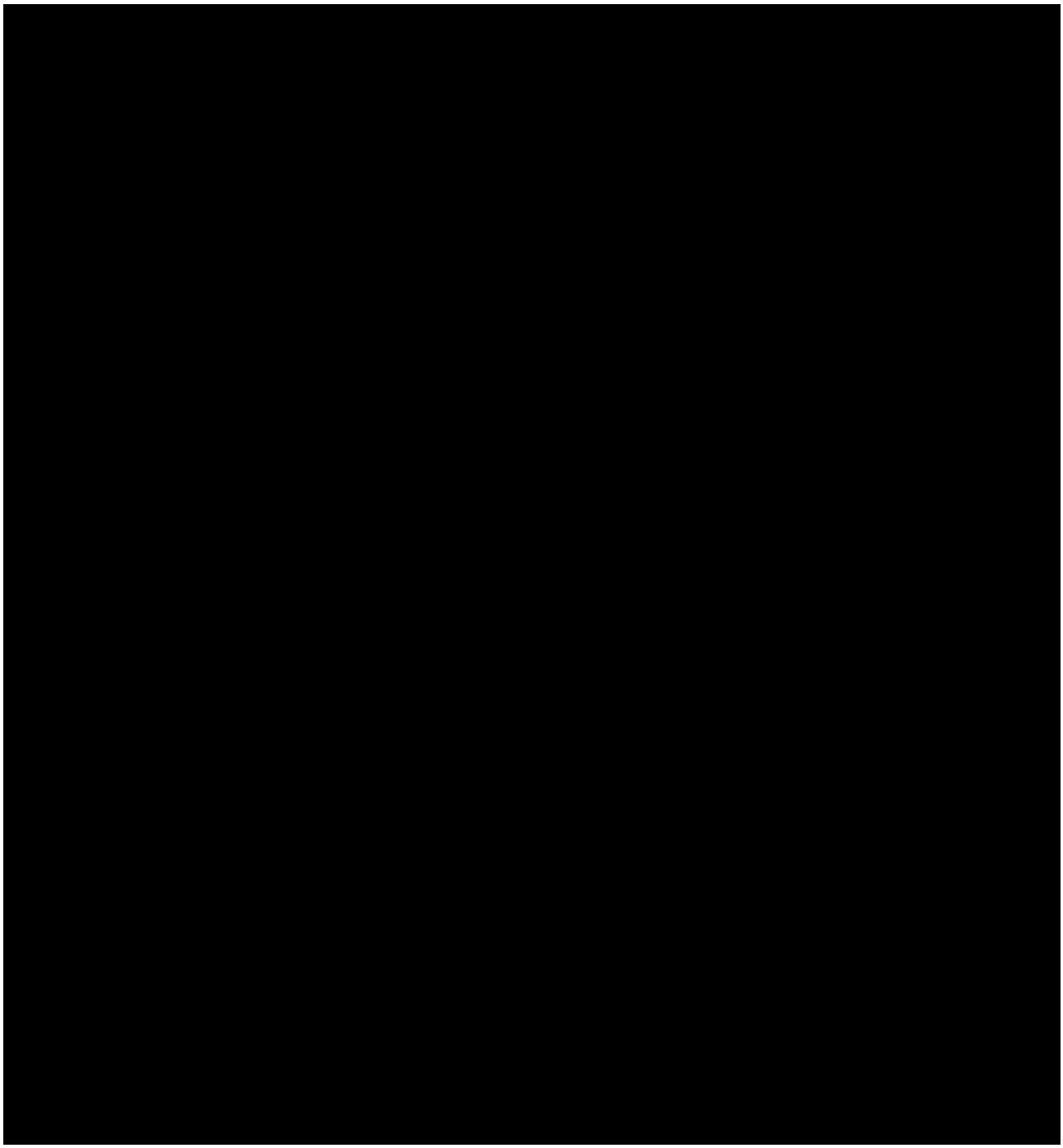
2.7.4.2 Vital signs

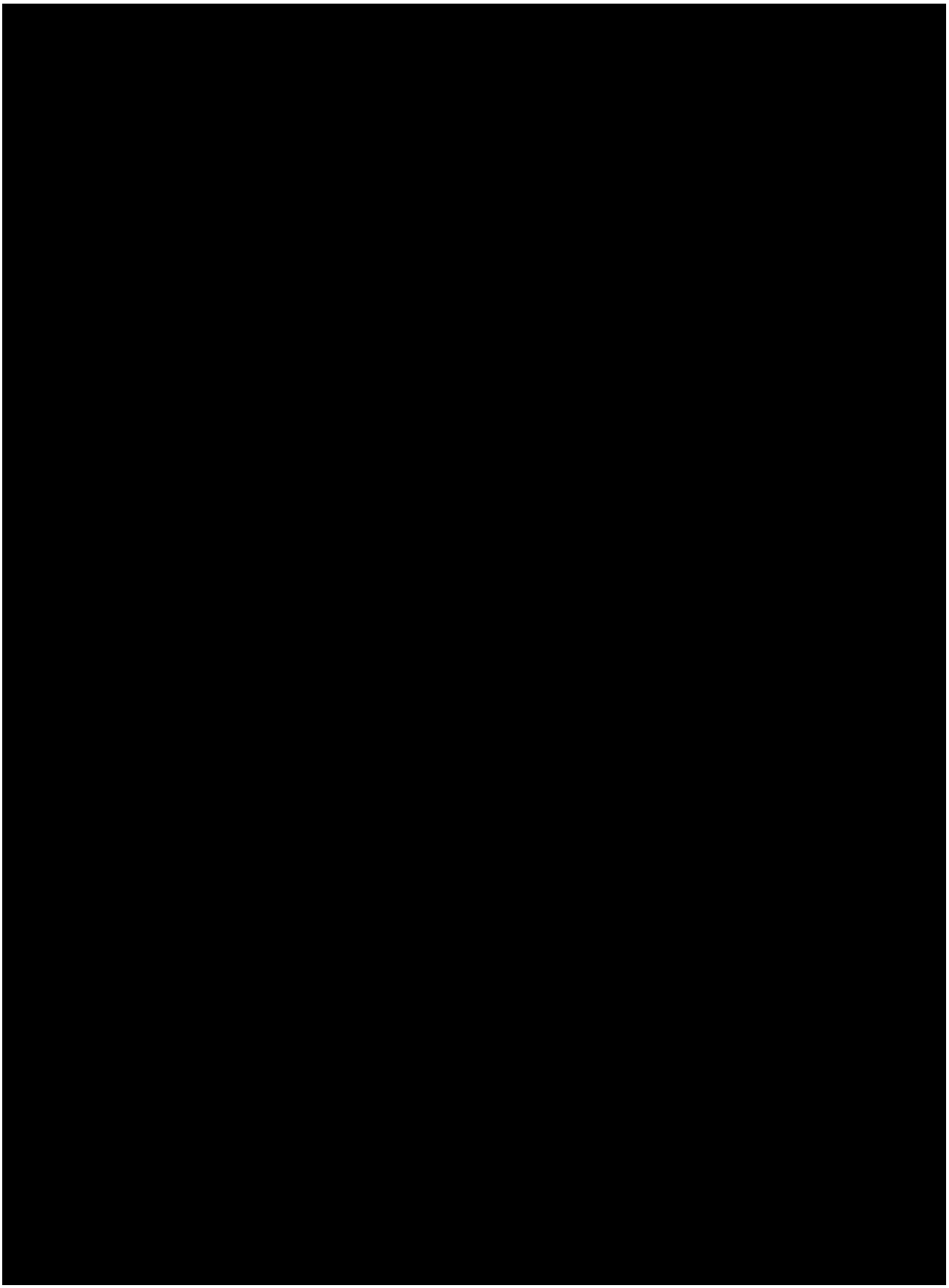
Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for subjects with both baseline and post-baseline values. The number of patients with newly occurring or worsening abnormalities during the study will be listed by treatment based on the notable vital signs defined as below:

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

[redacted]







[redacted]

2.10 Patient-reported outcomes

All PRO endpoints will be summarized using FAS. The data will be analyzed separately for adults and adolescents.

