Galápagos

STATISTICAL ANALYSIS PLAN

Project Number:	GLPG2222
Study Number:	GLPG2222-CL-202
Study Title:	A Phase IIa, randomized, double-blind, placebo-controlled study to evaluate multiple doses of GLPG2222 in subjects with Cystic Fibrosis who are homozygous for the F508del mutation.

Development Phase:	IIa		
Status:	Final		
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1. STUDY DESIGN

1.1. STUDY OBJECTIVES

1.1.1. Primary Objective

- To evaluate the safety and tolerability of 4 different doses of GLPG2222 administered orally and q.d. for 29 days in adult subjects with CF* who are homozygous for the F508del CFTR mutation.

  * Cystic Fibrosis

1.1.2. Secondary Objectives

- To assess changes in biomarkers of CFTR activity.
- To assess changes in respiratory symptoms.
- To assess the PK of GLPG2222.

1.2. STUDY ENDPOINTS

1.2.1. Primary Endpoint

- Safety and tolerability, assessed by the incidence of adverse events (AEs), as well as changes over time in weight, vital signs, oxygen saturation by pulse oximetry, 12-lead ECG, spirometry, and clinical safety laboratory data (hematology, chemistry, coagulation and urinalysis).

1.2.2. Secondary Endpoints

- Change from baseline in sweat chloride concentration through 29 days.
- Change from baseline in percent predicted FEV_1 through 29 days.
- Change from baseline in the respiratory domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) through 29 days.
- PK parameters of GLPG2222.

1.3. STUDY DESIGN

This is a Phase IIa, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate 4 different doses of GLPG2222 administered orally and q.d. for 29 days to adult male and female subjects with a confirmed diagnosis of CF and homozygous for the F508del CFTR mutation. Eligible subjects must be on a stable concomitant medication regimen for at least 4 weeks prior to the first study drug administration and agree to continue the same regimen for the duration of the study.

A schedule of the study design is provided in Figure 1.

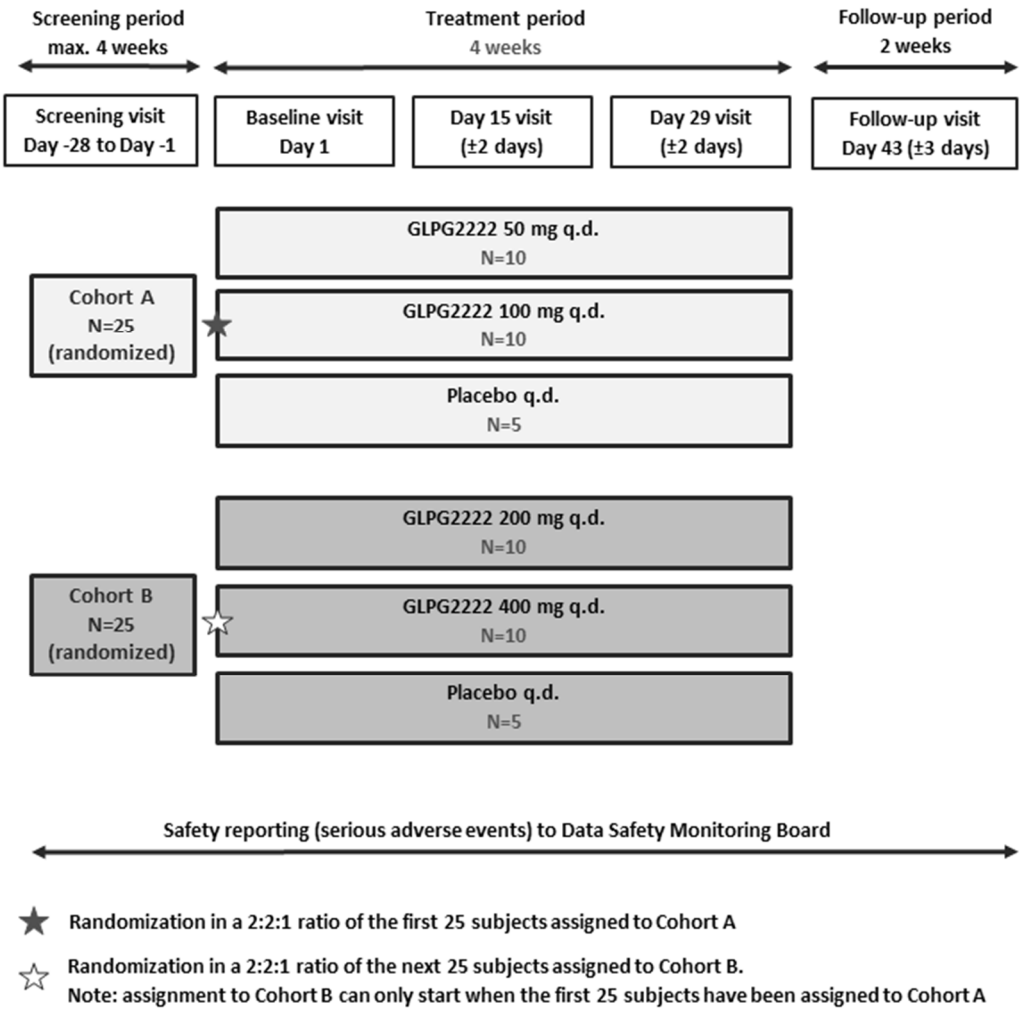

Figure 1: Study design

The study will consist of a screening period of maximum 4 weeks (starting when the subject has signed the informed consent form [ICF]), a treatment period of 4 weeks, and a follow-up period of 2 weeks. Enrolled subjects will come to the clinical study center at screening, on Day 1 (baseline), Day 15, Day 29, and at the follow-up visit (2 weeks after the last study drug administration).

Approximately 50 evaluable subjects are planned to be included sequentially in the study: the first 25 subjects will be assigned to Cohort A (i.e. subjects 1 to 25) and the next 25 subjects will be assigned to Cohort B (i.e. subjects 26 to 50). Subjects participating in Cohort A are not allowed to participate in Cohort B. In each study cohort, subjects will be randomized in a 2:2:1 ratio to receive:

- Cohort A: 50 mg GLPG2222, 100 mg GLPG2222 or placebo q.d. for 29 days.
- Cohort B: 200 mg GLPG2222, 400 mg GLPG2222 or placebo q.d. for 29 days.

Assessments for efficacy and safety will be performed during the study at the time points specified in the flow chart.

Additionally, subjects can choose to participate in the optional substudy, in which nasal brushings will be collected.

Subjects will be in the study for a duration of minimum 6 weeks and maximum 10 weeks (from screening until the follow-up visit, depending on the duration of the screening period).

The end of the study is defined as the last contact with the last subject.

1.4. PROTOCOL AND PROTOCOL AMENDMENTS

Protocol Versions	**Date (ddMMMyyyy)**
Final	06DEC2016

Protocol Amendments	**Date (ddMMMyyyy)**
Not Applicable	

This SAP was based on the latest version of the protocol.

1.5. FLOWCHART

The schedule of assessments is given in the flow chart below.

EVENT	**SCREENING**	**TREATMENT PERIOD[1]**				**FOLLOW-UP**
Study days (D)	**D-28 till D-1**	**D1**	**D15 (±2D)**	**D29 (±2D)**	**ED**	**D43 (±3D)**
Informed consent[2]	X					
Inclusion/exclusion criteria	X	X				
CFQ-R[3]	X	X	X	X	X	X
Demographics	X					
Medical history	X					
Physical examination[4]	X	X	X	X	X	X
Weight	X	X	X	X	X	X
Vital signs[5]	X	X	X	X	X	X
Pulse oximetry[6]	X	X	X	X	X	X
12-lead ECG[7]	X	X	X	X	X	X

[1] All assessments are to be performed pre-dose. In addition, some assessments are also to be performed at defined time points post-dose when specifically mentioned.
[2] Written informed consent to be obtained before any study-related procedures and/or assessments are performed.
[3] CFQ-R to be completed prior to any other assessments scheduled for that visit.
[4] Full physical examination at screening (including height); limited physical examination (ear, nose, throat, chest and neck) at subsequent visits.
[5] Vital signs include heart rate, blood pressure (systolic and diastolic), respiratory rate and oral body temperature. Heart rate and blood pressure to be captured after 5 minutes in supine position. Vital signs must be recorded pre-dose at all visits, and additionally between 3 and 4 hours post-dose on Day 1.
[6] Pulse oximetry to determine oxygen saturation is to be captured after at least 5 minutes of rest in seated or supine position.
[7] 12-lead ECG to be measured after at least 5 minutes of rest in supine position.

EVENT	SCREENING	TREATMENT PERIOD[1]				FOLLOW-UP
Study days (D)	**D-28 till D-1**	**D1**	**D15 (±2D)**	**D29 (±2D)**	**ED**	**D43 (±3D)**
Sweat collection	X	X	X	X	X	X
Spirometry[8]	X	X	X	X	X	X
Clinical safety laboratory tests[9]	X	X	X	X	X	X
Serology[10]	X					
Pregnancy test[11]	X	X		X	X	X
FSH test[12]	X					
CFTR genotyping		X				
PK blood samples[13]			X	X	X	
Exploratory biomarkers[14]		X	X	X		
Randomization		X				
Breakfast or snack to be provided[15]		X	X	X		
Study drug dosing		→	→	→		
Study drug dispensing		X	X			
Dispense subject diary	X	X	X	X		
Collect subject diary		X	X	X	X	X
AE assessment	→	→	→	→	→	
Concomitant medications	→	→	→	→	→	
Optional substudy[16]						

[8] Spirometry must be performed pre-dose at all visits, and additionally between 1 and 2 hours post-dose on Day 1 and Day 29.

CFQ-R = Cystic Fibrosis Questionnaire - Revised; ECG = electrocardiogram; ED = early discontinuation

[9] Blood and urine samples to be collected for clinical safety laboratory tests.

[10] Serology sample for hepatitis B virus surface antigen, hepatitis C virus antibody and human immunodeficiency type 1 and 2 antibodies.

[11] For female subjects of childbearing potential only; serum pregnancy test at screening, urine pregnancy test at other scheduled visits.

[12] For suspected post-menopausal female subjects only (age < 55 years and no menses for ≥ 12 months without a medical cause).

[13] PK blood samples for GLPG2222 to be taken pre-dose and 0.5, 1, 2, 3, 4, 6 and 8 hours post-dose on Day 15 (or on Day 29 if subject is not available for full PK profiling on Day 15), and pre-dose on Day 29. In case of an early discontinuation visit, one additional sample to be taken pre-dose if study drug is still taken, or at any time during the visit if study drug is no longer taken.

[14] Exploratory biomarkers [redacted].

[15] Study drug to be taken once daily in the morning with a breakfast or snack.

[16] Only for subjects who give separate consent to participate in the optional substudy.

AE = adverse event; CFTR = cystic fibrosis transmembrane conductance regulator; FSH = follicle stimulating hormone, PK = pharmacokinetic(s)

EVENT	SCREENING	TREATMENT PERIOD[1]				FOLLOW-UP
Study days (D)	**D-28 till D-1**	**D1**	**D15 (±2D)**	**D29 (±2D)**	**ED**	**D43 (±3D)**
Nasal brushing		X	X	X		

2. ANALYSIS POPULATIONS

The analysis population will always be indicated in a subtitle in the table, listing or figure.

2.1. ALL SCREENED SUBJECTS POPULATION

All subjects who provided informed consent by signing the ICF.

2.2. ALL ENROLLED POPULATION

All subjects who were enrolled into the study, i.e. randomized into the study.

2.3. INTENT TO TREAT POPULATION

All enrolled subjects who received at least one dose of study drug and had at least one post-baseline assessment with efficacy data.

2.4. SAFETY POPULATION

All subjects who received at least one dose of study drug.

2.5. PHARMACOKINETICS POPULATION

Subpopulation of the Safety population, including all subjects who were exposed to GLPG2222 and who have available and evaluable PK data (e.g. excluding all protocol violations/deviations or AEs that may have an impact on the PK analysis).

3. TREATMENT GROUPS

3.1. RANDOMIZED VERSUS ACTUAL TREATMENT

For efficacy parameters, the treatment group as assigned by the randomization will be used in the analysis (i.e., as-randomized analysis).

For safety, the treatment that was actually used by the subject will be applied in the analysis (i.e., as-treated analysis).

Differences between as-treated and as-randomized will be flagged in the listing on subject randomization.

3.2. TREATMENT GROUP LABELS

The following treatment group labels will be used in the tables, listings and figures:

- Pooled placebo
- GLPG2222 50 mg q.d.
- GLPG2222 100 mg q.d.
- GLPG2222 200 mg q.d.
- GLPG2222 400 mg q.d.

3.3. POOLING OF GROUPS

Both placebo groups (from cohort A and from cohort B) will be pooled into one placebo group for the tables/figures but not for the listings. Note that for some tables and some figures, placebo from each cohort can be provided as well.

