STATISTICAL ANALYSIS PLAN

Project Number:	GLPG1690
Study Number:	GLPG1690-CL-206
Study Title:	A multicenter, open-label extension study to evaluate the long-term safety, tolerability and efficacy of orally administered GLPG1690 in subjects with systemic sclerosis

Development Phase:	II		
Status:	Final		
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VERSION HISTORY

SAP Amendment #	Date	Description of changes

LIST OF ABBREVIATIONS

AE	adverse event
ATC	anatomical therapeutic chemical
BMI	body mass index
CI	confidence interval
CRF	case report form
[redacted]	[redacted]
CSP	clinical study protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
ECG	electrocardiogram
ED	early discontinuation
eGFR	estimated glomerular filtration rate
EoT	end of treatment
FAS	Full-Analysis Set
[redacted]	[redacted]
FSH	follicle stimulating hormone
[redacted]	[redacted]
H	high, above the upper limit of the normal range
[redacted]	[redacted]
ICF	informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IP	investigational product
INF	infinity
L	low, below the lower limit of the normal range
LLN	lower limit of the normal range
[redacted]	[redacted]
MCID	Minimal Clinically Important Difference
MedDRA	medical dictionary for regulatory activities
[redacted]	[redacted]
N	normal, with the limits of the normal range
OC	observed case
OLE	open-label extension
PAH	pulmonary arterial hypertension
PT	preferred term
q.d.	once daily
[redacted]	[redacted]
QTcF	QT interval corrected for the heart rate using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
[redacted]	[redacted]
SD	standard deviation

SE	standard error
[redacted]	[redacted]
SI	Standard International
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	treatment-emergent adverse event
TLF	tables, listings and figures
ULN	upper limit of the normal range
VAS	visual analogue scale
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) defines the statistical analysis methods and data preparations to be used in the analysis and presentation of data for Galapagos protocol number GLPG1690-CL-206 entitled 'A multicenter, open-label extension study to evaluate the long-term safety, tolerability and efficacy of orally administered GLPG1690 in subjects with systemic sclerosis'.

A decision was taken to halt the GLPG1690-CL-206 clinical study with the investigational autotaxin inhibitor ziritaxestat (sponsor product code GLPG1690) in subjects with systemic sclerosis. The decision is based on the recommendations of the Independent Data Monitoring Committee of the ISABELA Phase 3 clinical studies (study numbers GLPG1690-CL-303 and GLPG1690-CL-304) which, following a regular review of unblinded data on February 9, concluded that ziritaxestat's benefit-risk profile no longer supported continuing these studies.

In view of the above, no market authorisation application will be submitted for ziritaxtestat for the treatment of systemic sclerosis. Therefore, it was decided to limit the analyses to the primary safety endpoints and any analyses important to better understand the reason for the results seen, or for scientific knowledge for future compounds.

The results will be presented in an abbreviated clinical study report (CSR).

All descriptions as documented in the SAP were kept for reference, but endpoints and analyses deemed not applicable for the abbreviated CSR are in *Italic font* and will not be included for the final analysis. A list of analyses that will not be performed can be found in section **Error! R eference source not found.**.

The statistical analysis will process and present the results following the International Council for Harmonization (ICH) standards, particularly the ICH-E3, ICH-E6 and ICH-E9 guidelines, and [redacted] Global Biostatistics and Programming & Galapagos Standard Operating Procedures (SOPs). This SAP is created based on the latest Clinical Study Protocol (CSP) as referred in section 2.4. Technical details on derivations and mock Tables, Listings and Figures (TLFs) will be presented in a separate document.

Data from both the GLPG1690-CL-204 (CL-204) and GLPG1690-CL-206 (CL-206) protocols will be stored in CL-206 SDTM and ADaM datasets, the CSR prepared for CL-206 study will report cumulative data across both protocols.

2. STUDY DESIGN AND OBJECTIVES

2.1. STUDY OBJECTIVES

Primary Objective

- To evaluate the long-term safety and tolerability of ziritaxestat in subjects with systemic sclerosis.

Other Objectives

- [redacted]

2.2. STUDY ENDPOINTS

Primary Endpoint

- Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events (AEs) over time.

Other Endpoints

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- [redacted]

2.3. STUDY DESIGN

This is an open-label, multicenter, single-arm, 104-week extension study for subjects with systemic sclerosis who completed the 24-week double-blind treatment period of study CL-204. Up to 30 subjects may roll over from study CL-204 into this open-label extension (OLE) study.

Subjects will enter this OLE study at the Rollover visit on Day 1, which will occur on the same day as the Week 24 visit (the last visit of the treatment period) of the preceding CL-204 study. Subjects who roll over to this OLE study will participate in the post-treatment follow-up period of the OLE study instead of Follow-up in study CL-204.

After the Rollover visit, the subsequent visits during the open-label treatment period will take place at Weeks 2, 4, 8, 16, 28, 40, 52, 64, 76, 88, and at Week 104 (End of Treatment [EoT]). In case of withdrawal, an Early Discontinuation (ED) visit will be scheduled. After the 104-week open-label treatment period (or early discontinuation of treatment), 2 follow-up visits will be planned 4 weeks and 12 weeks after the last administration of IP. Additional unscheduled visits are allowed for any safety assessments if clinically indicated. The assessments performed at each visit are detailed in the Schedule of Activities (see Appendix 1).

Subjects will receive 600 mg ziritaxestat, orally once daily (q.d.), starting the day after the Rollover visit.

A schematic diagram of the clinical study design, procedures, and stages is provided in Figure 1 (section 2.5).

Each subject will be in the study for up to 116 weeks (104 weeks of treatment and 12 weeks of follow-up).

2.4. CSP AND CSP AMENDMENTS

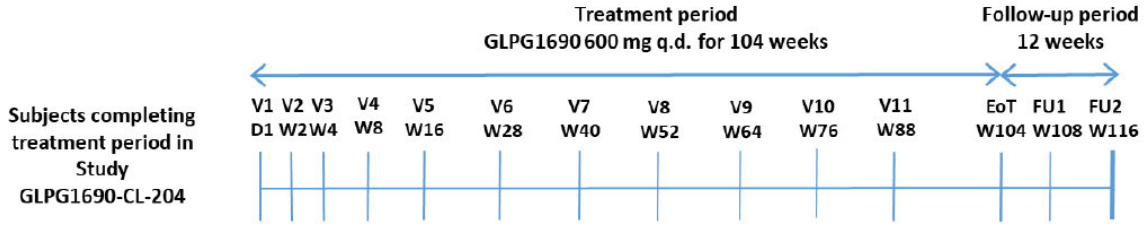
Protocol Versions	Date (ddMMMyyyy)
Version 1	30JAN2019
Version 1 updated	09APR2019
Amendment 1: Version 2	08JAN2020

This SAP was based on the latest version of the protocol that was available at the time of its finalization.

2.5. FLOW CHART

A schematic diagram of the clinical study design, procedures, and stages is provided in Figure 1.

Figure 1: Schematic Study Overview



D=Day, EoT=End of Treatment, FU=Follow-up, V=Visit, W=Week.

