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Clinical Development

QGE031C/Ligelizumab

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A multicenter, randomized, double-blind, placebo-controlled phase2b dose-finding study to investigate the efficacy and safety of ligelizumab (QGE031) in adolescent patients with Chronic Spontaneous Urticaria (CSU)

Statistical Analysis Plan (SAP)

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		Consistency with previous studies.	"Non-responder" imputation added	Section 2.7.1 Secondary endpoints
		Include COVID 19 related impact.	Added Covid-19 impact related details	Section 5: COVID related analysis
09-Oct-2020	Prior to CSR DR	Interim analysis requested	Updated TEAE definition	Section 2.8.1 Adverse events (AEs)
			Corrected upper limit for HR for age category 17 years	Section 2.8.4.2 Vital signs
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			Updated COVID-19 related details	Section 5.0 COVID-19 Impact Assessment and related analysis
			Updated non-responder imputation related details	6.1 Scoring and data handling rules in eDiary

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
13_Feb-2021	Prior to CSR DR	Final analysis request	Non-responder imputation related update	Section 2.7.1 Secondary endpoints, 5.16.1 Scoring and data handling rules in eDiary
			Updated for Placebo switcher related analysis information	Section 2.8.1 Adverse events (AEs), 2.8.3 Laboratory data, 2.8.4.1 Electrocardiogram (ECG), 2.8.4.2 Vital signs
			Updated for time-period details	Section 2.8.1.1 Adverse events of special interest / grouping of AEs
			[redacted]	[redacted]
			Updated COVID-19 related analysis details	Section 5 COVID-19 Impact Assessment and related analysis
05-Mar-2021	Prior to CSR DR	Final analysis request	Added section for Other safety topics	Section 2.8.1.2 Other safety topics
11-Mar-2021	Prior to CSR DR	Final analysis request	Added clarification population title will be ENR since the table also includes the number of patients screened	2.3 Analysis sets and 2.4.1 Patient disposition
			Added baseline ISS7, HSS7 score and duration of CSU (years)	Section 2.4 Patient disposition, demographics and other baseline characteristics
			Prior medications will be based on SAF, to be consistent with protocol. Added clarification about which	Section 2.5.2 Prior, concomitant and post therapies

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			analysis are produced for which periods	
			Removed condition 'for the week 12 assessment of the placebo-ligelizumab group, only data before switching to ligelizumab will be used', to follow in-tent-to treat principle	Section 2.6.1 Primary endpoint
			Added 95% CI of proportion of responses for UAS7, HSS7, ISS7 and CDLQI responses. Added 95% CI of mean for CDLQI. Added mean differences of the change from baseline in UAS7, HSS7 and ISS7 between groups with 95% CI	Section 2.7.1 Secondary endpoints
			Added clarification about which analysis are produced for which periods. Added description of in-text tables and referenced section 6.5 for ClinicalTrials.gov and EudraCT tables	Section 2.8.1 Adverse events (AEs)
			Stool samples taken after the end of study visit will be flagged in the listing	Section 2.8.3 Laboratory data
			Added maximum/minimum post-baseline value will be summarized	Section 2.8.4.2 Vital signs
			Updated the changes comparing final SAP to protocol	Section 4 Change to protocol specified analyses
			Added clarification for HSS7, ISS7 and UAS7 daily score derivation for duplicate records	Section 6.1 Scoring and data handling rules in eDiary
			Clarified ENR exclusion rule since disposition not done at screening per protocol, so not required	Section 6.7 Rule of exclusion criteria of analysis sets
			Updated AE of special interest individual term related details	Section 2.8.1.1

Table of contents

List of abbreviations

[redacted]	[redacted]
AE	Adverse event
AESI	Adverse Events of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ATC	Anatomical Therapeutic Classification
AST	Aspartate aminotransferase
ATEs	Arterial thromboembolic events
BMI	Body Mass Index
BUN	Blood urea nitrogen
CDLQI	Children Dermatology Life Quality Index
CM	Concomitant medication
CRO	Contract Research Organization
CSR	Clinical Study report
CSU	Chronic Spontaneous Urticaria
DMC	Data Monitoring Committee
DRP	Data Review Plan
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eCRS	Electronic Case Retrieval Strategy
eDiary	Electronic diary
eGFR	Estimated glomerular filtration rate
FAS	Full Analysis Set
FPFV	First Patient First Visit
[redacted]	[redacted]
HSS	Hive Severity Score
IgE	Immunoglobulin E
INR	International Normalized Ratio
IRT	Interactive Response Technology
ISS	Itch Severity Score
LDH	Lactate dehydrogenase
LLOQ	Lower Limit of Quantification
LOQ	Limit of Quantification
MedDRA	Medical Dictionary for Drug Regulatory Affairs
M&S	Modelling and Simulation
N/A	Not Applicable
PDev	Protocol Deviation
PD	Pharmacodynamics
PK	Pharmacokinetics