The long term efficacy analyses for Week 24 and Week 52 will be provided based on individual study data, as well as based on the pooled dataset.

2.10.1 Urticaria Patient Daily Diary (UPDD)

- Absolute change from baseline of UAS7, ISS7 at Week 24.

The absolute change from baseline in UAS7 or ISS7 score at Week 24 will be analyzed using the same MMRM model for absolute change from baseline of UAS7 score at Week 12. Intercurrent events occurred post baseline and before Week 24 will be handled analogously to the primary estimand strategy. Specifically,

- The COVID-19 unrelated intercurrent events prior to Week 24 will be handled through the treatment policy strategy, similar as the primary analysis.
- Intercurrent events related to COVID-19 operational complications occurring between Week 12 and Week 24 will be handled through the hypothetical strategy, similar as the primary analysis.

Of note, for the Placebo-QGE120mg q4w group, if the first dosing date transitioning to QGE happened more than 1 week earlier than the Week 24 eDiary efficacy assessment date, the efficacy data (UAS7, ISS7, HSS7) after first QGE dosing date will be excluded from the Week 24 analysis, and the resulting missing data after this step will be imputed under the MAR assumption using the multiple imputation.

In addition, a supplementary analysis for the absolute change from baseline of UAS7 at Week 24 will also be performed analogously to that for absolute change from baseline of UAS7 at Week 12. Use of rescue medication taken will be handled by composite strategy. Of note, after week 12, patients are permitted to use two types of rescue medications, the H1-AH rescue medication and oral corticosteroids, which will be considered differently. More details are provided in the supplementary estimand section in the Appendix.

- Absolute change from baseline of UAS7, ISS7 at Week 52.

The absolute change from baseline in UAS7 or ISS7 score at Week 52 will be analyzed using the same MMRM model for absolute change from baseline of UAS7 score at Week 12. Additional baseline variables might be included in the model, if needed. According to Phase II clinical data, the treatment effect will reach the stable status after 24 weeks treatment. Therefore, all the efficacy data collected will be included in MMRM modelling analysis. The missing data caused by intercurrent events or any other reasons will be multiply imputed following the MAR assumption for the treatment effect at Week 52.

- Proportion of subjects achieving UAS7=0 response at Week 24.

The proportion of subjects achieving UAS7=0 response at Week 24 will be analyzed using the same logistic regression model for UAS7=0 at Week 12. Additional baseline variables

might be included in the model, if needed. Intercurrent events occurred post baseline and before Week 24 will be handled analogously to the secondary estimand strategy for UAS7=0 at Week12. Specifically:

- The COVID-19 unrelated intercurrent events prior to Week 24 will be handled through treatment policy strategy, and the missing data will be imputed as non-response following the secondary estimand strategy.
- For intercurrent events related to COVID-19 operational complications prior to Week 24, they will be handled through hypothetical strategy, and the resulting missing data will be multiply imputed following the MAR assumption.

- Proportion of subjects achieving UAS7=0 response at Week 52.

The proportion of subjects achieving UAS7=0 response at Week 52 will be analyzed using the same logistic regression model for UAS7=0 at Week 12. Additional baseline variables might be included in the model, if needed. The missing UAS7=0 response will be multiply imputed following the MAR assumption.

[redacted]

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 patients enrolled by mistake with UAS7=0 at the baseline visit, they will be excluded from this time to achievement of complete UAS7 response analysis. 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.

[redacted]

For Placebo - QGE031 120mg group, only the placebo treated period will be included for this analysis. That is, time to achievement of response analysis will only include the efficacy information during the placebo only period. The information after the patients transitioned to QGE031 120mg will be censored from the first dose of QGE031 treatment.

- 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 loss of complete UAS7 response from Week 52 will be analyzed using a Cox regression model and 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.

For all the time-to-event analyses, if any patient has taken concomitant omalizumab (outside of study assigned treatment) (e.g., Omalizumab use during the follow-up period), time to event will be considered censored at the date of the last observation before the first time of the unplanned omalizumab use.

- Time to UAS7 ≥ 16 for patients having achieved UAS7 ≤ 6 at week 52

[redacted]

2.10.2 Dermatology Life Quality Index (DLQI/CDLQI)

The Dermatology Life Quality Index (DLQI) is a 10-item dermatology-specific health-related quality of life measure presented to each subject, from randomization 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 2-5).

Table 2-5 DLQI domains

Domain	Relevant Question	Maximum score
Symptoms and feelings	Questions 1 and 2	6

Domain	Relevant Question	Maximum score
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 2-6).

Table 2-6 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

- Improvement of quality of life, assessed as absolute and relative change from baseline of DLQI/CDLQI score at Week 12

  The baseline and week 12 overall DLQI/CDLQI scores will be derived from the questionnaires assessed at the Day 1 and Week 12 visits. Change from baseline to week 12 in overall DLQI/CQLQI score will be made using an MMRM model with treatment group, geographic region, visit, baseline DLQI/CDLQI score and both treatment-by-visit interaction and interaction of baseline DLQI/CDLQI score by visit as covariates.

- Percentage of subjects achieving DLQI=0-1 at Week 24

The proportion of subjects achieving DLQI=0-1 at Week 24 will be analyzed using the same logistic regression model for DLQI=0-1 at Week 12. Additional baseline variables might be included in the model, if needed.

The intercurrent events will be handled as below:

- The COVID-19 unrelated intercurrent events prior to Week 24 will be handled through composite strategy, and the missing data will be imputed as non-response following the secondary estimand strategy for DLQI=0-1 at week 12.
- For intercurrent events related to COVID-19 operational complications, they will be handled analogously to the analysis for percentage of subjects achieving UAS7=0 at Week 24 following the hypothetical strategy, and the resulting missing data will be imputed under MAR assumption.

- Percentage of subjects achieving DLQI=0-1 at Week 52.
  The proportion of subjects achieving DLQI=0-1 at Week 52 will be analyzed using the same logistic regression model for DLQI=0-1 at Week 12. Additional baseline variables might be included in the model, if needed. The missing DLQI=0-1 response will be multiply imputed following the MAR assumption.