2.6. SAMPLE SIZE JUSTIFICATION

Thirty subjects (20 on 600 mg oral q.d. ziritaxestat and 10 on placebo) are planned to be randomized in the preceding CL-204 study. All subjects who completed the 24-week double-blind treatment in this preceding study, signed the informed consent form (ICF) of the OLE study, and are eligible for the OLE will be included. Thus, up to 30 subjects may roll over and be enrolled in this OLE study. No formal sample size calculation was performed.

2.7. RANDOMIZATION AND BLINDING

Randomization

This is an open-label study with one dose level of IP; no randomization will be performed.

At the Rollover visit (visit 1), subjects confirmed to be eligible for this OLE study will be enrolled. Subjects will retain the subject identification number assigned in CL-204.

Blinding and Unblinding

This is an open-label clinical study and treatment in this extension study will not be blinded.

3. GENERAL METHODOLOGY

Subjects will be analyzed as per their CL-204 study treatment assignment; therefore, this will be meant by the 'treatment group' reference.

3.1. ANALYSIS SETS

The analysis sets used in the statistical analyses are detailed in the following subsections. The analysis set will always be indicated in a subtitle in the TLF.

3.1.1. Full Analysis Set

The full analysis set (FAS) is defined as all randomized subjects who had received at least 1 intake of IP in the preceding CL-204 study.

3.1.2. OLE All Enrolled Subjects

All subjects who were found eligible to participate in the OLE clinical study.

3.1.3. OLE Full Analysis Set

The OLE full analysis set (OLE FAS) is defined as all subjects who had at least one intake of IP in the OLE study.

3.2. RANDOMIZED VERSUS ACTUAL TREATMENT GROUP

This is an open-label study with one dose level of IP; no randomization will be performed. Subjects will be analyzed according to the treatment arm to which they were randomized in the preceding CL-204 study.

3.3. ANALYSIS PERIODS AND ANALYSIS TIME POINTS

3.3.1. Relative Day

The timing of an assessment or an event relative to a reference date will be calculated as follows:

Relative day (DY)

$$= \text{concerned date} - \text{reference date} + 1 \text{ day, when concerned date} \geq \text{reference date}$$
$$= \text{concerned date} - \text{reference date, when the concerned date} < \text{reference date}$$

- The reference date is the date of the first CL-204 IP intake, unless specified otherwise. The first OLE IP intake can also be used as reference date, if specifically stated.

- The concerned date could be the measurement date of the assessment, or the start or end date of the event.

- Date implies a complete date. If the date is (partially) missing, the relative day will be missing.

Exception: if the end date of an event is fully missing at database lock (in case of an interim analysis) or at the subject's study termination, the event will be considered as ongoing. The end date will be imputed by the database cutoff date or the date of last visit for cases where subject terminated study.

3.3.2. Duration

The duration of an assessment or an event will be calculated as follows:

$$\text{Duration (days)} = \text{end date} - \text{start date} + 1 \text{ day}$$

Date implies a complete date. If the date is (partially) missing, the duration will be missing.

Exception: If the end date of an event is fully missing at database lock (in case of an interim analysis) or at the subject's study termination, the event will be considered as ongoing. The end date will be imputed by the database cutoff date or the date of last visit for cases where subject terminated study. In listing, the duration will be printed as "> X days".

3.3.3. Analysis Periods

All event-type data (e.g., AEs) and assessments will be allocated to analysis periods according to Table 1. Analysis periods will be defined based on cumulative data collected during both CL-204 and CL-206 studies.

Table 1: Analysis Periods

Analysis Period	Sub-period within Analysis Period	Start Analysis Period	End Analysis Period
Screening	NA	Date of signing the ICF.	Date of first CL-204 IP intake - 1 day
Treatment	Double-blind (CL-204 study)	Date of first CL-204 IP administration.	Date of last intake of CL-204 IP + 30 days or date of first OLE IP administration (excluded), whichever comes first.
	OLE (CL-206 study)	Date of first OLE IP administration.	Date of last intake of OLE IP + 30 days
Post-Treatment	NA	End date of the treatment period + 1 day.	Date of last contact in CL-206 study.

3.3.4. Analysis Windows

All CL-204 study assessments prior to the first OLE IP dose day including data collected on unscheduled visits, will be allocated to analysis visits (time windows) based on the relative day of the assessment using the first CL-204 IP dose date as reference date (see section 3.3.1) and according to the algorithm in Table 2. All CL-206 study assessments from the day of the first OLE IP dose onwards including data collected on unscheduled visits will be allocated to analysis visits where the reference date will be regarded as the first OLE IP dose date. All non-follow-up post-baseline visits will fall within the treatment period as defined in Table 1. TLFs will present the analysis visits when analysis is derived.

Table 2: Analysis Windows

Analysis Visit label	Target Day	Interval Lower Bound	Interval Upper Bound
Vital signs, Clinical Laboratory tests			
Baseline*	1	-INF	1
Week 2	15	2	22
Week 4	29	23	43
Week 8	57	44	85
Week 16	113	86	141
Week 24	169	142	197
Week 28	198	198	+INF (CL-204)
OLE visits**			
OLE Week 2	15	2	22
OLE Week 4	29	23	43
OLE Week 8	57	44	85
OLE Week 16	113	86	155
OLE Week 28	197	156	239
OLE Week 40	281	240	323
OLE Week 52	365	324	407
OLE Week 64	449	408	491
OLE Week 76	533	492	575
OLE Week 88	*617*	*576*	*673*
OLE Week 104	*729*	*674*	*743*
OLE Follow-up	Date of last intake of OLE IP + 31 days	Date of last intake of OLE IP + 31 days	+ INF (CL-206)
12-Lead ECG			
Baseline*	1	-INF	1
Day 1***	1	1	2
Week 2	15	3	64
Week 16	113	65	141
Week 24	169	142	197
Week 28	198	198	+INF (CL-204)
OLE visits**			
OLE Week 2	15	2	22
OLE Week 4	29	23	43
OLE Week 8	57	44	85
OLE Week 16	113	86	155
OLE Week 28	197	156	239
OLE Week 40	281	240	323
OLE Week 52	365	324	407
OLE Week 64	449	408	491
OLE Week 76	533	492	575
OLE Week 88	*617*	*576*	*673*

Analysis Visit label	Target Day	Interval Lower Bound	Interval Upper Bound
OLE Week 104	*729*	*674*	*743*
OLE Follow-up	Date of last intake of OLE IP + 31 days	Date of last intake of OLE IP + 31 days	+ INF (CL-206)
[redacted]			

Analysis Visit label	Target Day	Interval Lower Bound	Interval Upper Bound
[redacted]			

*: includes only assessments performed before first CL-204 IP administration.
**: target days and OLE visit windows are derived based on the first OLE IP dose day.
***: includes only assessments performed from first CL-204 IP administration onwards (post-dose timepoints). OLE follow-up visits take always precedence over all other post-baseline visits.