PRO	Patient-reported Outcomes
PT	Preferred Term
q4w	Every 4 weeks
QTcF	Fridericia QT Correction
RAN	Randomized set
RBC	Red Blood Cell
s.c.	Subcutaneous
SAE	Serious Adverse Event
SAF	Safety set
SAP	Statistical Analysis Plan
sCr	Serum Creatinine
SOC	System Organ Class
UAS	Urticaria Activity Score
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantification
UPDD	Urticaria Patient Daily Diary
TBL	Total Bilirubin
WBC	White Blood Cell
WHO	World Health Organization

1 Introduction

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

This SAP is based on the original version of protocol (i.e. version 00), dated 18-Jan-2018.

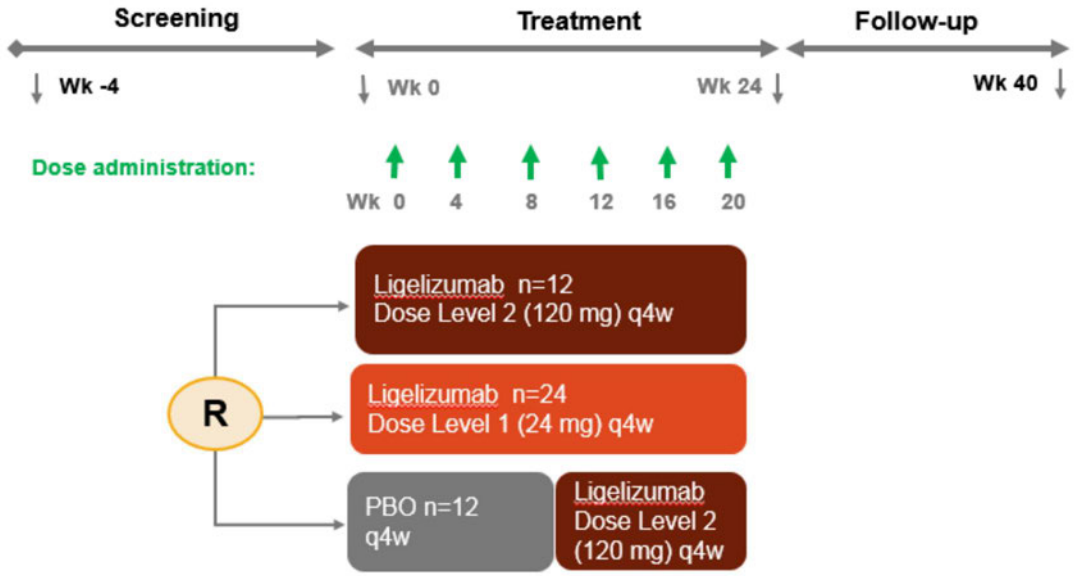
1.1 Study design

This is a Phase 2b dose-finding, randomized, double-blind, parallel group, placebo controlled multicenter study in adolescent patients. It consists of 3 distinct study periods, as outlined in Figure 1-1 below. After the screening period, at Day 1 patients are randomized into one of the three treatment arms in 1:2:1 fashion to ligelizumab 120 mg q4w vs. ligelizumab 24 mg q4w vs. placebo. No stratification will be considered for the randomization.

During the 24 weeks of treatment, doses are administered on Day 1, then on week 4, 8, 12, 16, and 20 after randomization. Subjects randomized to placebo will receive placebo on Day 1, Week 4 and 8; thereafter they will receive 120 mg ligelizumab on Week 12, 16 and 20 such that the same number of patients will, by the end of the study, receive 120 mg as 24 mg. The treatment period (24 weeks) is followed by a follow-up period of 16 weeks to a maximum of Week 40.

The planned number of patients is 48. Week 24 is considered as primary endpoint in the study. Data from both the treatment and follow-up periods, will be forwarded to a separate modelling study.

Figure 1-1 Study design



R: randomization

1.2 Study objectives and endpoints

Table 2-2 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective	**Endpoint for primary objective**
• Change in the Urticaria Activity Score (UAS7) between baseline and Week 24	• The primary endpoint will be change in UAS7 from baseline to Week 24.
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the efficacy of ligelizumab doses 24 mg and 120 mg with respect to UAS7 change from baseline	• UAS7 change from baseline over time (at each protocol defined study visit, in addition to the primary endpoint)
• To evaluate the efficacy of ligelizumab doses 24 mg and 120 mg on complete response in Urticaria Activity Score (UAS7=0), Hives Severity Score (HSS=0), Itch Severity Score (ISS=0)	• Rate of complete responders (UAS7=0, HSS7=0, ISS7 =0) over time (at each protocol defined study visit)
• To investigate the effects on ISS7 and HSS7 when compared to baseline	• Itch severity score change from baseline over time (at each protocol defined study visit) • Hives severity score change from baseline over time (at each protocol defined study visit)
• To investigate the pharmacokinetics of ligelizumab	• Model-based estimate of clearance and volume of distribution using at least 7 samples
• To investigate the pharmacodynamics of ligelizumab	• Summary statistics of change in Total IgE over time.