[redacted]

Duplicate data handling of DLQI

For post baseline assessments of DLQI, if any questionnaires are completed more than once per visit, then the pre-dosing assessment closest to the dosing date (or visit date if missing treatment) will be used.

If multiple assessments are taken at one visit with same date, then select the first one with earlier time. If the time part is the same or missing, then the worst outcome (i.e., the highest score) of the duplicate observation will be used in analysis.

2.10.3 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.

- Cumulative number of weeks that subject achieve AAS7=0 responses between baseline and Week 24

The cumulative number of weeks achieving AAS7=0 responses between baseline and Week 24 will be analyzed analogously to the analysis for cumulative number of weeks achieving AAS7=0 between baseline and Week 12 using a negative binomial regression model with log link. Intercurrent events occurred post baseline and before Week 24 will be handled analogously to the secondary estimand strategy at Week 12.

- Cumulative number of weeks that subject achieve AAS7=0 responses between baseline and Week 52

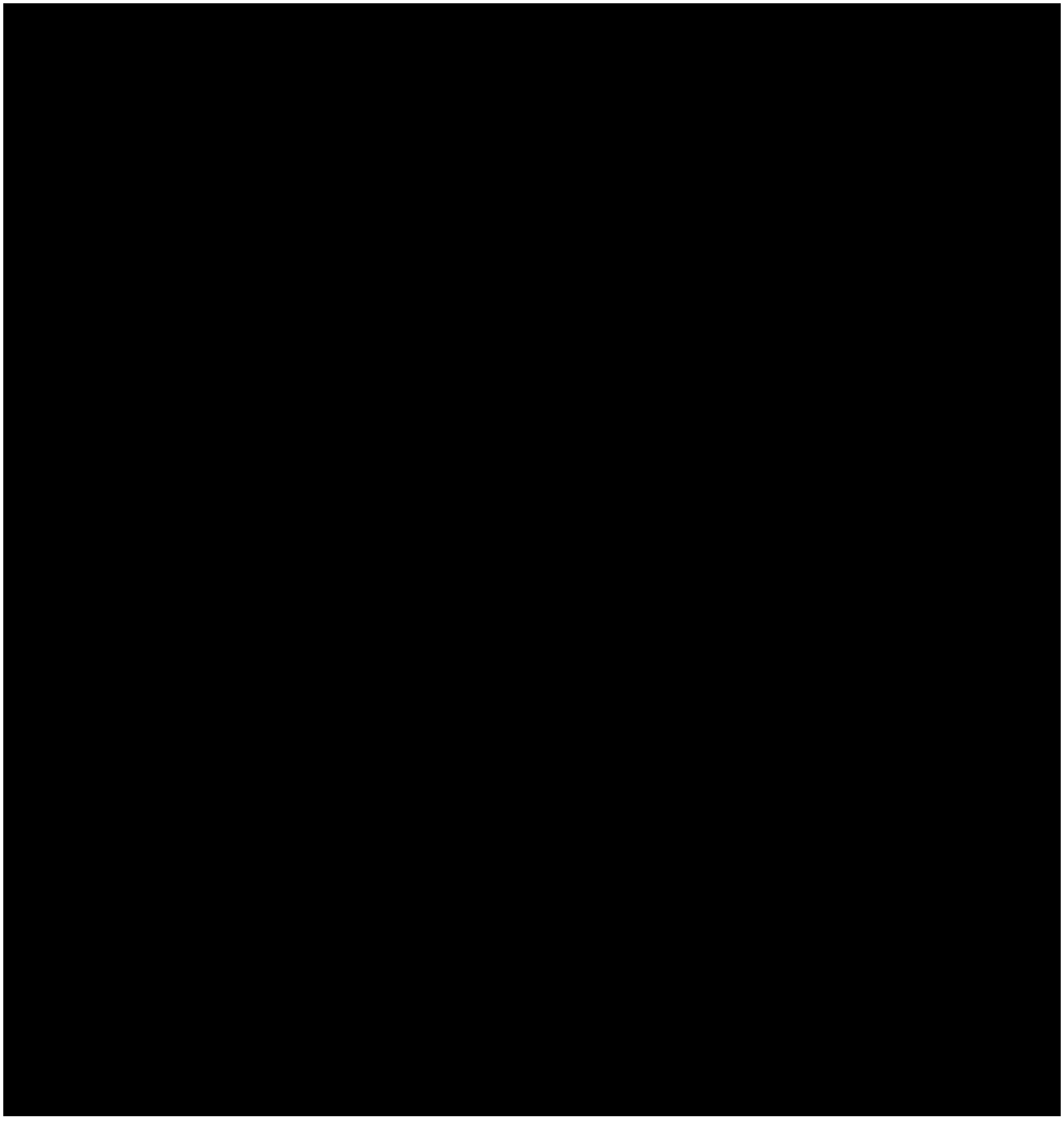
The cumulative number of weeks achieving AAS7=0 responses between baseline and Week 52 will be analyzed analogously to the analysis for cumulative number of weeks achieving AAS7=0 between baseline and Week 52 using a negative binomial regression model with log

link. The missing AAS7=0 response up to Week 52 will be multiply imputed following MAR assumption.

- Cumulative angioedema burdened weeks (AAS7=0) by visit up to end of study

Summary statistics will be provided for cumulative angioedema burdened weeks (AAS7 = 0) up to end of treatment and up to end of study. Also, summary statistics will be provided for absolute values as well as for the absolute scores by visit and treatment group.

In patients with angioedema at baseline (AAS7 > 0), a separate summary table will be provided.



[redacted]

2.12 Other Exploratory analyses

Not applicable.

2.13 Interim analysis

DMC meeting will be held at least [redacted] for periodical safety review.

To maintain the blind the outputs for the DMC will be conducted in a [redacted] manner (using [redacted] treatment code) by the independent statistician and programmer [redacted] who are not involved in CSR reporting. Details will be provide charter.

Outputs to be provided to the DMC will be specified in the separate document.

A primary analysis will be performed after all adults subjects have completed the treatment period (Week 52 visit). All available study data will be included in the Week 52 interim analyses, including the data from the follow-up period. An unblinded study team will conduct

the Week 52 primary efficacy analysis and a separate blinded study team will oversee the conduct of the study until the final database lock, after all the subjects have completed end of study participation. All investigators, site personnel, subjects, and the blinded study team will remain blinded until the final database lock has occurred. No access to the interim results or individual treatment assignment will be provided to the investigators, site personnel, subjects, and blinded study team.

2.14 Final analysis

The final analysis will focus on the data collected after the interim DBL. The results that were final at the time of the interim DBL will not be repeated, [redacted] Additionally, any output based on a pooled analysis set will not be repeated. Any analysis that would include new data not present at the time of the interim DBL will be refreshed, e.g., outputs up to the end of the study.