Definition of Baseline

Generally, baseline is defined as the last non-missing value before first IP administration in the preceding CL-204 study, based on both date and time information (if available). If multiple values qualify as the last value, the mean of these values will be used as baseline value in the analysis. If multiple categorical results are applicable for the baseline, the worst-case baseline will be determined using all non-missing baseline records:

- Normal: if all the baseline results are normal
- Abnormal: if at least one baseline result is abnormal.

[redacted]

For electrocardiogram (ECG), where triplicates (or duplicates) results are measured, the baseline is defined as the mean of the last recorded triplicates (or duplicates) results before first IP administration. If no triplicate (or duplicate) results are available before the first dose, the last value before first study drug administration will be used.

Selection of Visits

Per parameter, analysis visit and timepoint, the value closest to the target date will be used in analysis tables and figures. Other values will be listed only. If more than one value is located at the same distance from the target day, then the latest in date/time will be selected. If there are

multiple values on the same day and no time indicating which one is last, the average of the values will be calculated.

3.4. HANDLING OF DATA

3.4.1. Handling of Missing Data

3.4.1.1. Handling of Missing Date Time Data

Generally, no imputations will be done in case of missing date (time) fields, nor for the missing parts of partially known date (time) fields apart from partially missing initial diagnosis dates.

When the date of initial diagnosis is partially missing, the following rules will be used in order to determine the duration of disease:

- If the day of initial diagnosis is missing, then 01 will be assigned to the missing fields.
- If the month of initial diagnosis is missing, then January will be assigned to the missing fields.
- If date of initial diagnosis is completely missing, no imputation will be done.

Assessments with completely missing date (time) will be omitted from the analysis.

Event-type data (e.g. adverse events, concomitant medications) with missing date (time) will be allocated to analysis periods using a worst-case approach as explained in the respective sections. If the end date of an event is fully missing at database lock (in case of an interim analysis) or at the subject's study termination, the event will be considered as ongoing.

3.4.1.2. Handling of Missing Result Data

No imputation will be done of missing results unless specified otherwise in corresponding sections (i.e. observed cases (OC) analysis).

3.4.2. Handling of Values Below or Above a Threshold

Values below (above) the quantification limit will be imputed by the value one unit smaller (larger) than the quantification limit itself. In listings, the original value will be presented.

Example: if the database contains the value "<0.04", then for the descriptive statistics the value "0.03" will be used. The value ">1000" will be imputed by "1001".

3.4.3. Handling of Outliers

There will be no outlier detection, all measured values will be included in the analyses.

3.5. PRESENTATION OF RESULTS

3.5.1. Presentation of Treatment groups

A grand total "Total" will be added to summarize all subjects over all CL-204 treatment groups in all tables and figures.

3.5.2. Calculation of Descriptive Statistics

For continuous parameters, descriptive statistics will be presented when n≥2. When n=1, only the summary statistics for n and mean will be displayed, other summary statistics will be left blank.

Descriptive statistics will include:

- the number of non-missing data points (n)
- the arithmetic mean
- the standard error (SE) and standard deviation (SD)
- the median, minimum and maximum
- 95% confidence interval (CI) of the mean (if indicated in the relevant section).

3.5.3. Calculation of Percentages

Frequencies and percentages will be generated for categorical parameters.

For event-type data (e.g. Adverse Events), the denominator will be all subjects in the analysis set and analysis visit/period. For other data (e.g. worst-case analysis of assessments), the denominator will be all subjects with post-baseline data for the parameter, in the analysis set and analysis visit/period.

3.5.4. Additional Considerations

All data collected except for assessment that were not done will be listed in data listings.

4. INTERIM ANALYSES AND DATA MONITORING COMMITTEE REVIEW

Interim Analysis

Interim analyses may be performed during this clinical study, after unblinding of the CL-204 study, to allow sponsor planning of future clinical studies.

Data Monitoring

An independent medical safety review will be implemented for CL-204 as well as for this CL-206 clinical study. The review will be conducted by an independent clinician experienced in

the field of systemic sclerosis. The independent expert will review safety data and assess any potential safety issues arising during the conduct of the clinical study. [redacted]

5. STATISTICAL ANALYSES

5.1. CHANGES TO THE PLANNED ANALYSES, NOT COVERED BY PROTOCOL AMENDMENTS

Due to the early termination of the study, analyses will be reported only for cumulative data collected during both CL-204 and CL-206 studies. Analyses based on CL-206 study data only will not be reported. [redacted] The description of the analyses that will not be performed due to the early study termination is indicated in *italics* type format throughout this SAP.

5.2. SUBJECT INFORMATION

Subject information will be tabulated using the OLE FAS unless otherwise specified. No inferential testing will be performed, nor will p-values be provided.

Subject information will be tabulated with descriptive statistics per treatment group and overall.

5.2.1. Demographic and Baseline Disease Characteristics

The following parameters will be summarized:

- Sex: Male; Female
- Age at signing the ICF (years)
- Age, categorized (years): age $\leq$ 45; age > 45
- Ethnicity: Not Reported; Hispanic or Latino; Non-Hispanic or Latino; Unknown
- Race: American Indian or Alaskan Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; and White
- Is the Subject of Japanese Ancestry?: Yes; No
- Baseline Height (cm)
- Baseline Weight (kg)
- Baseline Body Mass Index BMI (kg/m^2)

Age, height, weight, and BMI will be summarized using descriptive statistics. The number and percentage of subjects by age category, sex, ethnicity, and race will also be reported.

A summary of baseline information will be presented and summarize the following parameters:

- Duration of disease (years) = $\frac{\text{(date of first IP intake)} - \text{(date of initial diagnosis)} + 1}{365.25}$.
- Duration of disease, categorized (years): duration < 2; duration ≥ 2
- [redacted]

[redacted]

All other baseline [redacted] and safety parameters will be presented together with post-baseline results by timepoint tables.

For more details on the imputation of date of initial diagnosis, refer to section 3.4.1.1.

5.2.2. Disposition Information

The following tabulations will be provided:

- The number of subjects randomized in the CL-204 study and number (percent) of subjects who completed the CL-204 study, subjects who rolled over in this CL-206 study and subjects in OLE FAS by treatment group and overall. This table will be based on the FAS.
- [redacted]
- The number (percent) of subjects who completed/discontinued the CL-206 study treatment and the reasons for discontinuation by treatment group and overall.
- The number (percent) of subjects who completed the CL-206 treatment period, subjects who completed the CL-206 treatment period and entered Follow-up phase, subjects who

completed Follow-up phase and subjects who discontinued the CL-206 study and the reasons for discontinuation.

5.2.3. Protocol Deviations and Eligibility

Major protocol deviations are determined and recorded while the study is ongoing, and the list is finalized prior to database lock. For more details, please refer to the Study Deviations Rules document.

The number (percent) of subjects with major protocol deviations will be tabulated, overall and per class of deviation, by treatment group and overall.

All available information concerning major protocol deviations, deviations on eligibility criteria and subjects not treated will be listed. Major and minor protocol deviations related to the COVID-19 pandemic will be displayed separately.

5.2.4. Inclusion and Exclusion Criteria

All CL-206 study inclusion and exclusion criteria that subjects did not fulfil will be listed in detail for the FAS.