3.4. SUB-GROUPS

In efficacy part, the following sub-groups analyses will be performed and the following labels will be used in the tables/figures:

- By target C_{trough} at Day 15 (only for GLPG2222 dose levels)
  - Reached target Ctrough at Day 15 (>= [redacted] ng/mL)
  - Not reached target Ctrough at Day 15 (< [redacted] ng/mL)
- By target C_{trough} at Day 29 (only for GLPG2222 dose levels)
  - Reached target Ctrough at Day 29 (>= [redacted] ng/mL)
  - Not reached target Ctrough at Day 29 (< [redacted] ng/mL)
- By target C_{trough} at Day 15 and 29 (only for GLPG2222 dose levels)
  - Reached target C_{trough} at Day 15 and reached target C_{trough} at Day 29
  - Not reached target C_{trough} at Day 15 and not reached target C_{trough} at Day 29
- By sweat chloride (from arm with greatest volume) at baseline
  - Baseline sweat < 40 mmol/L
  - Baseline sweat [40-50[mmol/L*
  - Baseline sweat [50-60[mmol/L*
  - Baseline sweat >= 60 mmol/L
- By sweat chloride (mean value from both arms) at baseline
  - Baseline sweat < 40 mmol/L
  - Baseline sweat [40-50[mmol/L*
  - Baseline sweat [50-60[mmol/L*
  - Baseline sweat >= 60 mmol/L
- By %FEV1 at baseline
  - Baseline %FEV1 < 40
  - Baseline %FEV1 [40-50[*
  - Baseline %FEV1 [50-70[*
  - Baseline %FEV1 [70-90[*
  - Baseline %FEV1 >= 90

*[X1-X2[means >= X1 and < X2

These sub-group analyses will be mainly for change from baseline tables, specific tables/figures will be created when needed (Tables and figures will be repeated for each subgroup category). In case no subject has been classified in one of the above category, so the table/figure planned for this category will not be displayed.

3.5. TOTALS OVER GROUPS

A total over all groups will be presented for the general part of the analysis, but not for Safety or Efficacy. Totals will only be shown on tables, but not on listings nor figures.

4. ANALYSIS PERIODS AND ANALYSIS TIME POINTS

4.1. RELATIVE NUMBER OF DAYS

The relative day (DY) is calculated as follows:

= Visit date – reference date + 1 day, when the visit date is on or after the reference date

= Visit date – reference date, when the visit date is before the reference date.

The reference date in the study is **Day 1 pre-dose**, which by definition has DY=1. There is no DY=0.

4.2. ANALYSIS PERIODS FOR NON-VISIT DATA

These analysis periods are to be used for allocation of events into periods (e.g., adverse events).

Analysis period	**Start period**	**End Period**
Screening	Date of signing the ICF, with 00:00 added as time part.	First treatment administration date(time) - 1 minute
Treatment	First treatment administration date(time)	Study termination date, with 23:59 added as time part in case the time part would be missing or incomplete.

Note that the last analysis period in case of early termination will always be ended by the study termination date (date of last contact, with 23:59 added as time part in case the time part would be missing or incomplete).

4.3. ALGORITHM OF ALLOCATING VISITS TO TIME WINDOWS

All visits (including unscheduled visits but excluding visits without data) will be placed into time windows according to their relative day (DY) in the study, according to the following allocation table:

Visits falling really late in the study will be allocated to a ">Day 29" interval, and will not be shown in tables nor figures, but will only be listed.

Time point label	Target day	Interval lower bound	Interval upper bound
Screening[3]	NAP[4]	NAP[4]	NAP[4]
Baseline[1]	NAP[4]	NAP[4]	NAP[4]
Day 1 post-dose[3]	NAP[4]	NAP[4]	NAP[4]
Day 15	15	2	21
Day 29	29	22	36
>Day 29[2]	NAP[4]	37	$+\infty$
Follow-up[3]	11-17 days after last visit	NAP[4]	NAP[4]

[1] The actual baseline reference value will be determined per parameter as the last available pre-dosing data point, so might differ from this "baseline" visit interval.
[2] Visits falling really late in the study (relative day > 36; excluding the follow-up visit) will be allocated to a ">Day 29" interval, and will not be shown in tables nor figures, but will only be listed.
[3] For the screening, day1 post-dose (vital signs) and follow-up visits, no time window is defined. The visit as recorded in the CRF will be used.
[4] NAP = Not applicable

For efficacy, PD data, all by-time-point summaries will be based on the visit indicated on the subject's CRF and will not be placed in time windows.

Tables, figures and listings will present the time points, not the visits.

4.4. SELECTION OF VISITS

It is possible that more than one visit gets allocated into the same time window. In that case, only one visit will be selected for analysis tables and figures. The nonselected visit(s) will only be listed, and flagged as use=no.

The visit with a relative day (DY) closest to the target day will be selected. If there are multiple visits at the same distance of the scheduled visit day (meaning: equal ABS(DY – target day)), then the one latest in time is selected.

In case of multiple screening visits, the last pre-baseline screening measurement (the last visit happening before the scheduled 'Day 1 predose') is selected for analysis. This value (not the original first screening value) was also used in the clinical center to include the subject in the study.

In case more than one parameter is measured per time point (e.g. for lab), the selection is performed per parameter and per time point, not per "sample" and per time point. Missing values are removed before the selection is made.

As baseline reference point, the last nonmissing pre-dosing value will be used. This is normally the scheduled baseline itself. A missing scheduled baseline value will be imputed with the last nonmissing value of a preceding pre-dosing visit. This can be a screening visit or an unscheduled visit prior to the first dose of study medication. If there is an unscheduled measurement taken after the scheduled baseline, before the first dose of study drug, then this unscheduled measurement will be used instead of the scheduled baseline. If there is an

unscheduled measurement at the same datetime as the scheduled baseline, then it is assumed that the unscheduled measurement is taken after the scheduled baseline.

In case the screening visit is used to impute the baseline, the original screening visit as well as the imputed baseline will be presented in the tables. In the listings, only original screening data will be shown: the original screening visit will be shown and flagged as "reference" visit. The imputed baseline will not be shown.

In case an unscheduled visit is used to impute the baseline, the visit will be renamed to "baseline". The imputed baseline will be presented in the tables. In the listings, the original unscheduled data will be shown and flagged as "reference" visit.

4.5. HANDLING OF UNSCHEDULED ASSESSMENTS

If there is an unscheduled measurement at the same datetime as a scheduled visit, then it is assumed that the unscheduled measurement is taken after the scheduled visit.

Unscheduled measurements prior to use of the study drug: see section 4.4.

Unscheduled measurements after the first dose of study drug: place into time window (section 4.3) and selection will be made according rules defined in section 4.4.

5. HANDLING OF DATA

5.1. CALCULATION OF DESCRIPTIVE STATISTICS

For continuous parameters, descriptive statistics will be presented when N≥2 unless otherwise specified. When N=1, the observation will not be shown in the table but only in the listing.

Descriptive statistics will include at least the following:

- the number of nonmissing data points (N)
- the arithmetic mean
- the standard error (SE)
- the median, minimum and maximum
- 95% confidence interval of the mean (only when requested).

For PK plasma concentrations, descriptive statistics will include:

- the number of nonmissing data points (N)
- the number of data points above the lower limit of quantification (LLOQ)
- the arithmetic mean
- the standard error (SE) and standard deviation (SD)
- the median, minimum, and maximum
- the coefficient of variation (CV%)
  = 100 x (standard deviation / arithmetic mean)
- the geometric mean = exp(arithmetic mean of ln-transformed data)
- the geometric coefficient of variation (CV%)
  = 100 x $\sqrt{e^{(standard\ deviation\ of\ ln-transformed\ data)^2} - 1}$.

Note that at least 50% of the subjects must have a plasma level above the lower limit of quantification before these descriptive statistics are calculated. If less than 50% of values were quantifiable, only the arithmetic mean (with minimum and maximum) will be presented with the original calculated value, the other descriptive statistics will be listed as "NC" (not calculated). If the calculated mean is below the lower limit of quantification, then it will be presented as below the limit of quantitation (BLOQ). The minimum will be "BLOQ", and the maximum will be derived from the actual data. Standard deviation (SD) and CV% will be reported as "NC". The plasma concentrations of GLPG2222 will be presented with 3 significant digits in the original concentration unit (i.e.: 8.356 and 1839 ng/mL will be rounded to 8.36 and 1840 ng/mL, respectively). The descriptive statistics should be rounded to the same number of significant digits as the individual values.

For derived PK parameters, descriptive statistics will include:

- the number of nonmissing data points (N)
- the arithmetic mean
- the standard error (SE) and/or standard deviation (SD)
- the median, minimum, and maximum
- the coefficient of variation (CV%)
- the geometric mean
- the geometric coefficient of variation (CV%).

Note that at least 50% of the subjects must have a nonmissing result before these descriptive statistics are calculated. If less than 50% of values were available, only the arithmetic mean will be presented with the original calculated value, the other descriptive statistics will be listed as "NC" (not calculated). Pharmacokinetic parameters will be presented with 3 significant digits (i.e.: 8.356 and 1839 ng/mL will be rounded to 8.36 and 1840 ng/mL, respectively) except for t_{max}, which will be presented with 1 decimal. The descriptive statistics should be rounded to the same number of significant digits as the individual values.

5.2. CALCULATION OF PERCENTAGES

Missing values will not be included in the denominator count when computing percentages.

5.3. HANDLING OF VALUES BELOW (OR ABOVE) A THRESHOLD

5.3.1. Safety Data

Values below (above) the detection limit will be imputed by the value of the detection limit itself. Listings will always present the original value.

Example: if the database contains values like "<0.04", then for the descriptive statistics the value of the detection limit (0.04) shall be used. A value like ">1000" will be imputed by "1000".

5.3.2. PK Data

Values below the quantification limit will be imputed by 0 for PK parameters calculation and descriptive statistics calculation except for geometric mean and geometric CV% where it will be imputed as LLOQ (lower limit of quantitation)/2 and listed as "BLOQ".

For the C_{trough}, values BLOQ will be imputed by LLOQ/2 when computing inferential statistics and between-group comparisons.

5.3.3. PD Data

PD data correspond to all [redacted] biomarkers and biomarkers [redacted] that have been collected as exploratory assessments.

Values below the lower detection limit will be imputed by the half of value of the detection limit itself. Values above the upper detection limit will be imputed by the value of the upper detection limit itself. Listings will always present the original value.

5.4. HANDLING OF MISSING DATA

5.4.1. Observed Cases (OC)

No imputation is done of missing values.

5.4.2. Last Observation Carried Forward (LOCF)

For efficacy parameters (see section 9), a LOCF analysis will be performed carrying forward the last nonmissing result (even if this would be a baseline result) except for the FU timepoint (FU timepoint will always provide observed cases values).

As spirometry has been assessed predose and between 1h and 2h post-dose at Day 1 and Day 29, LOCF imputation should be adapted with the following rule:

- If missing value corresponds to a predose timepoint, then the last nonmissing result assessed at pre-dose will be used for LOCF imputation.
- If missing value corresponds to a post dose timepoint, then the last nonmissing result assessed at post dose will be used for LOCF imputation (if there is no last non missing timepoint assessed at post-dose, then baseline value will be used).

5.4.3. Handling of Missing Date(Time) or Partially Known Date(Time)

No imputation will be done of missing date(time) fields, nor of the missing parts of partially known date(time) fields. When needed (e.g., a double phase allocation), a worst-case selection will be made.

5.5. HANDLING OF OUTLIERS

All measured values will be included in the analyses.

5.6. HANDLING OF SECONDS IN DATETIME FIELDS

If a datetime field contains seconds, these will be cut off (i.e., rounded down to the minute) prior to data analysis. The analysis will only use the date and time up to the minute.

6. SOFTWARE AND PROCEDURES

6.1. SOFTWARE

SAS version 9.4 will be used for programming.

SigmaPlot® 12.5, or higher (Systat Software, Inc., San Jose, California, United States) will be used for PK figures.

Phoenix WinNonlin® 6.4, or higher will be used for the figures and parameter calculation.

6.2. PROCEDURES

Analyses will comply with ICH regulations, in particular: (ICH-E3) , (ICH-E6) and (ICH-E9).

The following Galapagos SOPs will be followed:
- SOP-CLI-001: Developing Clinical Study Documents (version 1.0)
- SOP-CLI-003: Managing Data Processing Activities (version 1.0)
- SOP-CLI-004: Managing DSMB Activities (version 1.0)

The following CRO STAT SOPs will be followed:
- CS_OP_BS001: Statistical Principles
- CS_OP_BS0216: Ensuring Quality in Biostatistical Deliverables
- CS_WI_BS002: Randomization
- CS_WI_BS003: Unblinding
- CS_WI_BS005: Statistical Analysis Plans (Covering Table Shells)
- CS_WI_BS009: Interim Analysis
- CS_WI_BS011: Analysis Sets
- CS_WI_BS013: Derived Datasets
- CS_WI_BS014: Statistical Output
- CS_WI_BS015: Approaches to QC
- CS_WI_BS020: Handling Data transfer.