[redacted]

3 Sample size calculation

3.1 Sample size justification for adult subjects

The sample size justification is based on UAS7 change from baseline and achievement of UAS7 = 0. Due to the much larger effect sizes versus placebo, the sample sizes are driven by the assumptions underlying the comparisons of ligelizumab versus omalizumab 300 mg, as initial sample size estimation. To avoid assigning an unnecessary large number of subjects to placebo, subjects will be randomized in a 3:3:3:1 ratio to ligelizumab high dose, ligelizumab low dose, omalizumab and placebo, respectively. All initial sample size calculations were performed with nQuery Advisor 7.0.

UAS7 change from baseline at Week 12

Based on interim results from CQGE031C2201, it is assumed that the difference between ligelizumab and omalizumab 300 mg mean change of UAS7 from baseline to Week 12 is at least 3.5 in favor of ligelizumab, with common standard deviation of approximately 13. Although it is planned to use a repeated measures model for the analysis, an approximate sample size can be based on a simple t-test, assuming type I error 0.025 (one-sided) and power 90%, which results in 291 per group.

This will give > 99% power for the same comparison versus placebo, if the placebo sample size is only 97 and the assumed difference is 8.

Achievement of UAS7 = 0 at Week 12

A sample size of 291 per group, which is required for the UAS7 change from baseline, will provide more than 90% power based upon a 2 group continuity corrected χ^2 test with a 0.025

one-sided significance level to detect the difference between a proportion of 0.30 (omalizumab 300 mg) and a proportion of 0.45 (ligelizumab, odds ratio of 1.909).

As for the change from baseline, the power for the comparison versus placebo is > 99% even if the placebo sample size is only 97 and the proportion of placebo treated subjects achieving UAS7 = 0 responses is around 10%. These power calculations are an approximation of the power achieved with the logistic regression approach.

The primary and secondary endpoints analyses were planned to use the multiple testing strategy to control the family-wise error at α=0.025 (one-sided). It is considered, however, this hierarchical approach could impact the sample size comparing the separate endpoint approach, which depends on how the recycled alpha will be used.

The power of each included endpoint was estimated following the testing strategy described in Section 2.6.2 and the results are presented in Figure 3-1. The initial sample size of 291subjects per group for treatment group and 97 subjects for placebo justified above was used to calculated the power based on the observed ligelizumab 72mg and 240mg from phase IIb data. Ligelizumab 72mg and 240mg groups were used as the representative of the effect size for the efficacious dose range, which covers the dose levels we will test for this study. It seems that the primary endpoint (UAS7 change from baseline) comparing with omalizumab or placebo (H1 or H2) could maintain the power of at least 90%. Meanwhile, the achievement of UAS7=0 could maintain at least 80% power.

The analysis strategy has been adjusted to mitigate the potential COVID-19 impact on the study. The original proposed sample size will be still sufficient to maintain the statistical power of the overall multiple testing strategy (at least 90%) for the primary endpoint (UAS7 change from baseline at Week 12) based on individual study data (see Figure 3-1 and Figure 3-2). The power of the key secondary endpoint (UAS7=0 response rate at Week 12) will be maintained (at least 90%) through the pooled data set as well. Detailed simulation results of the statistical power for the updated testing strategy are provided in the sample size justification document.

Figure 3-1 Power for all endpoints included in the multiple testing strategy (independent correlation between endpoints)

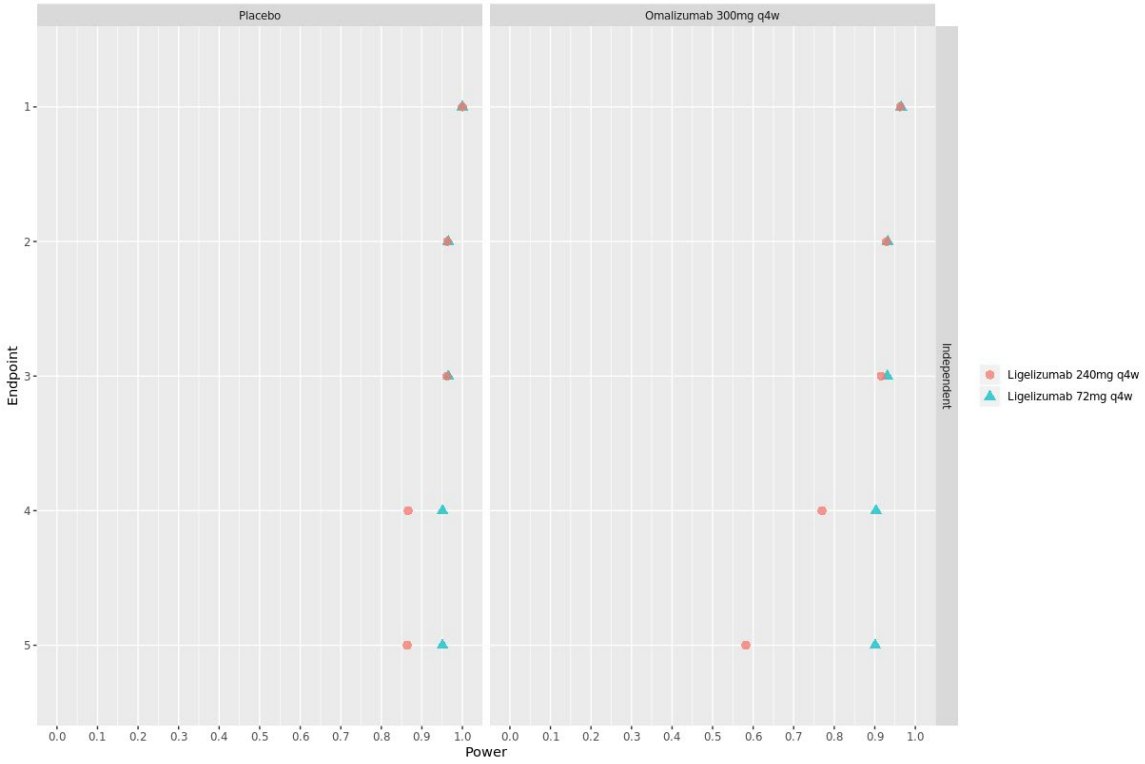
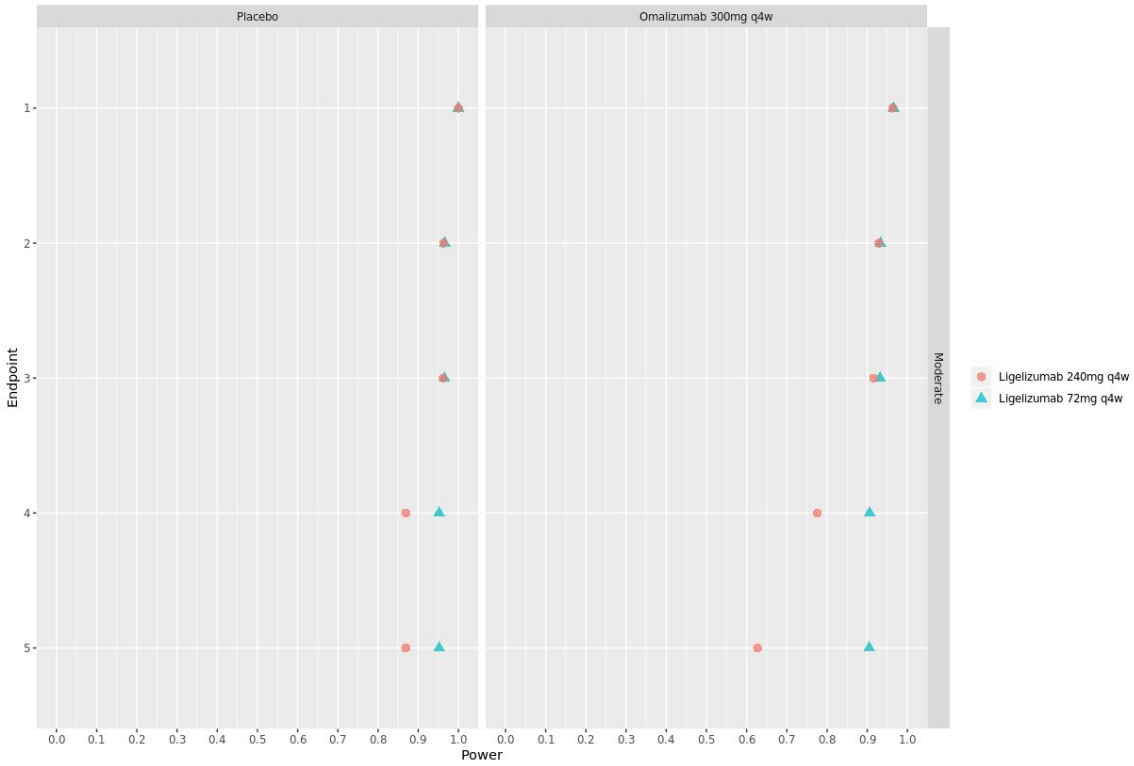