5.2.5. Medical History and Concomitant Diseases

Medical history will be coded using the version of the medical dictionary for regulatory activities (MedDRA) used in the preceding CL-204 study as per the data validation manual (DVM). The number and percentage of subjects with any medical history will be summarized overall and for each predefined system organ class (SOC) and preferred term (PT). Frequency tabulations per SOC and PT will be provided for the medical history findings: (i.e., any event with a stop date prior to first CL-204 IP intake) as well as for the concomitant diseases (i.e., ongoing conditions or conditions with a stop date on or after first CL-204 IP intake).

5.2.6. Prior and Concomitant Medications

A prior medication is defined as any medication that is taken prior to the first dose of CL-204 IP. A concomitant medication is defined as any medication that has a stop date that is on or after the date of first dose of CL-204 IP or is ongoing. Medications that started prior to the first dose of CL-204 IP and have stop date on or after the first dose of CL-204 IP or is ongoing are defined as both prior and concomitant medications.

5.2.6.1. Coding of Reported Terms

All prior and concomitant therapy terms will be coded in the database using the version of World Health Organization Drug Dictionary (WHO-DD) used in the preceding CL-204 study.

5.2.6.2. Classification of Medications

All prior and concomitant medication records will be categorized as follows, considering their date and flags indicating the relative timing versus study (IP) start or end (before, after, ongoing…):

- Prior only: when the record ended before first CL-204 IP administration date.

- Concomitant only: when the record started on or after the first CL-204 IP administration date.

- Prior and concomitant: when the record started before the date of first CL-204 IP administration, and ended on or after this point, or continued, or if end date is missing.

When the start or end date of the prior and concomitant medication records are incomplete (and no flags indicating relative timing are available), the date of first CL-204 IMP administration will be considered to the same level of information provided by these incomplete dates to categorize the timing of these records. This means that a record only having month and year will be categorized comparing only to the month and year of the date of first CL-204 IP administration. Worst case scenario will be used to categorize concomitant medications: if the same level of information provided by incomplete concomitant medication start date is identical to first CL-204 IP administration, then the medication will be considered as both prior and concomitant, given end date is not prior to first CL-204 IP administration. If the same level of information provided by incomplete concomitant medication end date is identical to first CL-204 IP administration, then the medication will be considered as both prior and concomitant, given start date is not after to first CL-204 IP administration.

5.2.6.3. Calculation of Relative Days

For both the start and the end dates of the concomitant medication records, their day relative to the day of first CL-204 IP administration will be calculated as described in section 3.3.1. *In addition, start and end dates relative to the day of first OLE IP administration will be presented.*

5.2.6.4. Presentation of Results

A frequency tabulation of the anatomical therapeutic chemical (ATC) classes Level 4 by therapeutic subgroup (ATC Level 2) and anatomical main group (ATC Level 1) of the prior medications (defined as 'prior only' and 'prior and concomitant') will be provided as well as of the concomitant medications (defined as 'concomitant only' and 'prior and concomitant'). *A separate table will be produced for concomitant medications taken during the CL-206 study.*

All medications will be listed in detail.

5.2.7. Prior and Concomitant Non-Drug Therapies

5.2.7.1. Coding of Reported Terms

All non-drug therapies used within 12 weeks prior to and during the screening period will be collected on the electronic case report form (eCRF). All non-drug therapies will be coded according to the version of MedDRA Dictionary used in the preceding CL-204 study.

A prior non-drug therapy is defined as any non-drug therapy that is taken prior to the first dose of CL-204 IP. A concomitant non-drug therapy is defined as any non-drug therapy that has a stop date that is on or after the date of first dose of CL-204 IP or is ongoing.

5.2.7.2. Classification of Non-Drug Therapies

All prior and concomitant non-drug therapy records will be categorized as specified in section 5.2.6.2.

5.2.7.3. Calculation of Relative Days

For both the start and the end dates of the concomitant non-drug therapy records, their day relative to the day of first CL-204 IP administration will be calculated as described in section 3.3.1.

5.2.7.4. Presentation of Results

A frequency tabulation of the SOC and PT term of non-drug therapies of the prior therapies (defined as 'prior only' and 'prior and concomitant') will be provided. Similarly, a separate table will be provided for concomitant therapies (defined as 'concomitant only' and 'prior and concomitant').

All non-drug therapies will be listed in detail.

5.2.8. Exposure to IP and Compliance

5.2.8.1. Derivation Rules

Derived Parameters: Extent of Exposure to IP

- Total treatment duration (weeks) =

$$\frac{\text{last OLE IP administration date} - \text{first CL}-204\text{ IP administration date} + 1\text{ day}}{7}.$$

- Total treatment duration, excluding weeks off study IP: Number of weeks with any IP administration based on both CL-204 and CL-206 study data.

- Total treatment duration, fully compliant (weeks): Number of weeks with IP administration, as planned per CSP based on both CL-204 and CL-206 study data.

Additionally, extent of exposure parameters will be derived separately for CL-206 study data:

- Total OLE treatment duration (weeks) =

$$\frac{\text{last OLE IP administration date} - \text{first OLE IP administration date} + 1\text{ day}}{7}.$$

- Total OLE treatment duration, excluding weeks off study IP: Number of weeks with any OLE IP administration.

- Total OLE treatment duration, fully compliant (weeks): Number of weeks with OLE IP administration, as planned per CSP.

Derived Parameters: Compliance

- Overall compliance (%) =

$$100 \text{ x } \left(\frac{\text{number of tablets actually used during both CL}-204\text{ and CL}-206\text{ studies}}{\text{number of tablets that should have been used during both CL}-204\text{ and CL}-206\text{ studies}}\right)$$

Number of tablets that should have been used will be calculated as:
Total treatment duration * 3

- Percentage weeks with any intake (%) =

$$100 \text{ x } \left(\frac{\text{total treatment duration,excluding weeks off IP}}{\text{total treatment duration}}\right).$$

- Percentage weeks fully compliant (%) = $100 \text{ x } \left(\frac{\text{total treatment duration,fully compliant}}{\text{total treatment duration}}\right)$

Additionally, compliance parameters will be derived separately for CL-206 study data:

- Overall OLE compliance (%) =

$$100 \text{ x } \left(\frac{\text{number of tablets actually used during CL}-206\text{ study}}{\text{number of tablets that should have been used during CL}-206\text{ study}}\right)$$

Number of tablets that should have been used will be calculated as:

Total OLE treatment duration * 3

- Percentage weeks with any intake OLE (%) =

$$100 \times \left(\frac{\text{total OLE treatment duration,excluding weeks off IP}}{\text{total OLE treatment duration}}\right).$$

- Percentage weeks fully compliant OLE (%) =

$$100 \times \left(\frac{\text{total OLE treatment duration,fully compliant}}{\text{total OLE treatment duration}}\right)$$

Number of tablets actually used will be based on the exposure records collected in the database for both CL-204 and CL-206 studies.

Extent of exposure and compliance parameters for CL-206 study data will only be listed.

5.2.8.2. Presentation of Results

Summary statistics will be provided for each compliance and extent of exposure parameter on the OLE FAS.