The following PK SOPs will be followed, unless otherwise specified
- PI_OP_PK0206: Pharmacokinetic/Pharmacodynamic Analysis
- PI_WI_BS0214: Generation of a WinNonlin Analysis Data File
- PI_WI_BS0217: Rounding of Numerical Values
- PI_WI_PK_0202: Pharmacokinetic and Pharmacodynamic Analysis Procedures
- PI_WI_PK0205: Standardization of Pharmacokinetic and Pharmacodynamic Symbols

6.3. FORMATS

Because the locked data is in CDISC SDTM format, the derived data will be following CDISC ADaM 2.1 ADAMIG version 1.0 format.

Tables, listings and figures will follow the Mock TLFs, as provided in a separate document.

7. STATISTICAL METHODS

7.1. PLANNED ANALYSES, PROTOCOL AMENDMENTS INCLUDED

7.1.1. General Statistical Considerations

Summary tabulations will display the number of observations, mean, standard error, median, minimum, and maximum for continuous variables, and the number and percent category for categorical data. Tabulated descriptive statistics and graphical data displays may be used to summarize the data. Inferential statistics will be interpreted at the 2-sided 5% level.

7.1.2. Analyses of Demographics and Baseline Characteristics

Subject disposition, protocol deviations, demographics, baseline characteristics, medical history, concomitant therapies, and exposure will be analyzed descriptively and/or listed and presented overall and by treatment group.

7.1.3. Analyses of Efficacy Parameters

Descriptive statistics of actual values, changes from baseline (pre-dose on Day 1), and percent changes from baseline will be provided.

An analysis of covariance (ANCOVA) model on the changes from baseline at each time point, with treatment as factor and baseline value as covariate, will be applied to the following parameters:

- Sweat chloride concentration;
- FEV_1;
- CFQ-R scores.

Between-group comparisons will be done for each GLPG2222 group versus the pooled placebo group (if the study is performed in both Cohorts A and B) or versus placebo in Cohort A (if the study is only performed in Cohort A).

Missing data will be imputed, also for subjects who prematurely discontinue the study. The primary imputation method will be the last-observation-carried-forward. An observed-case analysis will also be performed.

A sensitivity analysis will be performed by using non-parametric tests. The GLPG2222 groups and pooled placebo group (if the study is performed in both Cohorts A and B) or the GLPG2222 groups and placebo in Cohort A (if the study is only performed in Cohort A) will be compared using a Kruskal-Wallis test (overall treatment effect) and Wilcoxon rank sum tests (pairwise comparisons versus the corresponding placebo group).

Additional exploratory analyses and graphical presentations have been described in this SAP to better understand the data.

7.1.4. Analyses of Safety Data

Adverse events will be fully described and coded according to the Medical Dictionary for Regulatory Activities (version 20.0). Physical examination, weight, vital signs, oxygen saturation by pulse oximetry, 12-lead ECG, spirometry, and clinical safety laboratory data will be analyzed descriptively. Changes from baseline (pre-dose on Day 1) and shifts according to normal ranges will be presented as well. Analysis will be done per treatment group.

7.1.5. Pharmacokinetics Analyses

Descriptive statistics will be calculated by dose level and day for the plasma concentrations and PK parameters of GLPG2222.

Plasma concentrations of GLPG2222 will also be analyzed using a population PK approach including the assessment of covariates influencing the PK in CF subjects. The relation between exposures and selected efficacy and safety endpoints will also be investigated, if relevant. The modeling approach will be described and reported separately.

7.1.6. Exploratory Biomarkers

Exploratory biomarker data ([redacted] will be analyzed using descriptive statistics of actual values, changes from baseline (pre-dose on Day 1), and percent changes from baseline.

7.1.7. Apical Expression of F508del CFTR (Optional Substudy)

For subjects who participate in the optional substudy, data on apical expression of F508del CFTR will be analyzed using descriptive statistics of actual values, changes from baseline (pre-dose on Day 1), and percent changes from baseline.

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

7.2.1. Changes before Database Lock

Not Applicable

7.2.2. Changes after Database Lock

Not Applicable

8. DEFINITIONS OF GENERAL ANALYSIS TABLES, LISTINGS AND FIGURES

8.1. SUBJECT DISPOSITION

Listing 16.2.1.1: Subject disposition: Randomization

Listing of subject numbers and randomization groups, any information on code breaking.

All discrepancies (as-randomized versus as-treated) will be flagged.

Population: all enrolled.

Listing 16.2.1.2: Subject disposition: Country and site identification

Listing of country and site with the list of all subjects that were enrolled in this study.

Population: all enrolled.

Table 14.1.1.1: Subject disposition: Analysis populations

Tabulation per treatment group (and overall) of the number of subjects in each of the analysis populations defined in section 2.

Population: all screened subjects.

Table 14.1.1.2: Subject disposition: Tabulation of the number of subjects at each time interval

Tabulation per treatment group (and overall) and per analysis time point of the number of subjects with data.

Population: safety.

Listing 16.2.1.3: Subject disposition: Number of days in study

Listing per treatment group, per subject and per time point the number of days in study at the time of the analysis time point (derivation of these "days": see section 4.1).

Population: safety.

Table 14.1.1.3: Subject disposition: First and last date in the study

List the following:
- Date of the first signature on study ICF
- Date of first and last screening
- Date of first study drug administration
- Last visit date (all visits; including unscheduled visits)
- Last date of contact in the study with any subject.

Population: all screened.

Listing 16.2.1.4: Subject disposition: Study termination

Listing per treatment group and per subject of the reason for completion/discontinuation and the number of days since first study drug administration at study termination. In case the discontinuation was due to AE, the AE preferred term will be presented in this listing. If there is a (verbatim) explanation on the discontinuation reason, this will also be presented in this listing.

Population: safety.

Listing 16.2.1.5: Subject disposition: Study analysis periods

Listing per treatment group and per subject of the analysis periods in the study, together with the start and end dates of each analysis period. With the date of first and last use of study drug, and the study termination date. (Analysis periods: see section 4.2)

Population: safety.

8.2. PROTOCOL DEVIATIONS AND ELIGIBILITY

Listing 16.2.2.1: Protocol deviations

Listing per treatment group and per subject of all protocol deviations, with indication major / minor.

Population: safety.

Listing 16.2.2.2: Eligibility criteria: Violations

Only violated in- and exclusion criteria will be listed per treatment group and per subject.

Population: safety.

Listing 16.2.2.3: Final eligibility statements

Listing per treatment group and per subject of the final eligibility statements at screening and at day 1.

Population: safety.

8.3. SUBJECTS EXCLUDED FROM ANALYSIS

Note that for the PK data there is a specific PK data handling listing. PK is therefore not included in this section, but is in section 10.

Listing 16.2.3.1: Subjects excluded from the safety analysis

Listing of all subjects that were not treated: the study termination reason and/or the reason for being a no-treatment subject will be listed, whichever is available.

Population: all screened subjects population, minus the Safety population.

Listing 16.2.3.2: Subjects excluded from the efficacy ITT analysis

Listing of all subjects that were exposed but who were not included in the ITT population: the study termination reason and the reason for being excluded will be listed.

Population: Safety population, minus the ITT population.

8.4. DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

8.4.1. Parameters

- Gender
- Age at the moment of signing the ICF (years): the age is not recalculated when already available in the database
- Date of birth: only listed
- Date of signing the ICF: only listed
- Race
- Ethnicity
- Height (cm)
- Weight (kg) at screening and baseline
- Body mass index BMI = (weight in kg) / (height in m)² (kg/m²), at screening and baseline: the BMI will be recalculated and rounded to the first decimal, even when already available in the database. The original BMI will not be used in that case
- BMI categorized as:
  ≤ 18.5 kg/m²
  ]18.5,25.0] kg/m²
  ]25.0,30.0[kg/m²
  ≥ 30.0 kg/m²
- Childbearing potential: yes / no, no: tubal ligation / total hysterectomy / other. Only listed

8.4.2. Analysis

Table 14.1.3.1: Demographic data: Descriptive statistics

Continuous parameters: descriptive statistics per treatment group (and overall).

Categorical parameters: frequency tabulation per treatment group (and overall).

No formal comparison between the treatment groups is planned.

Population: the table will show

- safety
- ITT.

Table 14.1.3.2: Demographic data: Sub-group analyses: Descriptive statistics

The following sub-groups will be shown:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29
- By sweat chloride (from arm with greatest volume) at baseline
- By sweat chloride (mean value from both arms) at baseline
- By %FEV1 at baseline

Population: the table will show

- safety
- ITT.

Table 14.1.3.3: Demographic data: Pooled analyses: Descriptive statistics

The following sub-groups will be shown:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29

Population: the table will show

- safety
- ITT.

Listing 16.2.4.1: Demographic data

Listing per treatment group and per subject of all demographic parameters.

Population: safety.

Table 14.1.3.4: Baseline laboratory data: Tabulation of normal range

Frequency tabulation per lab test of the baseline result, categorized as low/normal/high according to the normal ranges (see section 13.2.4).

Population: Safety.

Table 14.1.3.5: Baseline ECG data: Tabulation of the normal range

Frequency tabulation per parameter (QT, QTcF) of the baseline result, categorized as (same as in section 13.3.4):

- ≤ 450 ms
-]450,480] ms
-]480,500] ms
- > 500 ms

Population: Safety.

Table 14.1.3.6: Baseline vital signs data: Tabulation of the normal range

Frequency tabulation per parameter of the baseline result, categorized as low/normal/high according to the normal ranges (see section 13.4.3).

Population: Safety.

Table 14.1.3.7: Baseline physical examination: Tabulation of the normal range

Frequency tabulation per CRF body system of the baseline result, categorized as normal/abnormal.

Population: Safety.

Table 14.1.3.8: Baseline pulse oximetry data: Tabulation of the normal range

Frequency tabulation per parameter of the baseline result, categorized as low/normal according to the normal ranges (see section 13.5.3).

Population: Safety.

8.5. BASELINE DISEASE CHARACTERISTICS

8.5.1. Parameters

- Duration of CF (years) = $\frac{(\text{date of initial diagnosis}) - (\text{date of signing the ICF}) + 1}{365.25}$, rounded to the nearest integer. If the date of initial diagnosis is incomplete, then the following rules will be applied: Missing day: use the first of the month. Missing month: use January.
- Screening and baseline sweat chloride
- Change in sweat chloride (baseline – screening)
- Screening and baseline %FEV1
- Change in %FEV1 (baseline – screening)
- Mutation F508del (on both allele): Yes/No
- Number of exacerbations requiring hospitalization and/or intravenous antibiotics in the last 12 months.
- Currently have an infection with pseudomonas aeruginosa: yes / no
- Currently on inhaled antibiotics: yes / no
- Sweat categorized at baseline: <40, [40,50[, [50,60[, >=60
- %FEV1 categorized at Baseline: <40, [40,50[, [50,70[, [70,90[, >= 90
- Sweat categorized at screening: <40, [40,50[, [50,60[, >=60
- %FEV1 categorized at screening: <40, [40,50[, [50,70[, [70,90[, >= 90

8.5.2. Analysis

Table 14.1.3.9: Screening and baseline disease characteristics

Continuous parameters: descriptive statistics per treatment group (and overall).

Categorical parameters: frequency tabulation per treatment group (and overall).

No formal comparison between the treatment groups is planned.

Population: the table will show

- safety
- ITT.

Table 14.1.3.10: Screening and baseline disease characteristics: Sub-group analyses

The following sub-groups will be shown:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29
- By sweat chloride (from arm with greatest volume) at baseline
- By sweat chloride (mean value from both arms) at baseline
- By %FEV1 at baseline

Population: the table will show

- safety
- ITT.

Table 14.1.3.11: Screening and baseline disease characteristics: Pooled analyses

The following sub-groups will be shown:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29

Population: the table will show

- safety
- ITT.

Listing 16.2.4.2: Screening and baseline disease characteristics

Listing per treatment group and per subject of all screening and baseline disease characteristics. Genotyping will be listed as well.

Population: Safety.

8.6. MEDICAL HISTORY AND CONCURRENT DISEASES

When the end date is only partially known, the missing parts will be imputed by the last day of the month/year.

Listing 16.2.4.3: Medical history

Listing per treatment group and per subject of the medical history data findings (i.e., condition no longer present at the start of the study): original terms as well as coded terms.

Population: safety.

Listing 16.2.4.4: Concomitant diseases

Listing per treatment group and per subject of the concomitant diseases data findings (i.e., condition still present or unknown): original terms as well as coded terms.

Population: safety.

8.7. PRIOR AND CONCOMITANT THERAPIES

8.7.1. Classification of Therapies

All prior and concomitant therapies will be allocated into exactly one of the following categories:

- Prior only: the therapy ended before the first study drug administration.
- Concomitant only: the therapy started on or after the first study drug administration.
- Post-treatment: the therapy started after the last study drug administration.
- Prior and concomitant: the therapy started before the first study drug administration, and ended on or after the first study drug administration.