Objective(s)	Endpoint(s)
• Change from baseline in the Children Dermatology Life Quality Index	• Children Dermatology Life Quality Index change from baseline over time (each protocol defined study visit)
• To evaluate the safety (including immunogenicity) and tolerability of ligelizumab (doses of 24 mg, 120 mg s.c. every 4 weeks) versus placebo in patients with CSU.	• Adverse events, ECG-intervals and interpretation, vital signs (blood pressure, pulse rate) and clinical laboratory evaluation

2 Statistical methods

This section contains information that will be used to draft Clinical Study Report (CSR) Section 9.7 on statistical analysis.

2.1 Data analysis general information

Data will be analyzed by [redacted], using SAS version 9.4 or above.

DMC analysis will be done by the independent statistician and programmers in the separate Contract Research Organization (CRO) ([redacted]). Statistical Analysis Plan for the DMC analysis will be prepared separately.

In general, summary tables will be presented by treatment group and visit/week (as applicable), using descriptive statistics, which include absolute and relative frequencies for categorical variables and arithmetic mean, standard deviation, minimum, maximum, median for continuous variables.

2.2 General definitions

2.2.1 Study day and Study Week

The first day of administration of study treatment (first dose) is defined as Day 1. All other study days will be labeled relative to Day 1.

Data from eDiary, 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

Study Week	Study Days
Baseline	(-7)-(-1)
1	1-7
2	8-14
w	7×(w−1)+1 - 7×w
40	274 – 280

Where w is all other remaining study weeks: Between Week 2 and 40, (e.g. 3, 4, 5, 6, 7, 8,..)

For the other data taken by scheduled visit, all by-visit summaries will be performed according to the scheduled reported visit.

2.2.2 Baseline

Unless otherwise specified, baseline is the last assessment (including unscheduled visits) obtained on the day of or before the first dose of study treatment. For patient without any administration of study dose, the baseline assessment will be their last assessment under the study. All assessments obtained after the first dose of study drug are considered as post-baseline.

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

For ECG numeric measurements, baseline will be defined as the mean of the measurements taken on the last date on or before the date of first dose of study treatment. For ECG overall

interpretation, baseline will be the most common interpretation (normal/abnormal) of the assessments taken on the last date on or before the date of first dose of study treatment (if there are an equal number of normal and abnormal assessments on the same date, then baseline will be set to 'abnormal').

For 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 worst outcome (i.e. the highest score) of the duplicate observations on that date will be used for baseline.

For PK/PD, baseline will include assessments on the date of first dose of study treatment, unless they are excluded by the inclusion flag derived by the PK analyst.

2.3 Analysis sets

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

The randomized set (RAN), which comprises all randomized patients, regardless of whether or not they actually received study medication.

For summaries of patient disposition and analysis sets RAN will be used for deriving percentages. ENR will be used for treatment epoch disposition and analysis sets tables population title since those tables will also include number of patients screened.

The Full Analysis set (FAS) comprises all patients to whom study treatment has been assigned. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to 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.

The safety set (SAF) will include all patients who received at least one dose of study drug whether or not being randomized. Patients will be analyzed according to the treatment they actually received. The safety set will be used in the analysis of all safety variables.

Note that the FAS and safety set are the same except that the safety set allows the inclusion of non-randomized patients who receive study drug in error, and the FAS may include patients that were randomized but not treated unless mis-randomization. Also the FAS assigns randomized treatment and the safety set assigns received treatment.

Rule of exclusion criteria of analysis set is described in Appendix 6.7.

Protocol deviations will be summarized by deviation category and treatment group for the RAN. The deviation categories defined in the DRP for the study are presented below:

- SELECTION CRITERIA NOT MET

- SUBJECT NOT WITHDRAWN AS PER PROTOCOL
- TREATMENT DEVIATION
- PROHIBITED CONCOMITANT MEDICATION
- OTHER

For COVID-19 related Protocol deviation summary report include all those categories and they will be further classified based on available COVID related sub-categories. This report will be on Safety set population.

2.3.1 Subgroup of interest

Not applicable for the CSR analysis considering the number of subjects.

2.4 Patient disposition, demographics and other baseline characteristics

Demographics and baseline characteristics will be summarized using the SAF by treatment group, including disease characteristics, prior and background medications to treat urticaria, and relevant medical histories.