Frequency tables will be provided for the compliance parameters, using the following categories: <80%; 80% ≤ x < 100%; 100%; 100% < x ≤ 120%; >120%. Percentages will be calculated out of the number of subjects who were dosed.

5.3. EFFICACY ANALYSES

[redacted]

5.3.1. Efficacy Parameters

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.3.1.3.1. Definition

[redacted]

5.3.1.3.2. Derivation Rules

[redacted]

- [redacted]

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[redacted] [redacted]

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5.3.1.6. [redacted]

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[redacted]

5.4. SAFETY ANALYSES

Safety analyses will be performed on the OLE FAS.

No formal testing will be performed to compare the treatment groups.

Tabulations will be shown by treatment group and overall.

5.4.1. Adverse Events

All AEs and changes in attributes (worsening and improvement) of AEs are reported in the database. An identification number serves to link the records considered by the investigator as describing the evolution of one and the same event.

5.4.1.1. Definition of Treatment-Emergent Adverse Events

The analysis of adverse events will be based on TEAEs. TEAEs are defined as

- AEs having a start date equal or after the date of the first CL-204 IP administration and no later than 30 days after the last OLE IP administration.
- And is either a newly reported event, or a worsening* of an existing event. Improvements are not considered treatment-emergent.

In addition, analyses of TEAEs will be repeated based on TEAEs that have an onset date on or after the OLE IP start date thus summarizing only TEAEs collected during CL-206 study.

*Worsening is defined as worsening in at least one of the following attributes: seriousness, severity, relationship and/or action taken.

5.4.1.2. Coding of Reported Terms

All AE terms will be coded in the database using the version of MedDRA Dictionary used in the preceding CL-204 study.

All tables in this section will show the AE terms coded into PT grouped into body SOC. Subject listings will also show the reported terms. Any other coding levels will only be shown in a listing summarizing coding or if explicitly mentioned.

Coding information (SOC, PT, high level group term, high level term, low level term and verbatim) based on all the collected AE data will be presented in a listing.

5.4.1.3. Allocation of Adverse Events to Analysis Periods

All AEs records will be placed into analysis periods considering their start date, aiming to report the incidence of these events only in the analysis period during which they started.

The general rule for allocation of AEs to analysis periods follows:

Analysis period start date ≤ AE start date ≤ analysis period end date

If the start date of an AE is missing or incomplete to a level preventing a clear allocation of the AE to one single analysis period and no flag indicating timing relative to study medication is available, a worst-case consideration (see below) will be done aiming to allocate the AE to one single analysis period, if possible. When a worst-case consideration is needed, the end date of the AE, if and as available, should also be considered; if such AEs clearly end on a given point, this will exclude the possibility to allocate the AE to an analysis period after that point.

- An AE which according to the available information of its start date could belong to the screening as well as to the treatment period will only be placed in the treatment period.

- An AE which according to the available information of its start date could belong to treatment period as well as to follow-up period will only be placed in the treatment period.

- An AE with a missing start date will be allocated to treatment period.

- If an AE can be allocated to both double-blind (i.e. CL-204 study) and open-label (i.e. CL-206 study) treatment sub-periods, then the event will be reported for CL-204 double-blind treatment sub-period during CL-206 study analyses.

5.4.1.4. Treatment Relatedness

Following ICH-E3 (ICH), the originally reported relatedness to IP of an AE will be dichotomized as follows:

- Not IP related: all non-missing weaker levels of relatedness than ‘possibly IP related’ (unrelated, unlikely).

- IP related: ‘possibly IP related’ and all stronger levels of relatedness (probable, certain) - this class also includes any missing IP relatedness, as a worst-case consideration.

Only this dichotomized relatedness will be used in tables. Relatedness as originally reported will only be listed.

5.4.1.5. Presentation of Adverse Events and of Event Episodes

All AEs tables will only show TEAEs and will show counts of the number of subjects with TEAEs. The number of event episodes will be shown only in tables where explicitly mentioned.

Tables will be produced for cumulative data collected during both CL-204 and CL-206 studies. *Separate tables will be produced for CL-206 study data.*

AEs starting before first CL-204 IP administration or later than 30 days after the last OLE dose of IP will only be listed.

AEs leading to death will be presented in a separate listing.

5.4.1.6. Worst-Case Selections

When cross-tabulating AE preferred terms versus an AE attribute (like severity), only the worst-case within each same preferred term, same subject and same analysis period will be considered, i.e., when a same subject has more than once the same AE preferred term reported in the same treatment group, the subject will be counted only once and will be shown under the worst outcome (like the worst severity for that AE in the concerned treatment period).

Worst-case will be defined based on cumulative data collected during both CL-204 and CL-206 studies. *Additionally, worst-case will be defined based on CL-206 study data.*

5.4.1.7. Calculation of Relative Days and Duration

For each AE record, its start day in study (the day of the AE start date relative to the date of first IP administration), its start day in the analysis period, and its duration (in days) will be calculated and shown only in listings.

See sections 3.3.1 and 3.3.2 for the calculation of relative days and duration respectively.

5.4.1.8. Presentation of Results

A summary table will be provided, showing then number (percentage) of subjects with:

- at least one TEAE,
- at least one IP-related TEAE,
- at least one serious TEAE,
- at least one TEAE leading to death,
- any TEAEs by worst severity (mild, moderate, severe, life threatening, and death),
- at least one TEAE leading to IP discontinuation,
- at least one TEAE leading to IP interruption.

Frequency tabulations, by SOC and PT, of the number (percent) of subjects with a TEAE will be presented by prior treatment group as assigned in the preceding study. Similar tables will be provided for the following groups:

- Severity (‘Grade 1 - Mild’, ‘Grade 2 - Moderate’, ‘Grade 3 - Severe’, ‘Grade 4 - Life Threatening’, and ‘Grade 5 - Death’)

- Related TEAEs
- Related TEAEs by severity
- Serious TEAEs
- TEAEs leading to IP discontinuation.

Serious adverse events, AEs leading to death, AEs leading to IP and trial discontinuation will be listed.

5.4.1.9. EudraCT Adverse Events Reporting

For the purpose of EudraCT reporting, the following tabulations will be added:

Frequency tabulations, by SOC and PT, of the number (percent) of subjects with non-serious TEAE will be presented. A similar table will be provided for serious TEAEs (counting events) that were reported in at least 5% of the subjects and another table for non-serious TEAEs reported in at least 5% of the subjects in any treatment group.

[redacted]

5.4.2.2. Derivation Rules

[redacted]

5.4.2.3. Analysis Methods

[redacted]

5.4.3. Laboratory Safety

5.4.3.1. Available Data

Laboratory tests scheduled are described in section 5.6.2 of the protocol.

The statistical analyses will only present results in Standard International (SI) units. Other units will not be presented.

Hematology, coagulation, and serum/plasma chemistry data provided by the central lab will be used in tables and figures. For hematology parameters, when both absolute and percentage of white blood cells (WBC) are available, only the absolute values will be presented in tables and figures.