When the start date is missing, the therapy is assumed to have started on the same day as the first administration of study drug.

When the end date is missing, the therapy is assumed to be still ongoing after the end of the study.

When the start date is only partially known, the missing parts will be imputed by the first day of the month/year, or the day of the first medication intake in case the nonmissing part matches.

When the end date is only partially known, the missing parts will be imputed by the last day of the month/year.

Imputation of start and end dates is only done for the classification into prior / concomitant / prior+concomitant. The listing will present the original start and end dates, also when incomplete. Fields like start and stop days will not be derived from imputed incomplete dates.

No further classification into analysis periods will be done.

The relative study day of therapy start and stop will be derived as follows (only listed):

Start day

= (Therapy start date) – (date of first study medication administration) + 1, when the start date of therapy is known and complete, and when the therapy start date is on or after the date of first study medication;

= (Therapy start date) – (date of first study medication administration), when the start date of therapy is known and complete, and when the therapy start date is before the date of first study medication;

= missing when the start date of therapy is unknown, missing, or incomplete.

Stop day

= (Therapy stop date) – (date of first study medication administration) + 1, when the end date of therapy is known and complete, and the end date of therapy is on or after the date of first study medication;

= (Therapy stop date) – (date of first study medication administration), when the end date of therapy is known and complete, and the end date of therapy is before the date of first study medication;

= (Study termination date) – (date of first study medication administration) + 1, when the therapy is still ongoing when the subject leaves the study; in such cases the stop day will be presented as ">XX days" in the listing;

= missing when the end date of therapy is unknown, missing or incomplete and the therapy isn't ongoing after the subject left the study.

8.7.2. Coding of Therapies

All therapies are coded using WHO-DRUG (version 01March2017). In the table(s), the generic term will be used. The ATC classification will not be used for analysis. Multiple records of the same generic term for the same subject with the same categorization will be counted only once. The table will therefore present subjects, not occurrences.

8.7.3. Analysis

Table 14.1.3.12: Prior and concomitant therapies: Tabulation

Frequency tabulation per treatment group (and overall) of the generic terms.

Population: safety.

Listing 16.2.4.5: Prior and concomitant therapies

Listing per treatment group and per subject of all data on prior and concomitant therapies. Flags for prior/concomitant will be added. In case the therapy was due to an AE or medical history, the AE preferred term and the original term from medical history page will be mentioned in this listing.

Population: safety.

8.8. EXPOSURE TO STUDY MEDICATION AND COMPLIANCE

8.8.1. Derivations

Derived parameters for GLPG2222/Placebo intakes:

- Total treatment duration (days) = (last dose administration date – first dose administration date) + 1 day.
- Total treatment duration, excluding days off drug (days): sum of all durations (last – first +1) in the drug log pages where there is a dose >0 tablets.

- Percentage days with an intake = 100% x $\left(\frac{\text{total treatment duration,excluding days off drug}}{\text{total duration}}\right)$
- Total compliant treatment duration (days): sum of all durations (last – first +1) in the drug log pages where there is a dose with exactly 1 tablet (for cohort A) or exactly 3 tablets (cohort B).
- Percentage compliance = 100% x $\left(\frac{\text{total compliant treatment duration}}{\text{total duration}}\right)$

The "total duration" used as denominator in the above formulae equals: (date of Day 29 visit or early termination visit) – (date of first drug intake) + 1.

8.8.2. Analysis

Table 14.1.4.1: Exposure to study drug: Descriptive statistics

Descriptive statistics of the treatment duration (days) and the compliance (%) by treatment group.

Population: safety.

Listing 16.2.5.1: Exposure to study drug: eCRF data

Listing per treatment group and per subject of all eCRF data related to the use of drug.

Population: safety.

Listing 16.2.5.2: Exposure to study drug: Derived data

Listing per treatment group and per subject of all derived data related to the use of drug.

Population: safety.

Listing 16.2.5.3: Study drug administration (clinic visit)

Listing per treatment group and per subject of all data related to the study drug administration (morning dose at clinic and previous day).

Population: safety.

8.9. COMMENTS

Listing 16.2.5.4: Comments

Listing per treatment group and per subject of remarks and comments written in the CRF. Comments that are already presented in other parts of the analysis (e.g., lab, ECG, exposure…) do not need to be repeated in this Comments listing.

Population: safety.

9. DEFINITIONS OF EFFICACY TABLES, LISTINGS AND FIGURES

9.1. SWEAT CHLORIDE

9.1.1. Parameters

Two sweat collections, one from each arm, will be obtained from each subject at each time-point indicated in the flow chart. Sweat samples will be immediately frozen and sent to the central laboratory for testing and interpretation of results.

For the analysis, the following step should be applied for each time-point:

- Select the chloride value obtained from the collection with the greater volume of sweat (variable LBORRES when LBTESTCD = 'VOLUME' and LBSPEC = 'SWEAT' in SDTM.LB dataset). And if for a specific visit, the volume of sweat is equal for both arms then the value with the highest chloride concentration will be used.
- Select only sweat collections that have been performed pre-dose

In tables, figures and listings, this parameter will be called: Sweat Chloride (from arm with greatest volume).

A first sensitivity analysis will be done by using another method for the derivation of the sweat chloride. At each time-point, the sweat chloride value used for the analysis will be derived:

- by taking the mean of the 2 sweat collection samples (right arm and left arm respectively) if the difference between the samples is not exceeding 25 mmol/L. If the difference between the 2 samples exceeds 25 mmol/L, the results will be discarded.
- by taking the available sweat chloride value if 1) only 1 arm was measured or 2) if sufficient volume for 1 arm only was collected.

In tables, figures and listings, this parameter will be called: Sweat Chloride (mean value from both arms).

Analysis will present:

- Actual values
- Categories of actual values:
  < 40 mmol/L
  [40,50[mmol/L
  [50,60[mmol/L
  ≥ 60 mmol/L
- Change from baseline (Day 1 pre-dose):
  change at time point t = (time point t value) – (baseline value)
- Percent change from baseline (Day 1 pre-dose):
  %change at time point t = 100 x (time point t value – baseline value) / (baseline value)

9.1.2. Tables

Table 14.2.1.1.1: Sweat Chloride (mmol/L): Descriptive statistics of the actual values per time point

Descriptive statistics of actual values per treatment group and analysis visit for both parameters.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The table will show:

- LOCF in ITT.
- OC in ITT.

Table 14.2.1.1.2: Sweat Chloride (mmol/L): Sub-group analyses: Descriptive statistics of the actual values per time point

Descriptive statistics of the actual values per treatment group and analysis visit for each sub-group.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The following sub-groups will be shown:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29
- By sweat chloride (from arm with greatest volume) at baseline [This sub-group will be applied only for the parameter Sweat Chloride (from arm with greatest volume)]
- By sweat chloride (mean value from both arms) at baseline [This sub-group will be applied only for the parameter Sweat Chloride (mean value from both arms)]
- By %FEV1 at baseline

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.1.3: Sweat Chloride (mmol/L): Pooled analyses: Descriptive statistics of the actual values per time point

Descriptive statistics of the actual values on pooled treatment group and analysis visit.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The following sub-groups will be also provided in this pooled analysis:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.1.4: Sweat Chloride (mmol/L): Descriptive statistics of the changes from baseline per time point

Descriptive statistics of changes from baseline per treatment group and analysis visit. The actual value at baseline will also be presented in this table.

P-values are generated from an ANCOVA model on the changes from baseline at each time point with treatment as factors and baseline value as covariate. Pairwise comparison (dose group vs pooled placebo) will be provided as well.

P-values will be generated also from a Kruskal-Wallis test (overall treatment effect) and Wilcoxon rank sum test (pairwise comparison with placebo) as sensitivity analysis.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The table will show:

- LOCF in ITT.
- OC in ITT (only descriptive, no inferential statistics)

Table 14.2.1.1.5: Sweat Chloride (mmol/L): Descriptive statistics of the changes from baseline per time point on Placebo groups

Descriptive statistics of changes from baseline per cohort, analysis visit on placebo (cohort A), on placebo (cohort B), on pooled placebo. The actual value at baseline will also be presented in this table.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.1.6: Sweat Chloride (mmol/L): Sub-group analyses: Descriptive statistics of the changes from baseline per time point

Descriptive statistics of changes from baseline per treatment group and analysis visit for each sub-group. The actual value at baseline will also be presented in this table.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The following sub-groups will be shown:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29
- By sweat chloride (from arm with greatest volume) at baseline [This sub-group will be applied only for the parameter Sweat Chloride (from arm with greatest volume)]
- By sweat chloride (mean value from both arms) at baseline [This sub-group will be applied only for the parameter Sweat Chloride (mean value from both arms)]
- By %FEV1 at baseline

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.1.7: Sweat Chloride (mmol/L): Pooled analyses: Descriptive statistics of the changes from baseline per time point

Descriptive statistics of changes from baseline on pooled treatment group and analysis visit. The actual value at baseline will also be presented in this table.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The following sub-groups will be also provided in this pooled analysis:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.1.8: Sweat Chloride (mmol/L): Descriptive statistics of the percent changes from baseline per time point

Descriptive statistics of percent changes from baseline per treatment group and analysis visit. The actual value at baseline will also be presented in this table.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.1.9: Sweat Chloride (mmol/L): Frequency tabulation per time point

Frequency table per dose group and per time point, showing the sweat chloride concentration in the following categories: < 40 mmol/L, [40,50[mmol/L, [50,60[mmol/L, ≥ 60 mmol/L.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.1.1.10: Sweat Chloride (mmol/L): Shift table versus baseline per time point

Shift table per dose group and time point versus baseline.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.1.11: Sweat Chloride (mmol/L): Sensitivity analyses on the changes from baseline values

Additional sensitivity analysis will be explored by using Mixed Effects Model for Repeated Measures (MMRM). The model will include treatment and analysis visit as fixed effects and baseline as a covariate, treatment*analysis visit as interaction terms and subject as random effect. Pairwise comparisons will be presented.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The table will show:

- OC in ITT.

9.1.3. Figures

Figure 14.2.1.1.1: Sweat Chloride (mmol/L): Subject profile plots over time

Subject profile plots over time. Each treatment group will be on a separate plot, with all subjects of the same treatment group on the same plot. With horizontal reference lines at 40 and 60 mmol/L. Any unscheduled results will also be part of this plot.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The figure will show:

- OC in ITT.

Figure 14.2.1.1.2: Sweat Chloride (mmol/L): Subject profile on change from baseline plots over time

Change from baseline subject profile plots over time. Each treatment group will be on a separate plot, with all subjects of the same treatment group on the same plot. With a horizontal reference line at zero, indicating no change., plots will start with a zero mean at baseline. Any unscheduled results will also be part of this plot.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The figure will show:

- OC in ITT.

Figure 14.2.1.1.3: Sweat Chloride (mmol/L): Mean (+/- SE) plots of the actual values over time

Mean (with SE) plots of the actual values over time. Unscheduled results will not be part of this plot.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The figure will show:

- LOCF in ITT.
- OC in ITT

Figure 14.2.1.1.4: Sweat Chloride (mmol/L): Mean (+/- SE) plots of the changes from baseline over time

Mean (with SE) plots of the changes from baseline over time. Unscheduled results will not be part of this plot. With a horizontal reference line at zero, indicating no change. Plots will start with a zero mean at baseline.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The figure will show:

- LOCF in ITT.
- OC in ITT

Figure 14.2.1.1.5: Sweat Chloride (mmol/L): Sub-group analyses: Mean (+/- SE) plots of the changes from baseline over time

Mean (with SE) plots of the changes from baseline over time for each sub-group. Each sub-group category will be done in a separate plot. Unscheduled results will not be part of this plot. With a horizontal reference line at zero, indicating no change. Plots will start with a zero mean at baseline.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The following sub-groups will be shown:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29
- By sweat chloride at baseline
- By %FEV1 at baseline

The figure will show:

- LOCF in ITT.
- OC in ITT

Figure 14.2.1.1.6: Sweat Chloride (mmol/L): Pooled analyses: Mean (+/- SE) plots of the changes from baseline over time

Mean (with SE) plots of the changes from baseline over time on pooled treatment. Each sub-group category will be done in a separate plot. Unscheduled results will not be part of this plot. With a horizontal reference line at zero, indicating no change. Plots will start with a zero mean at baseline.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The following sub-groups will be also provided in this pooled analysis:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29

The table will show:

- LOCF in ITT.
- OC in ITT

Figure 14.2.1.1.7: Sweat Chloride (mmol/L): Mean (+/- SE) plots of the percent changes from baseline over time

Mean (with SE) plots of the percent changes from baseline over time. Unscheduled results will not be part of this plot. With a horizontal reference line at zero, indicating no change. Plots will start with a zero mean at baseline.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The figure will show:

- LOCF in ITT.
- OC in ITT

Figure 14.2.1.1.8: Sweat Chloride (mmol/L): Boxplots on actual values

Boxplots at each timepoint with all treatment groups in the same figure

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The figure will show:

- LOCF in ITT.
- OC in ITT

Figure 14.2.1.1.9: Sweat Chloride (mmol/L): Boxplots on change from baseline

Boxplots on change from baseline at each timepoint with all treatment groups in the same figure

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The figure will show:

- LOCF in ITT.
- OC in ITT

9.1.4. Listings

Listing 16.2.6.1: Sweat Chloride (mmol/L): Full listing

Listing per subject and per time point of all data related to the sweat chloride: actual values, changes from baseline. A flag "H" and "HH" will be added to values above the upper limit of normal (Values > 60 mmol/L will be flagged as "HH". Values in [40,60[mmol/L will be flagged as "H").