Demographics (collected at Visit 1)

- Age (years)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown, Not reported)
- Weight (kg)
- Height (cm)
- Body Mass Index (BMI) – calculated as weight (kg) / (height (m))2
- BMI group (< 25, 25 - < 30, >= 30 kg/m**2)

Baseline characteristics (baseline is defined in section 2.2.2)

- Total IgE level (IU/mL)
- In-clinic UAS score
- Baseline ISS7, HSS7, UAS7 score
- Baseline UAS7 score category (see Table 2-2)
- Duration of CSU (years)

Table 2-2 Category of disease status based on UAS7 score

Disease status	UAS7 value
Free (0)	0
Well-controlled (1-6)	0<UAS7=<6
Mild (7-15)	6<UAS7<16
Moderate (16-27)	16=<UAS7<28
Severe (28-42)	28=<UAS7=<42

In-clinic assessment of UAS

The UAS will be recorded by the Investigator at the site by rating the patient's number of urticaria lesion (hives) and interviewing the patient for the assessment of pruritus reflective of the patient's condition over the 12 hours prior to the visit. In-clinic UAS score (0-6) will be summarized using summary statistics.

Medical history or current medical conditions

Medical history or current medical condition will be coded using MedDRA and summarized by SOC and PT. Protocol solicited medical history will be summarized separately.

2.4.1 Patient disposition

The number and percentage of patients who completed each study phase (treatment, post treatment follow-up) will be summarized by treatment group and percentages will be based on the RAN. The reason for discontinuation of each phase will also be summarized by treatment group. For the treatment epoch disposition table the population title will be ENR since the table also includes the number of patients screened.

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

2.5.1 Study treatment / compliance

Summary tables for exposure will be presented using the SAF.

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

The number of injections per patient which are correctly administered as per protocol will be summarized by treatment.

2.5.2 Prior, concomitant and post therapies

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Urticaria related prior medications will be summarized for the SAF by treatment group, pre-specified categories, preferred term and symptom treated.

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. Concomitant medications will be summarized by treatment for the SAF, for urticaria related medications and non-urticaria related medications (taken from eCRF). Background medication for urticaria selected for the patient will be summarized separately using the pre-specified drug name. Other urticaria related concomitant medication will be listed together with non-urticaria related medications. Medications will be coded using Anatomical Therapeutic Chemical (ATC) code and summarized by treatment, ATC class and preferred term. Concomitant medications will be summarized for the entire study and for up to week 12 separately. Background medication for urticaria will be summarized for the treatment epoch and for up to week 12 separately.

Concomitant non-drug therapies and medical procedures will be summarized by primary system organ class and MedDRA preferred term. Concomitant non-drug therapies and medical procedures will be summarized for the entire study and for up to week 12 separately.

For analysis "up to Week 12", for the ligelizumab groups concomitant medications up to Week 12 will be included and for the placebo-ligelizumab arm concomitant medications prior to ligelizumab switch will be included.

[redacted]

2.6 Analysis of the primary objective

2.6.1 Primary endpoint

The primary variable is absolute change in UAS7 from baseline to Week 24. UAS7 is the sum of HSS7 and ISS7.

HSS and ISS will be recorded by the patient twice daily in their eDiary, on a scale of 0 (none) to 3 (severe). A weekly score (HSS7/ISS7) is derived by summing the average daily scores of the 7 days preceding the planned visit date. The possible range of UAS7 is therefore 0-42.

The primary variable will be summarized by treatment group in the FAS using descriptive statistics.

2.6.2 Statistical hypothesis, model, and method of analysis

No formal statistical testing will be applied for the primary variable.

The mean of the change from baseline by treatment group will be shown descriptively with 95% confidence intervals based on the t-distribution.

2.6.3 Handling of missing values/censoring/discontinuations

As the primary analysis is to summarize the data descriptively, no imputation for the missing UAS7 will be applied. If ISS7 or HSS7 is missing, UAS7 will also be missing.

To calculate ISS7/HSS7 score from daily score, missing daily score will be handled according to the rules defined in the SAP appendix Section 6.1.

2.6.4 Supportive analyses

No sensitivity analysis is planned for the primary variable, as no statistical model is used.

2.7 Analysis of secondary efficacy objective(s)

All secondary efficacy analysis will be based on FAS.

2.7.1 Secondary endpoints

Urticaria Activity Score

The number and proportion of patients who achieve the complete UAS7 response (UAS7 = 0), hives response (HSS7 = 0), itch response (ISS7 = 0), and patients who achieve UAS7 <= 6, will be summarized by treatment and week. The 95% Clopper and Pearson confidence interval of the proportion will also be displayed. Non-responder imputation will be applied to missing data as described in SAP appendix section 6.1.

Change from baseline in UAS7, HSS7 and ISS7 will also be summarized by treatment and week. The mean of the change from baseline by treatment group will be shown descriptively with 95% confidence intervals based on the t-distribution.