Urinalysis tests will be presented as part of the descriptive statistics tables.

Results of serology testing, pregnancy test, and FSH will only be listed.

5.4.3.2. Derivation Rules

Fasted and Non-Fasted Results

Laboratory parameters that are sensitive to the fasting status: glucose, triglycerides.

These parameters will be tabulated with descriptive statistics by fasting/non-fasting and toxicity grade. Laboratory results for which the fasting status is missing, will be considered as taken non-fasted.

5.4.3.3. Definition of Toxicity Grades

Toxicity grades will only be derived for laboratory tests for which toxicity gradings are available.

For the analysis values of the following continuous laboratory parameters, toxicity grades will be determined as implemented in the next table (grading based on Common Terminology Criteria for Adverse Events (CTCAE), v5.0: November 27, 2017). Analysis results scoring below the lowest grade limits are defined to correspond to grade 0.

Table 3: Laboratory Toxicity Grades

Parameter	Direction of abnormality	Grade 1	Grade 2	Grade 3	Grade 4
Alanine amino transferase	high	>ULN-3 x ULN	>3 x ULN -5 x ULN	>5 x ULN - 8 x ULN	>8 x ULN
Albumin (g/L)	low	<LLN-30	<30-20	<20	-
Alkaline phosphatase	high	>ULN-2.5 x ULN	>2.5 x ULN -5 x ULN	>5 x ULN -20 x ULN	>20 x ULN
Aspartate amino transferase	high	>ULN-3 x ULN	>3 x ULN -5 x ULN	>5 x ULN -8 x ULN	>8 x ULN
Bilirubin [total]	high	>ULN-1.5 x ULN	>1.5 x ULN -3 x ULN	>3 x ULN -10 x ULN	>10 x ULN
Calcium, below (mmol/L)	low	<LLN-2.0	<2.0-1.75	<1.75-1.5	<1.5
Calcium, above (mmol/L)	high	>ULN-2.9	>2.9-3.1	>3.1-3.4	>3.4
Cholesterol (mmol/L)	high	>ULN-7.75	>7.75-10.34	>10.34-12.92	>12.92
Creatine kinase	high	>ULN-2.5 x ULN	>2.5 x ULN -5 x ULN	>5 x ULN -10 x ULN	>10 x ULN
Creatinine	high	>ULN-1.5 x ULN	>1.5 x ULN -3 x ULN or >1.5 x baseline -3 x baseline	>3 x ULN -6 x ULN or >3 x baseline	>6 x ULN
eGFR/ Creatinine clearance (mL/min/1.73 m2)	low	<LLN-60	<60-30	<30-15	<15
Eosinophils absolute count	high	>ULN	-	-	-
Eosinophils relative count (%)	high	>7	-	-	-
Gamma-glutamyl transferase	high	>ULN-2.5 x ULN	>2.5 x ULN -5 x ULN	>5 x ULN -20 x ULN	>20 x ULN
Glucose [fasting], below (mmol/L)	low	<LLN-3.0	<3.0-2.2	<2.2-1.7	<1.7
Hemoglobin, below (g/L)	low	<LLN-100	<100-80	<80	-
Hemoglobin, above (g/L)	high	Increase >0-20	Increase >20-40	Increase >40	-
Lymphocytes, below (10^9/L)	low	<LLN-0.8	<0.8-0.5	<0.5-0.2	<0.2
Lymphocytes, above (10^9/L)	high	-	>4.0-20.0	>20.0	-
Neutrophils, below (10^9/L)	low	<LLN-1.5	<1.5-1.0	<1.0-0.5	<0.5

Parameter	Direction of abnormality	Grade 1	Grade 2	Grade 3	Grade 4
Potassium, below (mmol/L)	low	<LLN-3.0	-	<3.0-2.5	<2.5
Potassium, above (mmol/L)	high	>ULN-5.5	>5.5-6.0	>6.0-7.0	>7.0
Sodium, below (mmol/L)	low	<LLN-130	<130-125	<125-120	<120
Sodium, above (mmol/L)	high	>ULN-150	>150-155	>155-160	>160
Triglycerides fasting and non-fasting (mmol/L)	high	>1.71-3.42	>3.42-5.7	>5.7-11.4	>11.4
Partial thromboplastin time [activated or not specified]	high	>ULN-1.5 x ULN	>1.5 x ULN -2.5 x ULN	>2.5 x ULN	-
International normalized ratio	high	>1.2 x ULN -1.5 x ULN	>1.5 x ULN -2.5 x ULN	>2.5 x ULN	-
Platelets (10^9/L)	low	<LLN-75	<75-50	<50-25	<25
White blood cells, below (10^9/L)	low	<LLN-3	<3-2	<2-1	<1
White blood cells, above (10^9/L)	high	-	-	>100	-

Legend:
[Specifications].
(Specific unit into which the defined grades apply).
Baseline value is defined as abnormal if the value is not within the normal range. For directional toxicity of high an abnormal baseline will be a baseline value which is higher than the upper limit of the reference range. For directional toxicity of low, an abnormal baseline will be a baseline value which is lower than the lower limit of the reference range.
x LLN / x ULN = times the lower / times the upper limit of the normal range.
Below / above = differentiate grade definitions in the low / high sense for a same parameter.

The following parameters will be analyzed and categorized based on pre-defined criterion without using the above defined grading system:

- Prothrombin time: >ULN-1.5 x ULN; >1.5 x ULN - 2.5 x ULN; >2.5 x ULN

- Glucose [fasting] (mmol/L): >7.2

- High density lipoprotein (mmol/L): <1.554

- Low density lipoprotein (mmol/L): >4.144

The analysis of these parameters will be performed in the same way as the analysis of the parameters with standard toxicity grade.

5.4.3.4. Definition of Non-Graded Abnormalities

Non-graded abnormalities will be determined only for the parameters having no definitions of toxicity grades (see section 5.4.3.3).

For laboratory tests provided by the laboratory, the position of the actual analysis values versus their normal ranges will be determined directly by using the position indicator provided in the database as reported, expressing the classes for these analysis values as low (L), normal (N) or high (H). L, N and H are further referred to as non-graded abnormalities.

5.4.3.5. Urinalysis Tests with Categorical Results

Results of urinalysis with qualitative results will be tabulated by time point. No toxicity grading or non-graded abnormalities will be derived.

5.4.3.6. Treatment Emergent Principle

Toxicity Grades

A post-baseline toxicity grade 1, 2, 3 or 4 is defined as treatment-emergent when higher than the toxicity grade of the baseline result. If the baseline result is missing, a post-baseline toxicity grade 1, 2, 3 or 4 will always be considered as treatment-emergent.

For prothrombin time parameter a post-baseline value meeting the defined abnormality criteria is regarded as treatment-emergent if the post-baseline criteria meet a higher degree of abnormality than the baseline value (e.g. post-baseline value meeting >1.5-2.5 x ULN category while baseline meeting >ULN-1.5 x ULN category) or the baseline value is missing or does not meet any abnormality criteria. For glucose [fasting], high density lipoprotein and low-density lipoprotein a post-baseline abnormal category will be regarded as treatment emergent, if the baseline value is missing or does not meet the defined abnormality criteria.