The listing will show: OC in ITT population.

9.2. SPIROMETRY

9.2.1. Parameters

During study visits on Days 1, 15 and 29, spirometry must be performed before the morning dose. On Day 1 and Day 29, the spirometry test is to be performed prior to the morning dose of study drug and an additional spirometry must be performed after the study drug intake around 1-2 hours post-dose.

Spirometry can be performed pre-bronchodilator* or post-bronchodilator at screening but should take place prior to bronchodilator use at all other visits. But in practice, if on Day 1, the subject forgets to withhold his/her dose of bronchodilator then all subsequent spirometry should be collected post-bronchodilator, to be consistent with the conditions for the baseline measurement. And if on Day 1 spirometry is collected pre-bronchodilator, but then at a subsequent visit the subject forgets to withhold his/her dose of bronchodilator, then spirometry should be collected post-bronchodilator for that visit only.

* pre-bronchodilator is defined as:

- short-acting more than 4 hours prior to the spirometry assessment
- long-acting bronchodilator at least 12 hours or 24 hours prior to the spirometry assessment

(a spirometry assessment with no use of bronchodilator is equivalent to a pre-bronchodilator assessment)

The values will be used as available via the data transfer from the central laboratory ([redacted]).

Note that at all post-baseline (Day 1) visits:

- Spirometry data taken inconsistently with the baseline will be excluded from the analysis (i.e. if spirometry was performed post-bronchodilator and the one at baseline was performed pre-bronchodilator or if spirometry was performed pre-bronchodilator and the one at baseline was performed post-bronchodilator).
- Spirometry that should be assessed pre-dose and was done post-dose will be excluded from the analysis.
- Spirometry, 1-2h post-dose assessment that was done pre-dose will be excluded from the analysis.

Data with a quality grade of D, E or F will be excluded too.

Quality*	Criteria
A	At least 3 acceptable efforts AND the difference between the best two FEV1 and FVC values is equal to or less than 100 ml (80 ml if FVC < 1.0 L)
B	At least 3 acceptable efforts AND the difference between the best two FEV1 and FVC values is equal to or less than 150 ml (100 ml if FVC < 1.0 L)
C	At least 2 acceptable efforts AND the difference between the best two FEV1 and FVC values is equal to or less than 200 ml (150 ml if FVC < 1.0 L)
D	At least 2 acceptable efforts but the results are not Reproducible
E	At least 1 acceptable effort
F	No acceptable test available

* SQ_QUALGRAD from SDTM.re dataset.

Available parameters:
- FEV_1 (L) and percent predicted FEV_1 for age, gender, and height
- Forced Vital Capacity (FVC) (L) and percent predicted FVC for age, gender, and height
- FEV_1/FVC ratio
- Forced expiratory flow between 25% and 75% of exhaled volume (FEF_{25-75})

Analysis will present (to be done on all available parameters unless specified):
- Actual values
- Change from baseline (Day 1 pre-dose):
  change at time point t = (time point t value) – (baseline value)
- Percent change from baseline (Day 1 pre-dose):
  %change at time point t = 100 x (time point t value – baseline value) / (baseline value)

9.2.2. Tables

Table 14.2.1.2.1: Spirometry: Descriptive statistics of the actual values per time point

Descriptive statistics of actual values per parameter, treatment group and analysis visit.

The table will show:
- LOCF in ITT.
- OC in ITT

Table 14.2.1.2.2: Spirometry: Sub-group analyses: Descriptive statistics of the actual values per time point

Descriptive statistics of the actual values per parameter, treatment group and analysis visit for each sub-group analysis.

The following sub-groups will be shown:
- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29
- By sweat chloride (from arm with greatest volume) at baseline

- By sweat chloride (mean value from both arms) at baseline
- By %FEV1 at baseline

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.2.3: Spirometry: Pooled analyses: Descriptive statistics of the actual values per time point

Descriptive statistics of the actual values per parameter on pooled treatment group and analysis visit.

The following sub-groups will be also provided in this pooled analysis:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.2.4: Spirometry: Descriptive statistics of the changes from baseline per time point

Descriptive statistics of changes from baseline per parameter, treatment group and analysis visit. The actual value at baseline will also be presented in this table.

P-values are generated from an ANCOVA model on the changes from baseline at each time point with treatment as factors and baseline value as covariate. Pairwise comparison (dose group vs placebo) will be provided as well.

P-values will be generated also from a Kruskal-Wallis test (overall treatment effect) and Wilcoxon rank sum test (pairwise comparison with placebo) as sensitivity analysis.

Descriptive statistics will be done on all available parameters, but inferential statistics will be done only on FEV1 and %FEV1.

The table will show:

- LOCF in ITT.
- OC in ITT (only descriptive, no inferential statistics)

Table 14.2.1.2.5: Spirometry: Descriptive statistics of the changes from baseline per time point on Placebo groups

Descriptive statistics of changes from baseline per cohort, analysis visit on placebo (cohort A), on placebo (cohort B), on pooled placebo. The actual value at baseline will also be presented in this table.

The table will show:

- LOCF in ITT.

Table 14.2.1.2.6: Spirometry: Sub-group analyses: Descriptive statistics of the changes from baseline per time point

Descriptive statistics of changes from baseline per parameter, treatment group and analysis visit for each sub-group. The actual value at baseline will also be presented in this table.

The following sub-groups will be shown:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29
- By sweat chloride (from arm with greatest volume) at baseline
- By sweat chloride (mean value from both arms) at baseline
- By %FEV1 at baseline

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.2.7: Spirometry: Pooled analyses: Descriptive statistics of the changes from baseline per time point

Descriptive statistics of changes from baseline per parameter, per pooled treatment group and analysis visit. The actual value at baseline will also be presented in this table.

The following sub-groups will be also provided in this pooled analysis:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.2.8: Spirometry: Descriptive statistics of the percent changes from baseline per time point

Descriptive statistics of percent changes from baseline per parameter, treatment group and analysis visit. The actual value at baseline will also be presented in this table.

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.2.9: Spirometry: Sensitivity analyses on the changes from baseline values

Additional sensitivity analysis will be explored by using Mixed Effects Model for Repeated Measures (MMRM). The model will include treatment and analysis visit as fixed effects and baseline as a covariate, treatment*analysis visit as interaction terms and subject as random effect. Pairwise comparisons will be presented.

This table will be done only on FEV1 and %FEV1.

The table will show:

- OC in ITT.

9.2.3. Figures

Figure 14.2.1.2.1: Spirometry: Subject profile plots over time

Subject profile plots over time for each parameter. Each treatment group will be on a new plot, with all subjects of the same treatment group on the same plot. Any unscheduled results will also be part of this plot.

The figure will show:

- OC in ITT.

Figure 14.2.1.2.2: Spirometry: Subject profile on change from baseline plot over time

Change from baseline subject profile plots over time for each parameter. Each treatment group will be on a new plot, with all subjects of the same treatment group on the same plot. Any unscheduled results will also be part of this plot.

The figure will show:

- OC in ITT.

Figure 14.2.1.2.3: Spirometry: Mean (+/- SE) plots of the actual values over time

Mean (with SE) plots of the actual values over time for each parameter. Unscheduled results will not be part of this plot.

The figure will show:

- LOCF in ITT.
- OC in ITT

Figure 14.2.1.2.4: Spirometry: Mean (+/- SE) plots of the changes from baseline over time

Mean (with SE) plots of the changes from baseline over time for each parameter. Unscheduled results will not be part of this plot. With a horizontal reference line at zero, indicating no change. Plots will start with a zero mean at baseline.

The figure will show:

- LOCF in ITT.
- OC in ITT

Figure 14.2.1.2.5: Spirometry: Sub-group analyses: Mean (+/- SE) plots of the changes from baseline over time

Mean (with SE) plots of the changes from baseline over time for each sub-group. Unscheduled results will not be part of this plot. With a horizontal reference line at zero, indicating no change. Plots will start with a zero mean at baseline.

The following sub-groups will be shown:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29
- By sweat chloride (from arm with greatest volume) at baseline
- By sweat chloride (mean value from both arms) at baseline
- By %FEV1 at baseline

The figure will show:

- LOCF in ITT.
- OC in ITT

Figure 14.2.1.2.6: Spirometry: Pooled analyses: Mean (+/- SE) plots of the changes from baseline over time

Mean (with SE) plots of the changes from baseline over time on pooled treatment. Unscheduled results will not be part of this plot. With a horizontal reference line at zero, indicating no change. Plots will start with a zero mean at baseline.

The following sub-groups will be also provided in this pooled analysis:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29

The table will show:

- LOCF in ITT.
- OC in ITT

Figure 14.2.1.2.7: Spirometry: Mean plots (+/- SE) of the percent changes from baseline over time

Mean (with SE) plots of the percent changes from baseline over time for each parameter. Unscheduled results will not be part of this plot. With a horizontal reference line at zero, indicating no change. Plots will start with a zero mean at baseline.

The figure will show:

- LOCF in ITT.
- OC in ITT

Figure 14.2.1.2.8: Spirometry: Boxplots on the actual values

Boxplots at each timepoint with all treatment groups in the same figure. Only for %FEV1 parameter.

The figure will show:
- LOCF in ITT.
- OC in ITT

Figure 14.2.1.2.9: Spirometry: Boxplots on the change from baseline

Boxplots at each timepoint for each treatment. Only for %FEV1 parameter.

The figure will show:
- LOCF in ITT.
- OC in ITT

9.2.4. Listings

Listing 16.2.6.2: Spirometry: Full listing

Listing per subject and per time point of all data related to spirometry: actual values, changes from baseline and percent changes from baseline.

The listing will show: ITT.

9.3. CYSTIC FIBROSIS QUESTIONNAIRE – REVISED (CFQ-R)

9.3.1. Parameters

The following scores will be derived from CFQ-R questionnaire:
- 9 Quality of life domains: Physical, role/school, vitality, emotion, social, body image, eating, treatment burden, health perceptions.
- 3 symptom scales: weight, respiratory and digestion.

Each Score will range from 0 to 100, with higher scores indicating better health.

For the analysis, the derivation of each score will be done with the following step for each time-point:
- Assigned a value for each questions (question 1 to question 50) with the following rules:

Questions	Categories	Score
Question 1 to 5	A lot of difficulty	1
	Some difficulty	2
	A little difficulty	3
	No difficulty	4
Question 6 to 12, 36 to 38, 44 to 50	Always	1
	Often	2
	Sometimes	3

	Never	4
Question 19 to 34	Very true	1
	Somewhat true	2
	Somewhat false	3
	Very false	4
Question 39 to 42	A great deal	1
	Somewhat	2
	A little	3
	Not at all	4
Question 13 to 18 and 35	1.XXXXXX	1 = SUBSTR(qstresn,1,1)
	2.XXXXXX	2 = SUBSTR(qstresn,1,1)
	3.XXXXXX	3 = SUBSTR(qstresn,1,1)
	4.XXXXXX	4 = SUBSTR(qstresn,1,1)
Question 43	Clear	4
	Clear to yellow	3
	Yellowish-green	2
	Green with traces of blood	1
	Don’t know	5

- Items in the questionnaire are expressed either "negatively" or "positively," therefore a number of the items must be recoded before the scores for each of the domains are calculated. The following items (6, 10, 13, 15, 17, 18, 23, 28, 30, 32, 34, 35) should be recoded by using this formulae: new score = 5-score.

- Calculation of each score

Score	Formulae (Qx = Question x)
Physical	= (Mean(Q1, Q2, Q3, Q4, Q5, Q13, Q19, Q20) -1)/3*100 if at least 50% of the question have non-missing data
Role/school	= (Mean (Q35, Q36, Q37, Q38) - 1)/3*100 if at least 50% of the question have non-missing data
Vitality	= (Mean(Q6, Q9, Q10, Q11) -1)/3*100 if at least 50% of the question have non-missing data
Emotion	= (Mean(Q7, Q8, Q12, Q31, Q33) -1)/3*100 if at least 50% of the question have non-missing data
Social	= (Mean(Q22, Q23, Q27, Q28, Q29, Q30) -1)/3*100 if at least 50% of the question have non-missing data
Body image	= (Mean(Q24, Q25, Q26) -1)/3*100 if at least 2 questions have non-missing data
Eating	= (Mean(Q14, Q21, Q50) -1)/3*100 if at least 2 questions have non-missing data
Treatment burden	= (Mean(Q15, Q16, Q17) -1)/3*100 if at least 2 questions have non-missing data

Health perceptions	= (Mean(Q18, Q32, Q34) -1)/3*100 if at least 2 questions have non-missing data
Weight	= (Q39-1)/3*100 if Q39 has non-missing value
Respiratory	= (Mean(Q40, Q41, Q42, Q44, Q45, Q46) -1)/3*100 if at least 50% of the question have non-missing data
Digestion	= (Mean(Q47, Q48, Q49) -1)/3*100 if at least 2 questions have non-missing data

- Select only score that correspond to a pre-dose assessment.