Placebo
Omalizumab 300mg q4w
Endpoint
1
2
3
4
5
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Power
Independent
Ligelizumab 240mg q4w
Ligelizumab 72mg q4w

Figure 3-2 Power for all endpoints included in the multiple testing strategy (moderate correlation between endpoints)



Study subjects will be encouraged to stay in the study and providing eDiary information even if they are discontinued early from the study treatment. The early discontinuation rate from study at Week 12 is only assumed to be around 5% based on the phase II study data.

In summary, the required adult sample size in each of the ligelizumab and omalizumab 300 mg arms is approximately 300, while the placebo sample size can be reduced to 100 for efficacy comparisons to maintain the statistical power based on the modified testing strategy.

3.2 Sample size justification for adolescent subjects

The target sample size of 50 adolescent subjects receiving ligelizumab treatment and completing the treatment period is based upon the expected prevalence of adolescent CSU patients in a representative patient population (see Table 12-1 of protocol for details). The annual prevalence of CSU in the pediatric population is low and comparable with adults (< 1%). Although the age-related prevalence of CSU for adolescent patients is similar to adults, the overall target for enrollment is impacted by the fact that 11 to 17 year old patients only comprise about 10% of the total population (9.5% of the population in the US Census Bureau).

A total of 100 adolescent subjects are planned to be enrolled equally across the CQGE031C2302 and CQGE031C2303 studies. Ninety adolescent subjects are planned to be randomized equally across the 2 ligelizumab and omalizumab treatment arms, and 10 adolescent subjects into the placebo arms.

Assuming an approximately 20% drop out rate for the adolescent subjects, this is anticipated to provide approximately 25 adolescent subjects in each of the 2 ligelizumab and the omalizumab arms, and 8 adolescent subjects in the placebo arms at the end of the studies.

4 Change to protocol specified analyses

NA

5 Appendix

5.1 Estimand charter

5.1.1 Primary estimand

This section describes the primary estimand and corresponding estimation procedures. These estimands are related to the primary efficacy endpoint expressed as a continuous PRO variable.

5.1.1.1 Main scientific objective

The scientific objective guiding the primary estimand is to show the superiority of ligelizumab compared to omalizumab and placebo, for the target population on the primary parameters.

A. To be evaluated using both itch (subjective) and hives (objective) components of the urticaria (UAS).

B. To be observed under the real clinical circumstance, i.e., to be evaluated regardless of the possible confounding effects caused by intake of background or rescue medication unrelated to the COVID-19 pandemic.

C. To be evaluated regardless of any other intercurrent events unrelated to the COVID-19 pandemic (following ITT principle), accounting for the other intercurrent events related to the COVID-19 pandemic due to operational complications.

5.1.1.2 The description of the primary estimand

The primary estimand is fully described by five attributes in Section 2.5.1.1.

[redacted]

[redacted]

[redacted]

5.3 Derivation rules for Week 24 treatment period

Week 24 treatment period cut-off date

The cutoff date for Week 24 treatment period is defined as below.

For the Placebo-QGE 120mg group,

1. The first QGE dosing date will be used if available;
2. Otherwise, if no QGE dosing happened, then the cutoff date = min(end of study date, withdrawal of ICF date, date of death, primary efficacy analysis cutoff date).

For other groups,

1. If patients complete treatment period or are still ongoing, the cutoff date is the first non-missing date of the following dates: Week 24 dosing date, Week 24 visit date, PD date of missing visit at Week 24, first dosing date + 24 weeks.
2. If patients early discontinue treatment,
    a. If last dosing visit is less than Week 24, then the cutoff date = min(end of study date, withdrawal of ICF date, date of death, primary efficacy analysis cutoff date)+1.
    b. If last dosing visit is great than or equal to Week 24, then the cutoff date is the first non-missing date of the following dates: Week 24 dosing date, Week 24 visit date, PD date of missing visit at Week 24, first dosing date + 24 weeks.

Lab/Vital Sign by-visit summary tables

For the Placebo-QGE 120mg group, the by-visit summary will be presented without splitting into "Placebo only" and "Transitioned to QGE 120mg", i.e., any assessments happened at Week 24 will contribute to Week 24 row – no need to consider if it happened before/on/after Week 24 dosing date; the maximum and minimum summary will be presented twice for the "Placebo only" and "Transitioned to QGE 120mg" periods, which are defined in Table 2-4.

Visit assessments happened at the same day with first QGE dosing date will be counted into "Transitioned to QGE 120mg".

Adverse events/Concomitant Medications summary tables:

The summary table is will be generated based on the cut-off date following the definition of "treatment period up to Week 24" in Table 2-4:

Adverse events/Concomitant Medications happened at the same day with this cut-off date NOT included in "treatment period up to Week 24" tables.

5.4 Imputation rules

5.4.1 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.

5.4.2 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	(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, 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.

5.4.3 Concomitant medication date imputation

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

- 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	**(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	**(3.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).
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, 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).
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, 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.

5.4.4 Prior therapies date imputation

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

5.4.5 Surgical and medical procedures date imputation

Missing data for surgical and medical procedures will be imputed following the same rule for CM date.

5.4.6 Medication history date imputation

Only missing medication history date for CSU diagnosis will be imputed to calculate the duration of CSU. No additional imputation will be performed for other medical history information.