Non-graded Abnormalities

A post-baseline non-graded abnormality class L or H is defined as treatment-emergent when it differs from the abnormality class of the baseline result. If the baseline result is missing, a post-baseline abnormality L or H will always be considered as treatment-emergent.

5.4.3.7. Worst-Case

Toxicity Grading

The worst-case post-baseline toxicity grade 0, 1, 2, 3 or 4 will be determined per subject, per parameter (and sense, if below and above) during the on-treatment analysis period, using all non-missing post-baseline records within that period (including unscheduled and follow-up visits).

The worst-case toxicity grade is the highest toxicity grade scored for the parameter (in each sense, if below and above).

Worst-case will be defined based on cumulative data collected during both CL-204 and CL-206 studies. *Additionally, worst-case will be defined based on CL-206 study data.*

Non-graded Abnormalities

The following worst-case post-baseline abnormalities L, N or H will be determined per subject, per parameter and for the on-treatment analysis period, using all non-missing post-baseline records within that period (including unscheduled and follow-up visits):

- L = low: at least one post-baseline result is classified as L.
- N = normal: all post-baseline results are classified as N.
- H = high: at least one post-baseline result is classified as H.

If, for a subject, both L and H are reported, the subject will be counted twice in the table: once with a worst-case L and once with a worst-case H.

5.4.3.8. Elevated Liver Function Test

To assess the potential of the IP to cause severe liver damage, possible Hy's Law cases will be identified. Count and percentage of subjects who have at least one assessment meeting the criteria defined in Table 4 will be summarized in the on-treatment analysis period.

Table 4 : Hepatotoxicity

Parameter	Thresholds
AST / ALT combination	AST > 1.5- <3 x ULN AST >= 3- <5 x ULN AST >= 5- <8 x ULN AST >= 8 x ULN ALT > 1.5- <3x ULN ALT >= 3- <5 x ULN ALT >= 5- <8 x ULN ALT >= 8 x ULN ALT and/or AST > 1.5 -<3 x ULN AST and /or ALT >= 3- <5 x ULN AST and /or ALT >= 5- <8 x ULN AST and /or ALT >= 8 x ULN
AST / ALT / bilirubin combination	Bilirubin >= 1.5 x ULN AND AST or ALT >= 3 x ULN Bilirubin >= 2 x ULN AND AST or ALT >= 3 x ULN

Hepatotoxicity values will also be listed including the timing of occurrence.

5.4.3.9. Presentation of Results

No formal inferential statistics (p-values) will be provided.

Continuous parameters will be summarized by means of descriptive statistics (including 95% CI of the mean change from t-test) by parameter, treatment group and analysis visit. Actual values and changes from baseline will be tabulated separately.

Figures of the mean (± SE) actual values over time and of the mean (± SE) change from baseline will be prepared for all parameters.

All laboratory abnormalities on or after the first dose of IP administration in the preceding CL-204 study up to the last contact after the last dose of OLE IP will be included.

Abnormalities of the actual values will be presented as shift tables of the worst-case abnormality versus the baseline abnormality/toxicity grade. The table will be created per parameter and treatment group for the on-treatment analysis period. The results of non-graded abnormalities and toxicities grades will be shown separately.

A frequency table of the number (percentage) of subjects with treatment-emergent worst-case abnormalities per parameter and treatment group for the on-treatment analysis period will be presented. The results of non-graded abnormalities and toxicities grades will be shown separately.

Urinalysis tests for which no normal range is available will be tabulated separately as categorical data.

Clinical laboratory values will also be listed including normal ranges and indicating if value is out of range. A separate listing will also be created to include all abnormal laboratory values.

Analyses will be performed for cumulative data collected during both CL-204 and CL-206 studies. *Additionally, analyses will be performed for CL-206 study data*.

5.4.4. Electrocardiogram

5.4.4.1. Available Data

All subjects will have a standard 12-lead electrocardiogram (ECG) performed at the time points specified in the Schedule of Activities (see Appendix 1). The following ECG parameters will be analyzed: heart rate (bpm), PR interval, QRS interval, uncorrected QT interval (ms), morphology, QT interval corrected for the heart rate using Fridericia's formula (QTcF) (ms).

5.4.4.2. Derivation Rules

Derived Parameters

The ECG parameters will be provided in the clinical database, no imputation will be done.

Handling of ECGs Measured in Triplicate

If ECG is collected in triplicates (or duplicates), the following approach will be taken.

The mean of the triplicate (or duplicate) ECG values will be calculated for each individual ECG parameter, without rounding the result. These calculated means will constitute the analysis values; any derivation (e.g. change from baseline, assignment of abnormalities) and statistic will be based on the mean value of the triplicates (or duplicates).

When a single ECG is performed, the actual results of the single ECG will be summarized.

The values of the individual triplicate (or duplicate) assessments will be listed, i.e. will not be summarized or graphically presented.

5.4.4.3. Abnormalities

The actual analysis values and changes from baseline of the QT and QTcF parameters will be categorized into the abnormality classes as defined in ICH E14:

Table 5: Abnormalities on ECG Parameters

Parameter	Abnormality	Limits
Abnormalities on actual values		
QT and QTcF (ms)	QT* ≤ 450 450 < QT* ≤ 480 480 < QT* ≤ 500 QT* > 500	≤ 450 450 < value ≤ 480 480 < value ≤ 500 > 500
Abnormalities on change from Baseline		
QT and QTcF (ms)	QT* change ≤ 30 30 < QT* change ≤ 60 QT* change > 60	≤ 30 30 < value ≤ 60 > 60

* Indicate which QT(c) parameter is analyzed in the label

For electrocardiogram (ECG), where triplicates (or duplicates) results are measured, the baseline is defined as the mean of the last recorded triplicates (or duplicates) results before first IP administration. If no triplicate (or duplicate) results are available before the first dose, the last value before first study drug administration will be used.

5.4.4.4. Worst-Case Abnormality

For the overall interpretation the worst-case post-baseline will be determined per subject, per parameter, and for on-treatment analysis period, using all non-missing post-baseline records (including unscheduled and follow-up visits) as follow:

- Normal: if all the post-baseline results are normal
- Abnormal: if at least one post-baseline result is abnormal.

Worst-case will be defined based on cumulative data collected during both CL-204 and CL-206 studies. *Additionally, worst-case will be defined based on CL-206 study data.*

5.4.4.5. Treatment Emergent Abnormalities

Actual value: An abnormal post-baseline abnormality is defined as treatment-emergent when the abnormality is worse compared to the abnormality at baseline. If the baseline result is missing, a post-baseline result outside of the normal range will always be considered as treatment-emergent.

An abnormal category for change from baseline is always treatment-emergent.

Additional analyses will be performed for CL-206 study data, where baseline will be regarded the last non-missing value before first OLE IP administration.

5.4.4.6. Presentation of Results

No formal inferential statistics (p-values) will be presented.