The number and proportion of patients who have UAS7<=6 at Week 12 and Week 24 then have relapse (UAS7>=12) will be summarized by treatment and week after Week 12/ Week 24.

Mean differences of the change from baseline in UAS7, HSS7 and ISS7 between treatment groups (ligelizumab 24 mg q4w vs. placebo - ligelizumab 120 mg q4w), (ligelizumab 120 mg q4w vs. placebo - ligelizumab 120 mg q4w) and (ligelizumab 24 mg q4w vs. ligelizumab 120 mg q4w) will be shown descriptively with 95% confidence intervals based on two sample t-test, at Week 12 and Week 24.

CDLQI assessment

The Children Dermatology Life Quality Index questionnaire (CDLQI) is designed for use in children, i.e. patients from age 4 to age 16. It will also be deployed to any 17-18 year olds participating in this trial. It is a 10-item dermatology-specific health-related quality of life measure. Patients rate their dermatology symptoms as well as the impact of their skin condition on various aspects of their lives. The CDLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0 according to Table 2-3. The higher the score, the more quality of life is impaired. An overall score will be calculated as well as for the following domains according to Table 2-4: Symptoms and Feelings, Leisure, School or Holidays, Personal Relationships, Sleep, and Treatment.

Absolute and percentage change from baseline in total Children Dermatology Life Quality Index (CDLQI) score will be summarized by treatment and visit. The mean of the change from baseline by treatment group will be shown descriptively with 95% confidence intervals based on the t-distribution.

The number and proportion of patients who achieve CDLQI=0 or 1 will be summarized by treatment and visit. The 95% Clopper and Pearson confidence interval of the proportion will also be displayed. Non-responder imputation will be applied to missing data as described in section 6.1.

Table 2-3 CDLQI scoring

Score	Answer
0	Question unanswered
	Not at all
1	Only a little
2	Quite a lot
3	Very much
	Question 7: “Prevented School”

Table 2-4 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

2.8 Safety analyses

All safety parameters will be summarized based on the SAF.

2.8.1 Adverse events (AEs)

Treatment emergent adverse events are defined as adverse events which start after the first dose of study medication, or events present prior to the first dose of study medication but increased in severity based on preferred term. Treatment emergent adverse events will be summarized by treatment groups in the following study period:

- Treatment period up to Week 12 for the ligelizumab groups and prior to ligelizumab switch in the placebo-ligelizumab arm.
- Treatment period.
- Post-treatment follow up period
- Entire study period.

Treatment emergent adverse events will be summarized by the actual treatment group.

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

- All adverse events (entire study, up to week 12, treatment epoch, follow-up epoch)
- Adverse events by maximum severity (up to week 12, entire study, treatment epoch)
- Adverse events suspected by the investigator as study drug-related (up to week 12, entire study, treatment epoch)
- Serious adverse events (entire study, treatment epoch)
- Adverse events leading to permanent discontinuation of study drug (treatment epoch)

In addition an overview of adverse events will be produced to summarize the number and percentage of patients with AEs, TEAES (overall and treatment related), treatment emergent SAEs (overall and treatment related), treatment emergent SAEs leading to death (overall and treatment related) and treatment emergent SAEs leading to treatment discontinuation (overall and treatment related).

Also, a separate summary table for most frequently reported TEAEs during the study, by PT will be produced. Most frequent TEAEs will be those with their PT representing at least 10% of subjects in any treatment group.

For the legal requirements of ClinicalTrials.gov and EudraCT, two additional tables of adverse events will be provided as described in section 6.5.

2.8.1.1 Adverse events of special interest / grouping of AEs

Adverse events of special interest

The following adverse events of special interest (AESI) will be summarized separately by each category standardized MedDRA query / PT for entire study, up to week 12 and treatment epoch.

Details will be provided in the separate document, called electronic 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.

Adjudicated AEs

In addition to the AESI listed above, the following AEs will be adjudicated by the independent committee. The adjudicated events will be listed.

- Hypersensitivity assessment
- Cardio- and Cerebrovascular events
- Malignancies

2.8.1.2 Other safety topics

The following other safety topics will be listed:

- COVID 19 infection
- Pregnancy
- Immunogenicity (anti-drug antibodies / ADA)
- Liver Toxicity

2.8.2 Deaths

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

2.8.3 Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, serum chemistry and urinalysis) and by treatment.

The change from baseline to each study visit with maximum/minimum post-baseline value will be summarized by visit presented for quantitative parameters. For the parameters with normal range, shift tables value will be provided based on the normal range assigned by the central lab.

- Ligelizumab groups: from baseline to the worst post-baseline.
- Placebo-ligelizumab:
    1. from baseline to the worst post-baseline up to treatment switch
    2. from baseline to the worst post-baseline after treatment switch

For categorical parameters, frequencies by categories at each visit will be summarized.