Rules for imputing the MH start date:

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

b) Else if the MH month is less than the *Treatment start date (TR01SDT)* month, the imputed MH start date is set to the mid-month point (15MONYYYY).

c) Else if the MH month is greater than the *Treatment start date (TR01SDT)* month, the imputed MH start date is set to the month start point (01MONYYYY).

5.5 AEs coding/grading

Not applicable.

5.6 Laboratory parameters derivations

Clinically notable criteria

The following notable criteria will be used in the study:

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

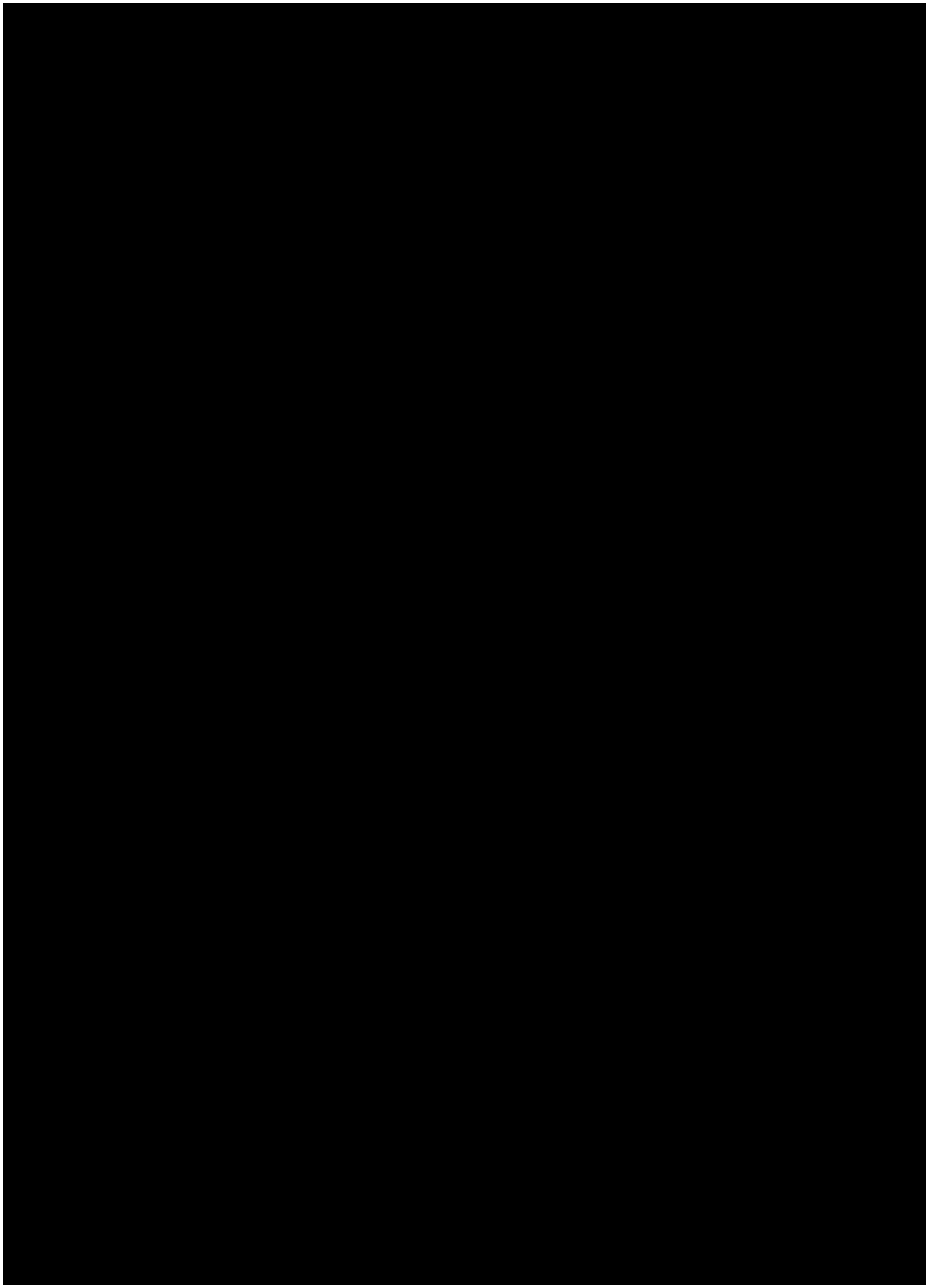
When the parameters have different criteria for different baseline status (e.g., ATL, AST), the patients with normal baseline will follow the criteria on the left side, and the patients with abnormal baseline will follow the criteria on the right side.