For each score, Analysis will present:
- Actual values
- Change from baseline (Day 1 pre-dose):
  change at time point t = (time point t value) – (baseline value)
- Percent change from baseline (Day 1 pre-dose):
  %change at time point t = 100 x (time point t value – baseline value) / (baseline value)

9.3.2. Tables

Table 14.2.1.3.1: CFQ-R: Descriptive statistics of the actual values per time point

Descriptive statistics of actual values per treatment group and analysis visit for each score.

The table will show:
- LOCF in ITT.
- OC in ITT

Table 14.2.1.3.2: CFQ-R: Sub-group analyses: Descriptive statistics of the actual values per time point

Descriptive statistics of the actual values, treatment group and analysis visit for each sub-group analysis will be done only for CFQ-R respiratory domain score.

The following sub-groups will be shown:
- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29
- By sweat chloride (from arm with greatest volume) at baseline
- By sweat chloride (mean value from both arms) at baseline
- By %FEV1 at baseline

The table will show:
- LOCF in ITT.
- OC in ITT

Table 14.2.1.3.3: CFQ-R: Pooled analyses: Descriptive statistics of the actual values per time point

Descriptive statistics of the actual values on pooled treatment group and analysis visit will be done only for CFQ-R respiratory domain score.

The following sub-groups will be also provided in this pooled analysis:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.3.4: CFQ-R: Descriptive statistics of the changes from baseline per time point

Descriptive statistics of changes from baseline per treatment group and analysis visit for each score. The actual value at baseline will also be presented in this table.

P-values are generated from an ANCOVA model on the changes from baseline at each time point with treatment as factors and baseline value as covariate. Pairwise comparison (dose group vs placebo) will be provided as well.

P-values will be generated also from a Kruskal-Wallis test (overall treatment effect) and Wilcoxon rank sum test (pairwise comparison with placebo) as sensitivity analysis.

The table will show:

- LOCF in ITT.
- OC in ITT (only descriptive, no inferential statistics)

Table 14.2.1.3.5: CFQ-R: Descriptive statistics of the changes from baseline per time point on Placebo groups

Descriptive statistics of changes from baseline per cohort, per treatment group and analysis visit. The actual value at baseline will also be presented in this table.

Descriptive statistics of changes from baseline per cohort, analysis visit on placebo (cohort A), on placebo (cohort B), on pooled placebo. The actual value at baseline will also be presented in this table.

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.3.6: CFQ-R: Sub-group analyses: Descriptive statistics of the changes from baseline per time point

Descriptive statistics of changes from baseline, treatment group and analysis visit for each sub-group analysis will be done only for CFQ-R respiratory domain score. The actual value at baseline will also be presented in this table.

The following sub-groups will be shown:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29
- By sweat chloride (from arm with greatest volume) at baseline
- By sweat chloride (mean value from both arms) at baseline
- By %FEV1 at baseline

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.3.7: CFQ-R: Pooled analyses: Descriptive statistics of the changes from baseline per time point

Descriptive statistics of changes from baseline per pooled treatment group and analysis visit will be done only for CFQ-R respiratory domain score. The actual value at baseline will also be presented in this table.

The following sub-groups will be also provided in this pooled analysis:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.3.8: CFQ-R: Descriptive statistics of the percent changes from baseline per time point

Descriptive statistics of percent changes from baseline per treatment group and analysis visit for each score. The actual value at baseline will also be presented in this table.

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.1.3.9: CFQ-R: Sensitivity analyses on the changes from baseline values

Additional sensitivity analysis will be explored by using Mixed Effects Model for Repeated Measures (MMRM). The model will include treatment and analysis visit as fixed effects and baseline as a covariate, treatment*analysis visit as interaction terms and subject as random effect for each score. Pairwise comparisons will be presented.

The table will show:

- OC in ITT.

9.3.3. Figures

Figure 14.2.1.3.1: CFQ-R: Subject profile plots over time

Subject profile plots over time for each score. Each treatment group will be on a new plot, with all subjects of the same treatment group on the same plot. Any unscheduled results will also be part of this plot.

The figure will show:

- OC in ITT.

Figure 14.2.1.3.2: CFQ-R: Subject profile on change from baseline plot over time

Change from baseline subject profile plots over time for each score. Each treatment group will be on a new plot, with all subjects of the same treatment group on the same plot. Any unscheduled results will also be part of this plot.

The figure will show:

- OC in ITT.

Figure 14.2.1.3.3: CFQ-R: Mean (+/- SE) plots of the actual values over time

Mean (with SE) plots of the actual values over time for each score. Unscheduled results will not be part of this plot.

The figure will show:

- LOCF in ITT.
- OC in ITT

Figure 14.2.1.3.4: CFQ-R: Mean (+/- SE) plots of the changes from baseline over time

Mean (with SE) plots of the changes from baseline over time for each score. Unscheduled results will not be part of this plot. With a horizontal reference line at zero, indicating no change. Plots will start with a zero mean at baseline.

The figure will show:

- LOCF in ITT.
- OC in ITT

Figure 14.2.1.3.5: CFQ-R: Sub-group analyses: Mean (+/- SE) plots of the changes from baseline over time

Mean (with SE) plots of the changes from baseline over time for each sub-group will be done only for CFQ-R respiratory domain score. Unscheduled results will not be part of this plot. With a horizontal reference line at zero, indicating no change. Plots will start with a zero mean at baseline.

The following sub-groups will be shown:

- By target C_{trough} at Day 15

- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29
- By sweat chloride (from arm with greatest volume) at baseline
- By sweat chloride (mean value from both arms) at baseline
- By %FEV1 at baseline

The figure will show:
- LOCF in ITT.
- OC in ITT

Figure 14.2.1.3.6: CFQ-R: Pooled analyses: Mean (+/- SE) plots of the changes from baseline over time

Mean (with SE) plots of the changes from baseline over time on pooled treatment will be done only for CFQ-R respiratory domain score. Unscheduled results will not be part of this plot. With a horizontal reference line at zero, indicating no change. Plots will start with a zero mean at baseline.

The following sub-groups will be also provided in this pooled analysis:
- By target C_{trough} at Day 15
- By target C_{trough} at Day 29
- By target C_{trough} at Day 15 and 29

The table will show:
- LOCF in ITT.
- OC in ITT

Figure 14.2.1.3.7: CFQ-R: Mean plots (+/- SE) of the percent changes from baseline over time

Mean (with SE) plots of the percent changes from baseline over time for each score. Unscheduled results will not be part of this plot. With a horizontal reference line at zero, indicating no change. Plots will start with a zero mean at baseline.

The figure will show:
- LOCF in ITT.
- OC in ITT

9.3.4. Listings

Listing 16.2.6.3: CFQ-R: Full listing

Listing per subject and per time point of all data related to CFQ-R: actual values, changes from baseline and percent changes from baseline.

The listing will show: ITT.

10. DEFINITIONS OF PHARMACOKINETICS ANALYSIS TABLES, LISTINGS AND FIGURES

- Compounds:
  - GLPG2222
- PK parameters are:
  - C_{max}, t_{max}, C_{trough}, AUC_{0-t}
  - C_{max}/dose, C_{trough}/dose, AUC_{0-t}/dose

C_{max}	Maximum concentration after multiple dosing (ng/mL), obtained directly from the observed concentration versus time data.
t_{max}	Time of occurrence of maximum concentration after multiple dosing (h), obtained directly from the observed concentration versus time data.
C_{trough}	Plasma concentration observed at pre-dose (ng/mL), obtained directly from the observed concentration versus time data.
AUC_{0-t}	Area under the concentration-time curve up from time 0 up to 24 h following multiple dosing (ng·h/mL), calculated by linear up/log down trapezoidal summation.

On Day 15, all PK parameters will be determined (or on Day 29 if the subject is not available for full PK profiling on Day 15). On Day 29, only C_{trough} will be determined.

10.1.1. PK Parameter Derivation Rules

Pharmacokinetic analysis of the plasma concentration data for GLPG2222 will be performed at [redacted], United States. PK parameters will be derived using standard non compartmental methods using Phoenix WinNonlin® 6.4 or higher (Pharsight Corp., Certara Company, Princeton, New Jersey, United States); and/or SAS® Version 9.4 or higher. Graphics may be prepared with SAS® Version 9.4, or higher; SigmaPlot® 12.5, or higher (Systat Software, Inc., San Jose, California, United States); or Phoenix WinNonlin® 6.4, or higher. For PK analysis, the following rules will be applied:

- BLOQ concentration will be imputed according to the rules mentioned in Section 5.3.2
- If the concentrations before and after a quantifiable timepoint are below the limit of quantification, the quantifiable timepoint will not be included in the PK analysis.
- Plasma concentrations that again become quantifiable at time points after being BLOQ at earlier time points will be excluded from analysis at those time points.
- Subjects with less than 3 concentrations > LOQ are excluded from that day.
- Day 15 (or Day 29) 24h post-dose plasma concentrations will be imputed using the pre-dose value, in order to complete the full dosing interval PK profile (of 24 hours).
- Exposures will be calculated according to linear up/log down trapezoidal method using theoretical sampling time points.

– Theoretical sampling time will be used for PK parameters calculation, except if the deviation of actual sampling time is >10%, when the actual sampling time will be used.

Handling of other potential anomalies in the plasma PK profiles will be discussed with Galapagos before PK parameter derivation.

Excluded data will be flagged in the TLFs.

10.1.2. Tables

Table 14.2.2.1: GLPG2222 Trough plasma concentrations (ng/mL): Individual data and descriptive statistics per dose and day

Subject data with descriptive statistics per dose, day of the predose plasma concentrations (Day 15, Day 29).

Compound: GLPG2222.

Population: PK.

Table 14.2.2.2: GLPG2222 Plasma concentrations (ng/mL): Individual data and descriptive statistics per dose level on the day of the full PK profile

Subject data with descriptive statistics per dose on the day of the full PK profile (PK profile data from day 15 and Day 29 will be pooled).

Compound: GLPG2222.

Population: PK.

Table 14.2.2.3: GLPG2222 PK parameters: Individual data and descriptive statistics per dose on the day of the full PK profile

Subject data with descriptive statistics per dose of the derived PK parameters (C_{max}, t_{max}, C_{trough}, AUC_{0-t}, C_{max}/dose, C_{trough}/dose, AUC_{0-t}/dose) on the day of the full PK profile (PK profile data from day 15 and Day 29 will be pooled).

Compound: GLPG2222.

Population: PK.

Table 14.2.2.4: GLPG2222 PK parameters: statistical assessment of dose-proportionality

Dose proportionality of PK parameters Cmax, AUC0-t ,Ctrough (Day 15) and Ctrough (Day 29) will be assessed statistically using the power model approach. The power model will be:

log (parameter) = α + β * log (dose) where 'α' is the intercept and 'β' is the slope.

Prior to the analysis, the assumption of a linear relationship between the log AUC0-t (Cmax, Ctrough (Day 15) and Ctrough (Day 29)) and log-dose was tested using analysis of variance by partitioning the sums of squares for treatments into those for linearity and departures from

linearity. If the departures from linearity were significant then the hypothesis of dose proportionality was rejected and the power model analysis was not performed.

The estimate obtained for β is a measure of dose proportionality. The estimate of β together with its 90% CI (βl, βu) was presented to quantify the degree of non-proportionality.

The intercept α and the slope β together with 90% CIs will be estimated and presented for each PK parameter. The power model parameters will be estimated using least-squares (LS) regression or an equivalent method. A minimum of 3 values per dose must be available for a given parameter to estimate dose proportionality with the power model.

The dose proportionality was confirmed if the 90% CI of β (βl, βu) was contained completely within the following critical region:

$$[\Theta_L;\Theta_H]=\left[1+\frac{\ln(0.8)}{\ln(r)};1+\frac{\ln(1.25)}{\ln(r)}\right]$$

where r, defined as the dose ratio, is equal to h/l , h being the highest dose and l the lowest dose.

In this decision rule, the dose proportionality was analyzed as an equivalence problem. If the 90% CI was excluded completely from the critical region $[\Theta_L;\Theta_H]$ defined here above, the hypothesis of dose proportionality was rejected. If the 90% CI of β included the lower or the upper bound of the critical region, no conclusion could be done on dose proportionality. The proportionality was tested at a 5% significance level.