The number of patients with newly occurring or worsening abnormality during the study will be summarized and listed by treatment based on the notable criteria specified in the protocol (See SAP section 6.4). For the placebo-ligelizumab group, the number of patients with newly occurring or worsening abnormality, prior to and after the treatment switch will be summarized

separately. A case is considered as 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 worsening abnormality if the value is notable at baseline and at least one post-baseline value during the study is worse than baseline.

To evaluate potential drug-induced liver injury, newly occurring liver enzyme abnormalities at any time post-baseline will also be summarized according to Table 5-1. For the placebo-ligelizumab group, the number of patients with newly occurring or worsening abnormality, prior to and after the treatment switch will be summarized separately.

Stool ova for assessment of parasitic infections and urine serum pregnancy test will be listed separately. Samples taken after the end of study visit will be flagged in the listing.

For laboratory test values below Lower Limit of Quantification (LLOQ) or above Upper Limit of Quantification (ULOQ) will be imputed as LLOQ or ULOQ value, 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 reported sign i.e. "<" or ">".

Hematology

Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential (Neutrophils, Basophils, Monocytes, Lymphocytes and Eosinophils), platelet count, will be summarized by treatment and visit. Coagulation will be assessed by International Normalized Ratio (INR) and listed only.

Chemistry

Albumin, total bilirubin, alkaline phosphatase, AST, ALT, chloride, calcium, sodium, potassium, magnesium, LDH, creatinine, inorganic phosphorus, urea/BUN and uric acid will be summarized by treatment and visit. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin will be differentiated and listed only.

Urinalysis

Semi-quantitative "dipstick" evaluation for specific gravity, glucose, protein, bilirubin, ketones, leukocytes and blood will be performed at site. When a dipstick evaluation is abnormal, e.g., positive for WBC and/or blood, a urine sample needs to be sent to the Central Lab for microscopic examination.

The categorical results of the dipstick at site will be summarized by treatment and visit. Results examined by the Central Lab will be listed only.

2.8.4 Other safety data

2.8.4.1 Electrocardiogram (ECG)

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

For ECG parameters, the number and percentage of patients with newly occurring or worsening notable abnormalities occurring post-baseline will be listed by treatment group. The definition of newly occurring or worsening is the same as laboratory values. For the placebo-ligelizumab group, the number of patients with newly occurring or worsening abnormality, prior to and after the treatment switch will be summarized separately.

The following were considered as notable values: QTcF >450 msec (males), QTcF >460 msec (females); QTcF change from baseline >30 msec, >60 msec; PR >250 msec.

2.8.4.2 Vital signs

Vital signs (blood pressure and pulse rate) and changes from baseline will be summarized by treatment group and visit, also maximum/minimum post-baseline value will be summarized.

The number and percentage of patients with newly occurring or worsening notable abnormalities occurring post-baseline will be summarized by treatment group. For the placebo-ligelizumab group, the number of patients with newly occurring or worsening abnormality, prior to and after the treatment switch will be summarized separately. The definition of newly occurring or worsening is the same as laboratory values.

A notable value is defined as follows: heart rate of < 40 and > 90 bpm; systolic blood pressure of < 90 and > 140 mmHg; diastolic blood pressure of < 65 and > 90 mmHg.

The vital signs will be also summarized according to the Table 2-5 and notable values defined for each age:

Table 2-5 Criteria for notable vital sign for pediatric patients (age 12 to 17 years)

Age	Systolic BP (mmHg)	Diastolic BP (mm Hg)	HR (bpm)
12 years	101-135	59-91	60-110
13 years	104-137	60-91	60-110
14 years	106-140	60-92	60-110
15 years	107-142	61-93	60-110

16 years	108-145	63-94	60-110
17 years	108-147	64-97	60-100

A notable value is one that falls outside the above ranges.

[redacted]

2.9 Pharmacokinetic endpoints

All subjects with a PK sample will be included in the pharmacokinetic (PK) data analysis.

Concentrations will be given in mass per volume units. Drug concentration of ligelizumab will be summarized descriptively by treatment and visit using SAF. Missing values or those below the limit of quantification (LOQ) will be indicated in the data listings and treated as zero in data presentations and calculations.