Continuous parameters will be summarized by means of descriptive statistics (including 95% CI of the mean change from t-test) by parameter, treatment group and analysis visit. Actual values and changes from baseline will be tabulated separately and tables will be produced including all time points in the preceding CL-204 and CL-206 studies. *Separate tables will be produced for CL-206 study data.*

All ECG abnormalities on or after the first dose of IP administration in the preceding CL-204 study up to the last contact after the last dose of OLE IP will be listed.

Abnormalities of the actual values will be presented as shift tables of the worst-case abnormality versus the baseline abnormality. The table will be created per parameter and treatment group for the on-treatment analysis period. Tables will be produced for cumulative data collected during both CL-204 and CL-206 studies. *Separate tables will be produced for CL-206 study data.*

A frequency table of the number (percentage) of subjects with treatment-emergent worst-case abnormalities per parameter and treatment group for the on-treatment analysis period will be presented. Overall interpretation as assessed by the investigator will also be summarized and listed.

5.4.5. Vital Signs

5.4.5.1. Available Data

The following vital signs parameters will be analyzed: Systolic Blood Pressure (SBP) (mmHg), Diastolic Blood Pressure (DBP) (mmHg), heart rate (bpm), respiratory rate (breaths/minute), and body temperature (°C). If blood pressure is collected supine, semi-recumbent, sitting, or standing, then results are presented by assessment position. If there are more values available for a subject taken by different positions for a visit, then selection rules for the analyses will be applied as described in Section 3.3.4. No adjustment to the temperature will be made to account for the possible different method of collection.

5.4.5.2. Abnormalities

The relevant vital sign values at each visit will be classified based on the reference ranges found in Table 6 below.

Table 6: Normal Ranges for Vital Signs

Normal ranges applicable in supine position:

Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Heart rate (bpm)	Tympanic temperature (°C)	Respiratory rate (breaths per min)
90≤ SBP ≤140	45≤ DBP ≤90	50≤ HR ≤100	35.5≤ t° ≤37.5	12≤ RR ≤20

5.4.5.3. Treatment Emergent Principle

A post-baseline abnormality class L or H is defined as treatment-emergent when it differs from the abnormality class at baseline. If the baseline result is missing, a post-baseline abnormality L or H will always be considered as treatment-emergent.

Baseline is defined as the last non-missing value before first IP administration in the preceding CL-204 study. *Additional analyses will be performed for CL-206 study data, where baseline will be regarded the last non-missing value before first OLE IP administration.*

5.4.5.4. Worst-Case Abnormality

The following worst-case post-baseline abnormalities low, below the lower limit of the normal range (L), normal, with the limits of the normal range (N) or high, above the upper limit of the normal range (H) will be determined per subject, per parameter and for the on-treatment analysis period, using all non-missing post-baseline records (including unscheduled and follow-up visits):

- L = low: at least one post-baseline result is classified as L.
- N = normal: all post-baseline results are classified as N.
- H = high: at least one post-baseline result is classified as H.

If, for a subject, both L and H are reported, the subject will be counted twice in the table: once with a worst-case L and once with a worst-case H.

Worst-case will be defined based on cumulative data collected during both CL-204 and CL-206 studies. *Additionally, worst-case will be defined based on CL-206 study data.*

5.4.5.5. Presentation of Results

No formal inferential statistics (p-values) will be derived.

Continuous parameters will be summarized by means of descriptive statistics (including 95% CI of the mean change from a t-test) for all vital sign parameters and analysis visits, by treatment group and overall. Actual values and changes from baseline will be tabulated separately and tables will be produced including all time points in the preceding CL-204 and CL-206 studies. *Separate tables will be produced for CL-206 study data.*

All abnormalities on or after the first dose of IP administration in the preceding CL-204 study up to the last contact after the last dose of OLE IP will be included.

Abnormalities of the actual values will be presented as shift tables of the worst-case abnormality versus the baseline abnormality. The table will be created per parameter (and position if applicable), and treatment group for the on-treatment analysis period. Tables will be produced for cumulative data collected during both CL-204 and CL-206 studies. *Separate tables will be produced for CL-206 study data.*

Frequency table of the number (percentage) of subjects with treatment-emergent worst-case abnormalities per parameter and treatment group for the on-treatment analysis period will be presented. Tables will be produced for cumulative data collected during both CL-204 and CL-206 studies. *Separate tables will be produced for CL-206 study data.*

Mean (± SE) plots over time for both treatment groups, with heart rate, respiratory rate, body temperature, and blood pressure by position on a new page, will be displayed. Separate plots will be produced for mean actual values and changes from baseline.

5.4.6. Physical Examinations

Abnormal physical examination results (including gynaecological exam results for female subjects) will be presented in a listing.

5.4.7. Hospitalization

All information recorded in the eCRF page “Hospitalization Details” will be listed.

6. REFERENCES

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APPENDIX 1

EVENT	TREATMENT PERIOD											FOLLOW-UP	
Study Visit	**Roll-over Visit 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**EoT/ ED**	**FU1**	**FU2**
Study Week (W) or Day (D) ± days (d)	**D1**	**W2 ±2d**	**W4 ±2d**	**W8 ±4d**	**W16 ±7d**	**W28 ±7d**	**W40 ±7d**	**W52 ±7d**	**W64 ±7d**	**W76 ±7d**	**W88 ±7d**	**W104 ±7d**	**W108 ±7d**	**W116 ±7d**
Informed consent	✓													
Inclusion/exclusion criteria	✓	✓												
Pregnancy test	(✓)[1]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Symptom-directed physical examination	(✓)[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Vital signs	(✓)[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
12-Lead ECG	(✓)[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Clinical laboratory tests	(✓)[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
[redacted]														
Dispense subject diary	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

EVENT	TREATMENT PERIOD											FOLLOW-UP	
Study Visit	**Roll-over Visit 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**EoT/ ED**	**FU1**	**FU2**
Study Week (W) or Day (D) ± days (d)	**D1**	**W2 ±2d**	**W4 ±2d**	**W8 ±4d**	**W16 ±7d**	**W28 ±7d**	**W40 ±7d**	**W52 ±7d**	**W64 ±7d**	**W76 ±7d**	**W88 ±7d**	**W104 ±7d**	**W108 ±7d**	**W116 ±7d**
Collect subject diary		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dispense IP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Review IP compliance		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Dose IP	q.d. from the day after the Rollover visit to the end of the treatment period													
AE assessment	Throughout the study													
Concomitant medications	Throughout the study													

W=Week(s), D=Day(s), EoT=End of Treatment, ED=Early Discontinuation, FU=follow-up, [redacted]

[1] Rollover visit data in parentheses are those collected as part of the activities at the last visit (Week 24) of the preceding core Study GLPG1690-CL-204, which is on the same day as the Day 1 Rollover visit of this study.

APPENDIX 2

[redacted]

EXAMPLE:

[redacted]

Signature Page for glpg1690-cl-206-sap 17838

Approval	[redacted]nager Biometrics 23-Apr-2021 09:54:22 GMT+0000

Approval	[redacted]al Director Phase I Translational Medicine 23-Apr-2021 12:43:32 GMT+0000

Signature Page for glpg1690-cl-206-sap43952_19643_47970