Assessment of the dose-proportionality will be performed on the complete dose range. In case of negative conclusion of dose-proportionality on the complete dose, further investigation using the same methodology might be done on a restrained dose range.

The calculation of the increase in AUC, Cmax, Ctrough (Day 15) and Ctrough (Day 29) for a two-fold increase in dose was performed by substituting the value of β in the equation 2^{β}. CI for this ratio was obtained by substituting βl and βu in the equation 2^{β}.

The non-parametric Kruskal-Wallis test will be applied to the non-transformed t_{max} to determine the difference between doses.

The "raw" SAS PROC output must be provided in a statistical appendix listing.

Population: PK

10.1.3. Figures

Figure 14.2.2.1: GLPG2222 Trough plasma concentrations (ng/mL): Subject plots (linear-linear scale)

Subject plots of the predose plasma concentrations per Day (Day 15, Day 29). Each dose group with all subjects of the same dose group on the same plot. With horizontal line (target C_{trough}) at [redacted] ng/mL for GLPG2222.

Compound: GLPG2222.

Population: PK.

This figure will be created using SAS® 9.4.

Figure 14.2.2.2: GLPG2222 Trough plasma concentrations (ng/mL): Mean (+/- SE) concentration over time (linear-linear scale)

Arithmetic mean with SE of the predose plasma concentrations per Day (Day 15, Day 29), with all dose levels on the same plot using different plot symbols.

Compound: GLPG2222.

Population: PK.

This figure will be created using SigmaPlot®.

Figure 14.2.2.3: GLPG2222 Plasma concentrations (ng/mL): Subject profile plots (linear-linear scale) on the day of the full PK profile

Subject profile plots of the plasma concentrations over time on the day of the full PK profile (PK profile data from day 15 and Day 29 will be pooled). Each dose group will be on a new plot, with all subjects of the same dose group on the same plot.

Compound: GLPG2222.

Population: PK.

This figure will be created using SAS® 9.4.

Figure 14.2.2.4: GLPG2222 Plasma concentrations (ng/mL): Subject profile plots (log-linear scale) on the day of the full PK profile

Subject profile plots of the plasma concentrations over time on the day of the full PK profile (PK profile data from day 15 and Day 29 will be pooled). Each dose group will be on a new plot, with all subjects of the same dose group on the same plot. With a log10-scaled vertical concentration axis.

Compound: GLPG2222

Population: PK.

This figure will be created using SAS® 9.4.

Figure 14.2.2.5: GLPG2222 Plasma concentrations (ng/mL): Mean (+/- SE) concentration over time (linear-linear scale) on the day of the full PK profile

Arithmetic mean with SE of the plasma concentrations over time on the day of the full PK profile (PK profile data from day 15 and Day 29 will be pooled)., with all dose levels on the same plot using different plot symbols.

Compound: GLPG2222.

Population: PK.

This figure will be created using SigmaPlot®.

Figure 14.2.2.6: GLPG2222 Plasma concentrations (ng/mL): Mean (+/- SE) concentration over time (log-linear scale) on the day of the full PK profile

Arithmetic mean with SE of the plasma concentrations over time on the day of the full PK profile (PK profile data from day 15 and Day 29 will be pooled)., with all dose levels on the same plot using different plot symbols. With a log10-scaled vertical concentration axis.

Compound: GLPG2222.

Population: PK.

This figure will be created using SigmaPlot®.

Figure 14.2.2.7: GLPG2222 PK parameters: Dose-proportionality

Arithmetic mean with SE of the GLPG2222 dose-normalized PK parameters (C_{max}/dose, C_{trough}/dose, AUC_{0-t}/dose) (with all individual results included as a scatterplot), with the dose levels on the horizontal axis

Population: PK.

This figure will be created using SAS® 9.4.

10.1.4. Listings

Listing 16.2.7.1: PK Data handling

Listing per subject, dose group and planned time point of any data issue and how the issue will be handled in the analysis.

Population: PK.

Listing 16.2.7.2: Actual PK blood sampling times (h)

Listing per treatment group, per day and per subject of the PK sampling times relative to the actual drug intake. Deviations from the scheduled sampling times of more than 10% will be flagged, as well as pre-dose samples that were actually taken post-dose.

Population: PK.

Listing 16.2.7.3: Plasma concentrations (ng/mL): Individual data (ED)

In case of early discontinuation: Subject data on the day of the early discontinuation.

Compound: GLPG2222.

Population: PK.

11. DEFINITIONS OF PHARMACODYNAMICS ANALYSIS TABLES, LISTINGS AND FIGURES

11.1. PARAMETERS

The following biomarkers may be evaluated:

–

For each biomarker, Analysis will present:

- Actual values
- Change from baseline (Day 1 pre-dose):
  change at time point t = (time point t value) – (baseline value)
- Percent change from baseline (Day 1 pre-dose):
  %change at time point t = 100 x (time point t value – baseline value) / (baseline value)

11.2. TABLES

Table 14.2.3.1: Biomarker: Descriptive statistics of the actual values per time point

Descriptive statistics of actual values for each biomarker per treatment group and analysis visit.

Parameter: all available biomarkers

The table will show:

- LOCF in ITT.
- OC in ITT.

Table 14.2.3.2: Biomarker: Sub-group analyses: Descriptive statistics of the actual values per time point

Descriptive statistics of the actual values per treatment group and analysis visit for each sub-group.

Parameter: and

The following sub-groups will be shown:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.3.3: Biomarker: Pooled analyses: Descriptive statistics of the actual values per time point

Descriptive statistics of the actual values on pooled treatment group and analysis visit.

Parameter: [redacted] and [redacted]

The following sub-groups will be also provided in this pooled analysis:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.3.4: Biomarker: Descriptive statistics of the changes from baseline per time point

Descriptive statistics of changes from baseline for each biomarker per treatment group and analysis visit. The actual value at baseline will also be presented in this table.

P-values are generated from an ANCOVA model on the changes from baseline at each time point with treatment as factors and baseline value as covariate. Pairwise comparison (dose group vs placebo) will be provided as well.

P-values will be generated also from a Kruskal-Wallis test (overall treatment effect) and Wilcoxon rank sum test (pairwise comparison with placebo) as sensitivity analysis.

Parameter: all available biomarkers

The table will show:

- LOCF in ITT.
- OC in ITT (only descriptive, no inferential statistics)

Table 14.2.3.5: Biomarker: Descriptive statistics of the changes from baseline per time point on Placebo groups

Descriptive statistics of changes from baseline per cohort, per treatment group and analysis visit. The actual value at baseline will also be presented in this table.

Descriptive statistics of changes from baseline per cohort, analysis visit on placebo (cohort A), on placebo (cohort B), on pooled placebo. The actual value at baseline will also be presented in this table.

Parameter: all available biomarkers

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.3.6: Biomarker: Sub-group analyses: Descriptive statistics of the changes from baseline per time point

Descriptive statistics of the changes from baseline per treatment group and analysis visit for each sub-group.

Parameter: [redacted] and [redacted]

The following sub-groups will be shown:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.3.7: Biomarker: Pooled analyses: Descriptive statistics of the changes from baseline per time point

Descriptive statistics of the changes from baseline on pooled treatment group and analysis visit.

Parameter: [redacted] and [redacted]

The following sub-groups will be also provided in this pooled analysis:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.3.8: Biomarker: Descriptive statistics of the percent changes from baseline per time point

Descriptive statistics of percent changes from baseline per treatment group and analysis visit. The actual value at baseline will also be presented in this table.

Parameter: all available biomarkers

The table will show:

- LOCF in ITT.
- OC in ITT

Table 14.2.3.9: Biomarker: Sensitivity analyses on the changes from baseline values

Additional sensitivity analysis will be explored by using Mixed Effects Model for Repeated Measures (MMRM) for each biomarker. The model will include treatment and analysis visit

as fixed effects and baseline as a covariate, treatment*analysis visit as interaction terms and subject as random effect. Pairwise comparisons will be presented.

Parameter: all available biomarkers

The table will show:

- OC in ITT.

11.3. FIGURES

Figure 14.2.3.1: Biomarker: Subject profile plots over time

Subject profile plots over time for each biomarker. Each treatment group will be on a new plot, with all subjects of the same treatment group on the same plot. Any unscheduled results will also be part of this plot.

Parameter: all available biomarkers

The figure will show:

- OC in ITT.

Figure 14.2.3.2: Biomarker: Mean (+/- SE) plots of the actual values over time

Mean (with SE) plots of the actual values over time for each biomarker. Unscheduled results will not be part of this plot.

Parameter: all available biomarkers

The figure will show:

- LOCF in ITT.
- OC in ITT

Figure 14.2.3.3: Biomarker: Mean (+/- SE) plots of the changes from baseline over time

Mean (with SE) plots of the changes from baseline over time for each biomarker. Unscheduled results will not be part of this plot. With a horizontal reference line at zero, indicating no change. Plots will start with a zero mean at baseline.

Parameter: all available biomarkers

The figure will show:

- LOCF in ITT.
- OC in ITT

Figure 14.2.3.4: Biomarker: Sub-group analyses: Mean (+/- SE) plots of the changes from baseline over time

Mean (with SE) plots of the changes from baseline over time for each sub-group. Unscheduled results will not be part of this plot. With a horizontal reference line at zero, indicating no change. Plots will start with a zero mean at baseline.

Parameter: [redacted] and [redacted]

The following sub-groups will be shown:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29

The figure will show:

- LOCF in ITT.
- OC in ITT

Figure 14.2.3.5: Biomarker: Pooled analyses: Mean (+/- SE) plots of the changes from baseline over time

Mean (with SE) plots of the changes from baseline over time on pooled treatment. Unscheduled results will not be part of this plot. With a horizontal reference line at zero, indicating no change. Plots will start with a zero mean at baseline.

Parameter: [redacted] and [redacted]

The following sub-groups will be also provided in this pooled analysis:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29

The figure will show:

- LOCF in ITT.
- OC in ITT

Figure 14.2.3.6: Biomarker: Boxplots on actual values

Boxplots at each timepoint for each biomarker with all treatment groups in the same figure.

Parameter: all available biomarkers

The figure will show:

- LOCF in ITT.
- OC in ITT

11.4. LISTINGS

Listing 16.2.8.1: Biomarker: Full listing

Listing per subject and per time point of all data related to biomarkers: actual values, changes from baseline and percent changes from baseline.

The listing will show: OC in ITT.

12. DEFINITIONS OF PK/EFFICACY ANALYSIS TABLES, LISTINGS AND FIGURES

No tables or listings are currently planned.

Figure 14.2.4.1: Correlation between GLPG2222 trough plasma concentrations and sweat chloride (linear-linear plot)

Scatterplot of the GLPG2222 trough plasma concentrations versus the sweat chloride concentration. With all doses on the same graph, in a different symbol. Time point to present: Day 15, Day 29.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

This figure will show: OC in ITT

Figure 14.2.4.2: Correlation between GLPG2222 trough plasma concentrations and change from baseline in sweat chloride (linear-linear plot)

Scatterplot of the GLPG2222 trough plasma concentration versus the change from baseline in sweat chloride. With all doses on the same graph, in a different symbol. Time point to present: Day 15, Day 29.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

This figure will show: OC in ITT

Figure 14.2.4.3: Correlation between GLPG2222 trough plasma concentrations and %FEV1 (linear-linear plot)

Scatterplot of the GLPG2222 trough plasma concentrations versus the percent predicted FEV1. With all doses on the same graph, in a different symbol. Time point to present: Day15, Day 29.

This figure will show: OC in ITT

Figure 14.2.4.4: Correlation between GLPG2222 trough plasma concentrations and change from baseline in %FEV1 (linear-linear plot)

Scatterplot of the GLPG2222 trough plasma concentrations versus the change from baseline in percent predicted FEV1. With all doses on the same graph, in a different symbol. Time point to present: Day15, Day 29.