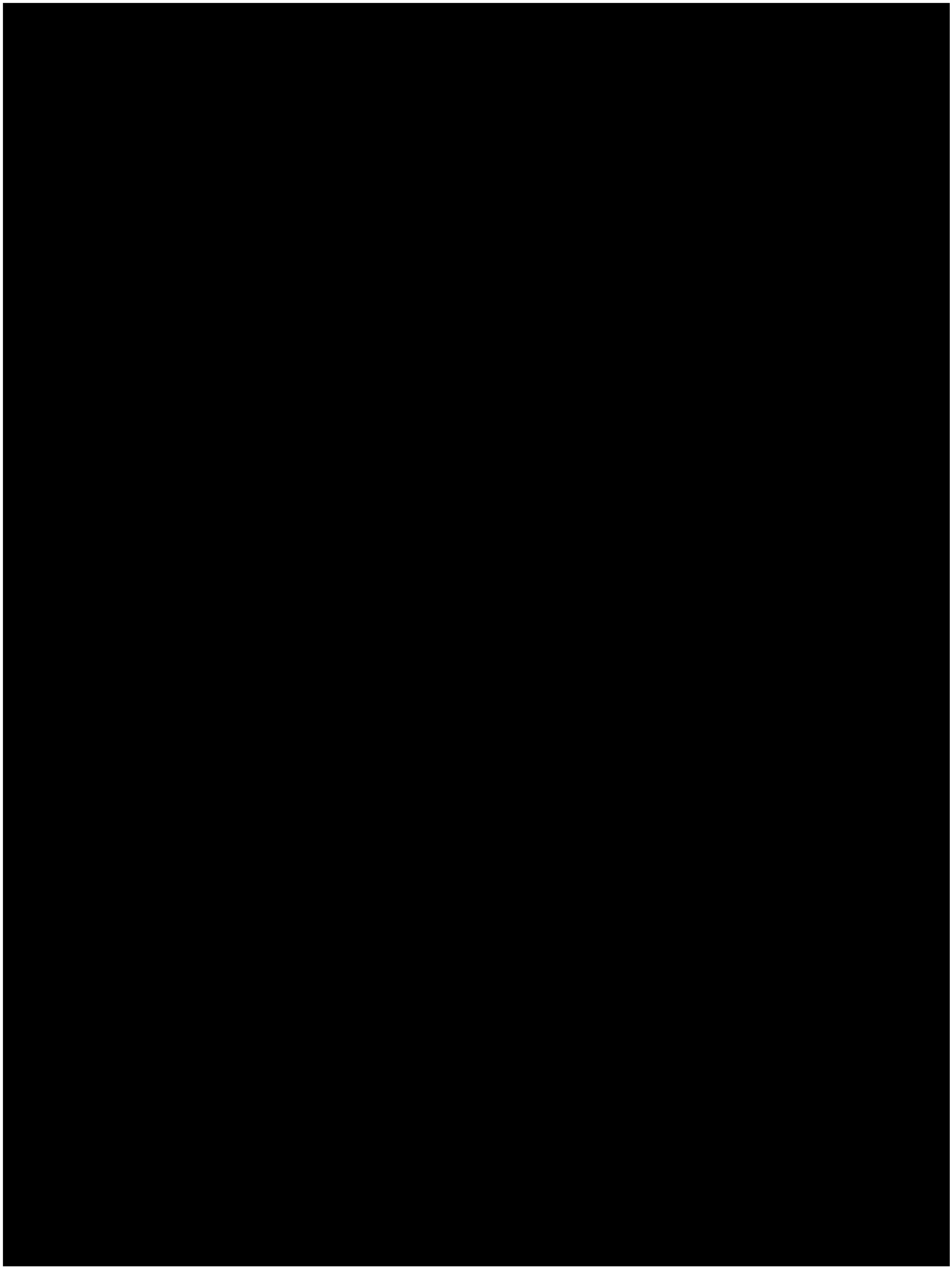
Liver-enzyme abnormalities

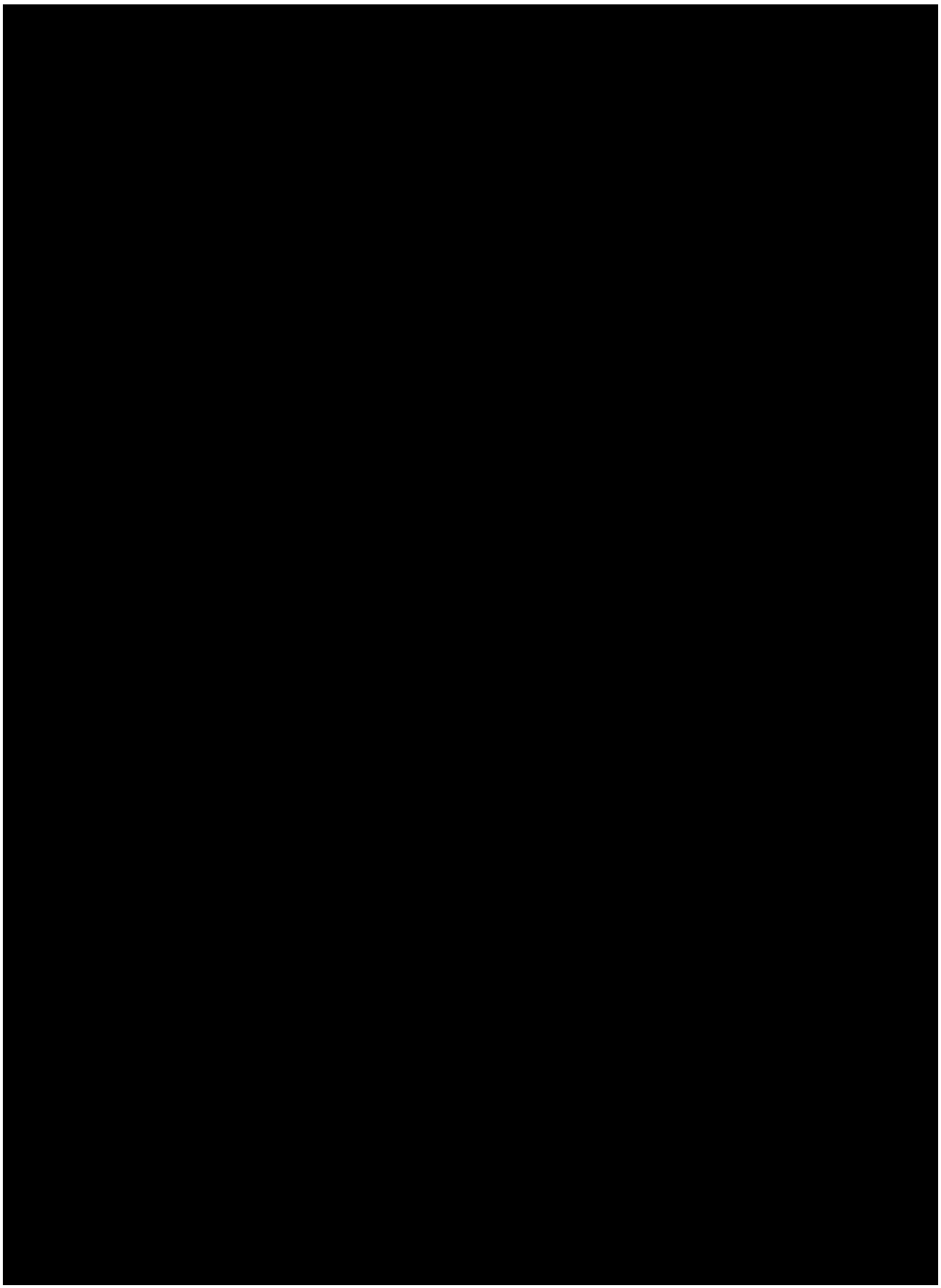
Table 5-3 Liver- enzyme abnormalities

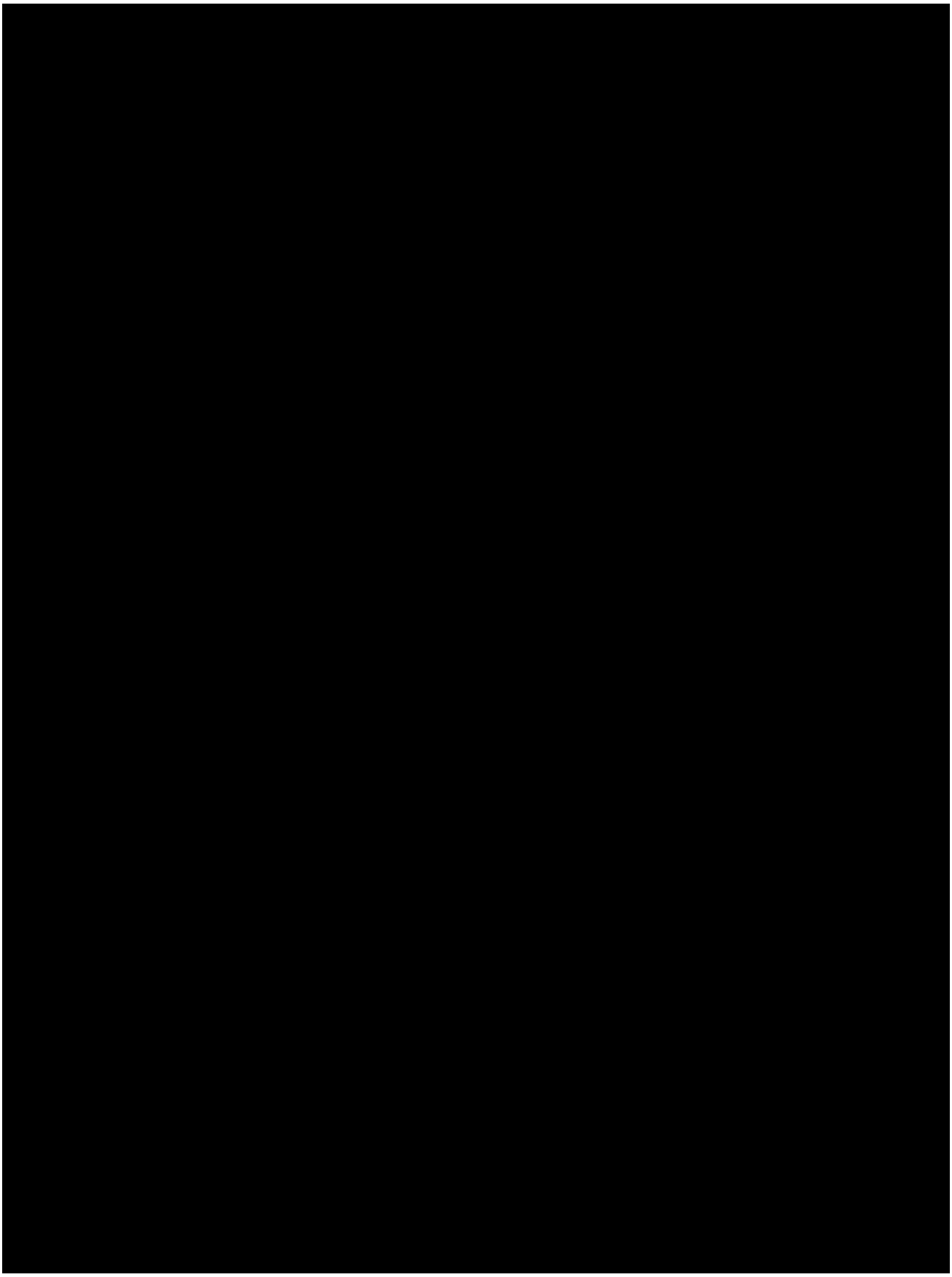
Parameter	Notable criterion
ALT	>3xULN; >5xULN; >10xULN; >20xULN
ALT or AST	>3xULN; >5xULN; >8 xULN;>10xULN; >20xULN
(ALT or AST) & TBL	>3xULN & (TBL >1.5xULN; >2xULN)
TBL	1 xULN; 1.5xULN ; >2xULN
ALP	1.5xULN ; >2xULN; >5xULN
ALP & TBL	> 3xULN; > 5xULN; & (TBL 2xULN;)
(ALT or AST) & TBL & ALP	ALT or AST>3xULN & (TBL)>2xULN & ALP<2xULN (potential Hy's Law case)

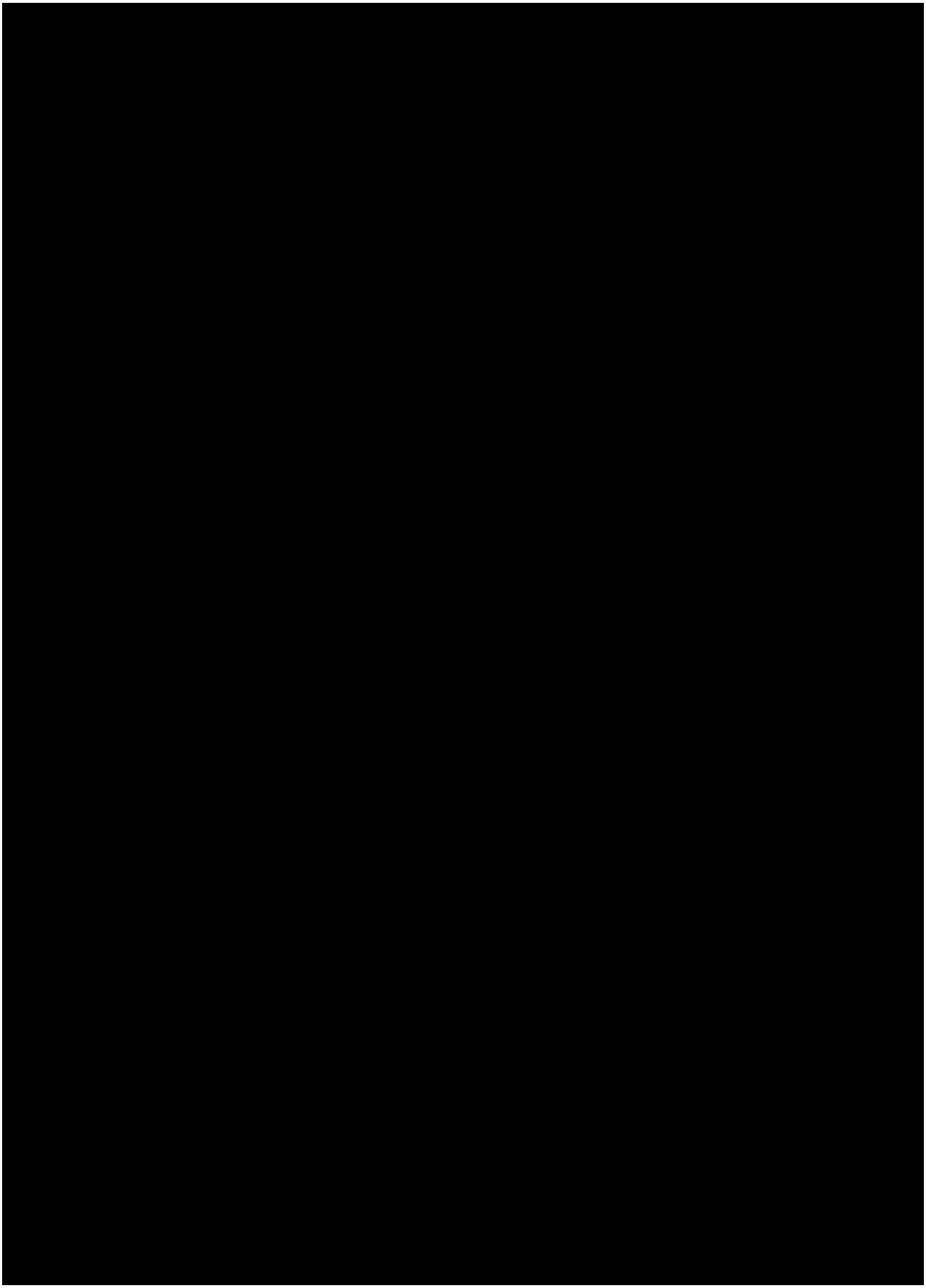
AST = Aspartate aminotransferase; also known as SGOT, ALT = Alanine aminotransferase; also known as SGPT, ALP = Alkaline phosphatase, TBL = Total bilirubin











[redacted]

5.8 Rule of exclusion criteria of analysis sets

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

Table 5-4 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
RAN	NA	Not randomized
FAS	NA	Not in RAN; Mistakenly randomized and no double-blind study drug taken
SAF	NA	No double-blind study drug taken
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

6 Reference

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