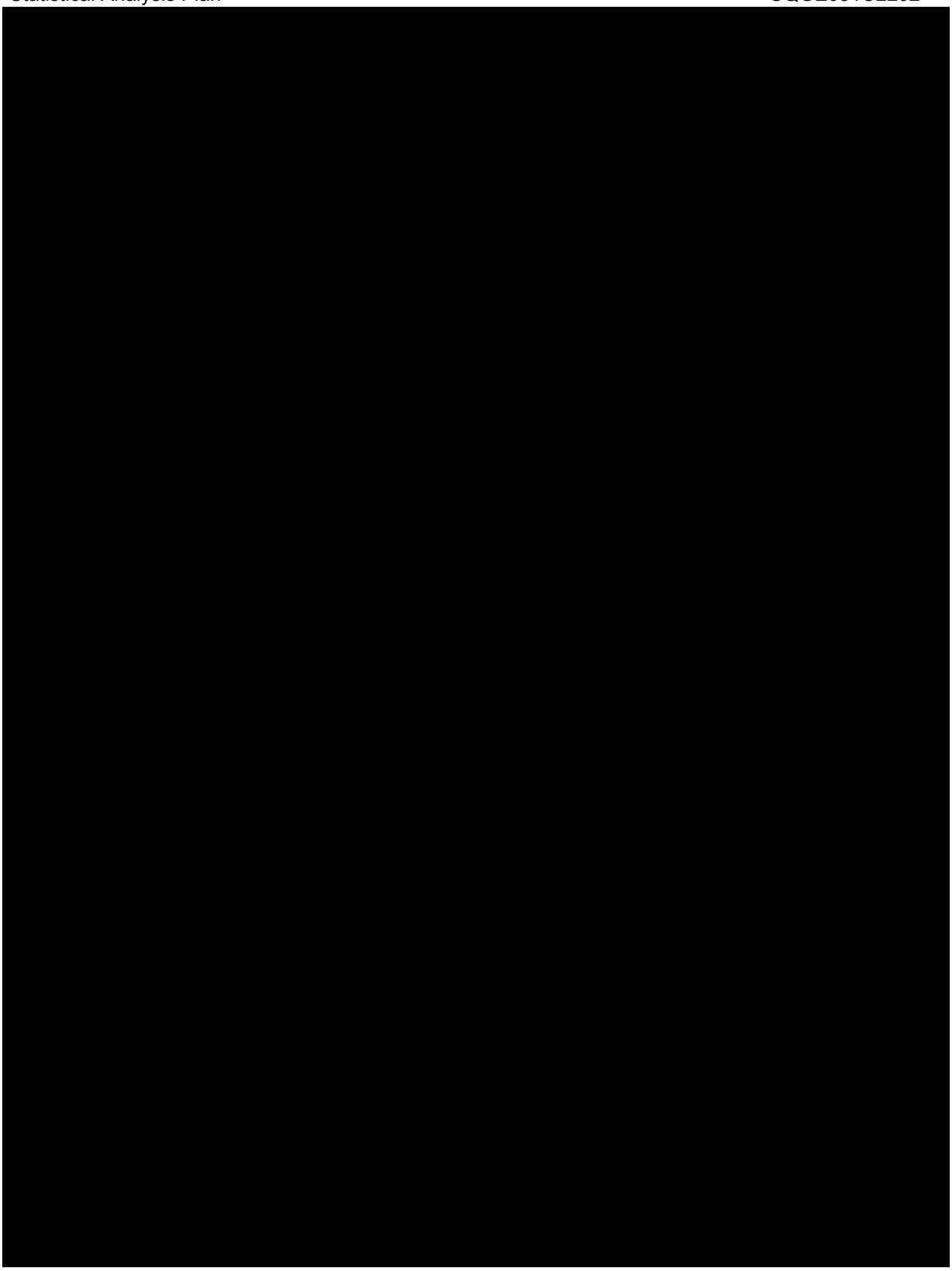
2.10 PD and PK/PD analyses

PK/PD modelling will be conducted in a separate modelling and simulation (M&S) study as the data from this study will be only one part of a pool from both adolescent and adult patients. Full details are available in a separate M&S study protocol and results will be provided in a separate PK/PD report.

[redacted]

[redacted]

[redacted]



2.14 Interim analysis

No interim analyses is planned other than the analyses for the independent DMC.-DMC meeting will be held at least once during the 6 months for periodical safety review.

To maintain the blind the outputs for the DMC will be conducted in a semi-blinded manner (using dummy treatment code) by the independent statistician and programmer in the separate CRO ( ) who are not involved in CSR reporting. Details will be provided by the DMC charter.

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

3 Sample size calculation

The expected half-width of 95% confidence intervals for the change from baseline in UAS7 for each group is 5.2, assuming 24 patients in ligelizumab 24 mg arm and SD=13. If the mean change from baseline in UAS7 for ligelizumab group is -22.0 (based on C2201 adult study), the 95% confidence interval of the mean change from baseline in UAS7 will be (-27.2, -16.8).

4 Change to protocol specified analyses

- Add enrolled set (ENR) to summarize all patients after informed consent including screening failure.
- Change the notable criteria for QTc to be used for the analysis, to be consistent with the definition in other section of the protocol and project standard.
- Treatment emergent adverse events definition was made more comprehensive by removing the restriction of events starting within 16 weeks of the last dose. i.e. definition is now all adverse events which start after the first dose of study medication, or events present prior to the first dose of study medication but increased in severity based on preferred term.
- Adjudicated AEs will only be listed and not summarized, since few adjudicated AEs are expected.

- CDLQI individual domain scores will only be listed and not summarized, since it was not medically relevant.
- Exposure to study drug will be summarized in weeks rather than days, for easier interpretation.

5 COVID-19 Impact Assessment and related analysis

The trial began in Jul 2018 and completed in Feb 2021, which included the period during which the COVID-19 pandemic was occurring globally. When the pandemic disruption occurred, most participants in the trial have been enrolled, no changes have been made to trial conduct, study design or planned statistical analyses, and as such, the impact of the pandemic was limited on the trial.

A summary table will be provided for COVID-19 related protocol deviations.

6 Appendix

6.1 Scoring and data handling rules in eDiary

Missing morning or evening score in UPDD

When either the morning or evening score is missing, the non-missing score for that day (morning or evening) will be used as the daily score.

Missing daily score in UPDD [redacted]

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

- If a patient has at least 4 non-missing daily scores within the 7 days prior to the study visit, the weekly score is calculated as the sum of the available eDiary scores in that week, divided by the number of days that have a non-missing diary score, multiplied by 7.
- If there are less than 4 non-missing daily scores within the prior 7 days, then the weekly score is missing for the week.

The rule will be applied for HSS7, ISS7, Angioedema occurrence score, [redacted]

Missing weekly score in UPDD [redacted]

For the response rate analysis, for patients with missing data either due to discontinuation or due to insufficient eDiary data during that week, imputation of the response will be done using the worst-case scenario (i.e. non-responder). For the patients completing the study, there

will be no more imputation applied after the end of study visit. For the patients discontinuing the study early, the imputation will be applied up to Week 40.

Missing CDLQI score

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

For the response rate analysis, for patients with missing data either due to discontinuation or due to insufficient information during that visit, imputation of the response will be done using the worst-case scenario (i.e. non-responder). The imputation will be applied up to Week 40.

Duplicate data handling of questionnaires

For HSS7, ISS7 and UAS7, the daily score is derived from the average of morning and evening scores, even if there is more than one score during the morning or evening, the average of all available scores during the day is used for the daily score. When either the morning or evening score is missing, the non-missing score for that day (morning or evening) will be used as the daily score, if there is more than one score during the morning/evening then the average of those scores will be used. 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.

6.2 Imputation rules

6.2.1 Study drug

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

6.2.2 AE date imputation

Rules for imputing the AE end date:

- If the AE end date month is missing, then the imputed end date should be set to the earliest of the (study end date, 31DECYYYY, 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, date of death).
- If AE year is missing, 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. Else 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. Else if AE month is not missing, then the imputed AE start date is set to the mid-month point (15MONYYYY).

3. If the AE start date year value is greater than the treatment start date year value, 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. Else if the AE month is not missing, then the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

4. If the AE start date year value is equal to the treatment start date year value:

   a. And the AE month is missing, then the imputed AE start date is set to the AE reference start date + 1 day.

   b. Else if the AE month is less than the treatment start month, then the imputed AE start date is set to the mid-month point (15MONYYYY).

   c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, 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 imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to (imputed) AE end date.

6.2.3 Concomitant medication (CM) date imputation

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

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

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

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

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

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

Rules for imputing the CM start date:

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

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

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

The following matrix explains the logic behind the imputation.

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

1. If the CM start date year value is missing, 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.

6.2.3.1 Prior therapies date imputation

Same as concomitant medication.

6.3 Adverse event coding/grading

Not applicable.

6.4 Laboratory parameters derivations

Clinically notable criteria

The following notable criteria will be used in the study:

- Platelets < 75 000/μL
- 25% decrease in eGFR and eGFR ≤ 90ml/min/1.731 m2 compared to baseline
- New dipstick glycosuria ≥3+
- New dipstick hematuria ≥3+

eGFR is calculated with Schwartz formula for use in children 1-18 years old:

- For height in cm and sCr in mg/dL: eGFR (mL/min/1.73 m2) = 0.413 x (height/sCr)
- For height in cm and sCr in μmol/L: eGFR (mL/min/1.73 m2) = 36.5 x (height/sCr)

Liver-enzyme abnormalities

Table 6-1 Liver- enzyme abnormalities

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

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

6.5 Analysis for Clinicaltrials.gov and EudraCT

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

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

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

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

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

6.6 Statistical models

6.6.1 Primary analysis

Not applicable.

6.7 Rule of exclusion criteria of analysis sets

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

Table 6-2 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
ENR	NA	Not having informed consent; Not having screening epoch
RAN	NA	Not randomized
FAS	NA	Not in RAN; Mis-randomized
SAF	NA	No double-blind study drug taken

7 Reference

There is no statistical reference for the study..