This figure will show: OC in ITT

Figure 14.2.4.5: Correlation between change from baseline in sweat chloride and change from baseline in %FEV1 (linear-linear plot)

Scatterplot of the change from baseline in sweat chloride concentration versus the change from baseline in percent predicted FEV1. Time point to present: Day15, Day 29, FU. Placebo group will be part of this figure.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

This figure will show: OC in ITT

Figure 14.2.4.6: Mean (+/- SE) sweat chloride (mmol/L) and mean (+/- SE) GLPG2222 trough plasma concentrations: Plots over time

Plots of the mean (+/- SE) in sweat chloride and mean (+/- SE) trough plasma concentration over time. Unscheduled results will not be part of this plot. With 2 y-axis on the same plot, one for the mean in sweat chloride, one for the mean trough plasma concentrations. With horizontal line (target C_{trough}) at [redacted] ng/mL. Each dose level will be in a separate plot.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

This figure will show: OC in ITT

Figure 14.2.4.7: Mean (+/- SE) sweat Chloride (mmol/L) and mean (+/- SE) GLPG2222 trough plasma concentrations: Sub-group analyses: Plots over time

Plots of the mean (+/- SE) in sweat chloride and mean (+/- SE) trough plasma concentration over time. Unscheduled results will not be part of this plot. With 2 y-axis on the same plot, one for the mean in sweat chloride, one for the mean trough plasma concentrations. With horizontal line (target C_{trough}) at [redacted] ng/mL. Each dose level and sub-groups will be in a separate plot.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The following sub-groups will be shown:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29

This figure will show: OC in ITT

Figure 14.2.4.8: Mean (+/- SE) sweat Chloride (mmol/L) and mean (+/- SE) GLPG2222 trough plasma concentrations: Pooled analyses: Plots over time

Plots of the mean (+/- SE) in sweat chloride and mean (+/- SE) trough plasma concentration over time. Unscheduled results will not be part of this plot. With 2 y-axis on the same plot, one for the mean in sweat chloride, one for the mean trough plasma concentrations. With horizontal line (target C_{trough}) at [redacted] ng/mL. Sub-groups will be in a separate plot.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

The following sub-groups will be shown:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29

This figure will show: OC in ITT

Figure 14.2.4.9: Sweat chloride (mmol/L) and GLPG2222 trough plasma concentrations: Plots over time

Plots of the sweat chloride (individual data) and trough plasma concentration (individual data) over time. Unscheduled results will be part of this plot. With 2 y-axis on the same plot, one for the sweat chloride, one for the trough plasma concentrations. Each dose group will be on a new plot, with all subjects of the same dose group on the same plot. With horizontal line (target C_{trough}) at [redacted] ng/mL.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

This figure will show: OC in ITT

Figure 14.2.4.10: Mean (+/- SE) %FEV1 and mean (+/- SE) GLPG2222 trough plasma concentrations: Plots over time

Plots of the mean (+/- SE) in %FEV1 and mean (+/- SE) trough plasma concentration over time. Unscheduled results will not be part of this plot. With 2 y-axis on the same plot, one for the mean in %FEV1, one for the mean trough plasma concentrations. With horizontal line (target C_{trough}) at [redacted] ng/mL. Each dose level will be in a separate plot.

This figure will show: OC in ITT

Figure 14.2.4.11: Mean (+/- SE) %FEV1 and mean (+/- SE) GLPG2222 trough plasma concentrations: Sub-group analyses: Plots over time

Plots of the mean (+/- SE) in %FEV1 and mean (+/- SE) trough plasma concentration over time. Unscheduled results will not be part of this plot. With 2 y-axis on the same plot, one for the mean in %FEV1, one for the mean trough plasma concentrations. With horizontal line (target C_{trough}) at [redacted] ng/mL. Each dose level and sub-groups will be in a separate plot.

The following sub-groups will be shown:

- By target C_{trough} at Day 15

– By target C_{trough} at Day 29

This figure will show: OC in ITT

Figure 14.2.4.12: Mean (+/- SE) %FEV1 and mean (+/- SE) GLPG2222 trough plasma concentrations: Pooled analyses: Plots over time

Plots of the mean (+/- SE) in %FEV1 and mean (+/- SE) trough plasma concentration over time. Unscheduled results will not be part of this plot. With 2 y-axis on the same plot, one for the mean change in %FEV1, one for the mean trough plasma concentrations. With horizontal line (target C_{trough}) at [redacted] ng/mL. Sub-groups will be in a separate plot.

The following sub-groups will be shown:

– By target C_{trough} at Day 15
– By target C_{trough} at Day 29

This figure will show: OC in ITT

Figure 14.2.4.13: %FEV1 and GLPG2222 trough plasma concentrations: Plots over time

Plots of the %FEV1 (individual data) and trough plasma concentration (individual data) over time. Unscheduled results will be part of this plot. With 2 y-axis on the same plot, one for the %FEV1, one for the trough plasma concentrations. Each dose group will be on a new plot, with all subjects of the same dose group on the same plot. With horizontal line (target C_{trough}) at [redacted] ng/mL.

This figure will show: OC in ITT

Figure 14.2.4.14: Mean (+/- SE) sweat Chloride (mmol/L) and mean (+/- SE) in %FEV1: Plots over time

Plots of the mean (+/- SE) in sweat chloride and mean in %FEV1 over time. Unscheduled results will not be part of this plot. With 2 y-axis on the same plot, one for the mean in sweat Chloride (mmol/L), one for the mean in %FEV1. Placebo group should be part of this figure. Each treatment group will be in a separate plot.

Parameters:

– Sweat Chloride (from arm with greatest volume)
– Sweat Chloride (mean value from both arms)

This figure will show: OC in ITT

Figure 14.2.4.15: Correlation between CFQ-R respiratory domain and change from baseline in %FEV1 (linear-linear plot)

Scatterplot of the CFQ-R respiratory domain versus the change from baseline in %FEV1. With all treatment groups on the same graph, in a different symbol. Time point to present: Day15, Day 29, FU. Placebo group should be part of this figure.

This figure will show: OC in ITT

Figure 14.2.4.16: Correlation between CFQ-R respiratory domain and percent change from baseline in %FEV1 (linear-linear plot)

Scatterplot of the CFQ-R respiratory domain versus the percent change from baseline in %FEV1. With all treatment groups on the same graph, in a different symbol. Time point to present: Day15, Day 29, FU. Placebo group should be part of this figure.

This figure will show: OC in ITT

Figure 14.2.4.17: Correlation between change from baseline in CFQ-R respiratory domain and change from baseline in %FEV1 (linear-linear plot)

Scatterplot of the CFQ-R respiratory domain changes versus the change from baseline in %FEV1. With all treatment groups on the same graph, in a different symbol. Time point to present: Day15, Day 29, FU. Placebo group should be part of this figure.

This figure will show: OC in ITT

Figure 14.2.4.18: Correlation between change from baseline in CFQ-R respiratory domain and percent change from baseline in %FEV1 (linear-linear plot)

Scatterplot of the CFQ-R respiratory domain changes versus the percent change from baseline in %FEV1. With all treatment groups on the same graph, in a different symbol. Time point to present: Day15, Day 29, FU. Placebo group should be part of this figure.

This figure will show: OC in ITT

Figure 14.2.4.19: Mean (+/- SE) CFQ-R respiratory domain and mean (+/- SE) in %FEV1: Plots over time

Plots of the mean (+/- SE) in CFQ-R respiratory domain and mean (+/- SE) in %FEV1 over time. Unscheduled results will not be part of this plot. With 2 y-axis on the same plot, one for the mean in CFQ-R respiratory domain, one for the mean in %FEV1. Placebo will be part of this figure. Each treatment group will be in a separate plot.

This figure will show: OC in ITT

Figure 14.2.4.20: Mean change from baseline (+/- SE) in CFQ-R respiratory domain and mean change from baseline (+/- SE) in %FEV1: Plots over time

Plots of the mean change from baseline (+/- SE) in CFQ-R respiratory domain and mean change from baseline (+/- SE) in %FEV1 over time. Unscheduled results will not be part of this plot. With 2 y-axis on the same plot, one for the mean change from baseline CFQ-R respiratory domain, one for the mean change from baseline in %FEV1. Placebo will be part of this figure. Each treatment group will be in a separate plot.

This figure will show: OC in ITT

Figure 14.2.4.21: Mean (+/- SE) CFQ-R respiratory domain and mean (+/- SE) GLPG2222 trough plasma concentrations: Plots over time

Plots of the mean (+/- SE) in CFQ-R respiratory domain and mean (+/- SE) trough plasma concentration over time. Unscheduled results will not be part of this plot. With 2 y-axis on the same plot, one for the mean in CFQ-R, one for the mean trough plasma concentrations. With horizontal line (target C_{trough}) at [redacted] ng/mL. Each dose level will be in a separate plot.

This figure will show: OC in ITT

Figure 14.2.4.22: Mean (+/- SE) [redacted] and [redacted] and mean (+/- SE) GLPG2222 trough plasma concentrations: Plots over time

Plots of the mean (+/- SE) in [redacted] and [redacted] and mean (+/- SE) trough plasma concentration over time. Unscheduled results will not be part of this plot. With 2 y-axis on the same plot, one for the mean in [redacted] and [redacted] one for the mean trough plasma concentrations. With horizontal line (target C_{trough}) at [redacted] ng/mL. Each dose level will be in a separate plot.

Parameter: [redacted] and [redacted]

This figure will show: OC in ITT

Figure 14.2.4.23: Mean (+/- SE) [redacted] and [redacted] and mean (+/- SE) GLPG2222 trough plasma concentrations: Sub-group analyses: Plots over time

Plots of the mean (+/- SE) in [redacted] and [redacted] and mean (+/- SE) trough plasma concentration over time. Unscheduled results will not be part of this plot. With 2 y-axis on the same plot, one for the mean in [redacted] and [redacted] one for the mean trough plasma concentrations. With horizontal line (target C_{trough}) at [redacted] ng/mL. Each dose level and sub-groups will be in a separate plot.

The following sub-groups will be shown:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29

Parameter: [redacted] and [redacted]

- This figure will show: OC in ITT

Figure 14.2.4.24: Mean (+/- SE) [redacted] and [redacted] and mean (+/- SE) GLPG2222 trough plasma concentrations: Pooled analyses: Plots over time

Plots of the mean (+/- SE) in [redacted] and [redacted] and mean (+/- SE) trough plasma concentration over time. Unscheduled results will not be part of this plot. With 2 y-axis on the same plot, one for the mean in [redacted] and [redacted] one for the mean trough plasma concentrations. With horizontal line (target C_{trough}) at [redacted] ng/mL. Sub-groups will be in a separate plot.

The following sub-groups will be shown:

- By target C_{trough} at Day 15
- By target C_{trough} at Day 29

Parameter: [redacted] and [redacted]

This figure will show: OC in ITT

Figure 14.2.4.25: [redacted] and [redacted] and GLPG2222 trough plasma concentrations: Plots over time

Plots of the [redacted] and [redacted] (individual data) and trough plasma concentration (individual data) over time. Unscheduled results will be part of this plot. With 2 y-axis on the same plot, one for the [redacted] and [redacted] one for the trough plasma concentrations. Each dose group will be on a new plot, with all subjects of the same dose group on the same plot. With horizontal line (target C_{trough}) at [redacted] ng/mL.

This figure will show: OC in ITT

Figure 14.2.4.26: Waterfall plot on change from baseline in Sweat Chloride

Waterfall plot on change from baseline in Sweat Chloride at Day 15 and Day 29.

Parameters:

- Sweat Chloride (from arm with greatest volume)
- Sweat Chloride (mean value from both arms)

This figure will show: OC in ITT

Figure 14.2.4.27: Waterfall plot on change from baseline in %FEV1

Waterfall plot on change from baseline in %FEV1 at Day 15 and Day 29.

This figure will show: OC in ITT

13. DEFINITIONS OF SAFETY ANALYSIS TABLES, LISTINGS AND FIGURES

13.1. ADVERSE EVENTS

13.1.1. Treatment-Emergent Principle

All adverse events starting on or after first dosing are considered treatment-emergent adverse events (TEAE).

Adverse events will be placed into analysis periods according to their start date(time). Analysis periods: see section 4.2. The AE will only be presented in the analysis period during which it started. Rule: period start date(time) ≤ AE start date(time) ≤ period end date(time).

In case the AE start date(time) is incomplete, a worst-case allocation will be done according to the available parts of the AE start date(time), i.e. the AE will be allocated to the treatment period. If the AE start date is equal to the date of the turning point between the screening and treatment analysis periods, and no AE start time is available, then the AE will be allocated to the treatment period. This is considered a worst-case allocation.

All adverse events emerging during the screening period will only be listed, not presented in any of the tables. These events are not TEAEs. All tables will present TEAEs only.

13.1.2. Treatment Relatedness

Following (ICH-E3), the drug relatedness will be dichotomized as follows:

Drug related: at least possibly drug related, OR with missing drug relatedness (= worst-case)

Not drug related: less than possibly drug related.

In tabulations this dichotomized parameter will be used, but in the listings the original parameter will be presented.

13.1.3. Worst-Case Principle

When cross-tabulating AE preferred terms versus an AE attribute (e.g., intensity), the worst-case is always applied within each analysis period. I.e., when a subject has multiple times the same AE preferred term in the same analysis period, then the subject is reported only once: only with the worst intensity. If this happens in two different analysis periods, the AE is reported twice: once in each analysis period.

13.1.4. Adverse Event Onset Day and Duration

AE onset day in the study

= ((AE start date) – (date of first study drug administration)) + 1, when the AE start date is completely known; the “+1” is not needed if the AE start date is before the first study drug administration date;

= missing when the AE start date is incomplete or unknown.

AE onset day in the period

= ((AE start date) – (start date of the period into which the AE was allocated)) + 1, when the AE start date is completely known;

= missing when the AE start date is incomplete or unknown.

AE duration

= ((AE stop date) – (AE start date)) + 1, when both dates are completely known;

= ((Study termination date) – (AE start date)) + 1, when the AE start date is fully known but the AE is not resolved at the end of the study; in this case the duration will be presented as ">x days" in the listing to identify it as a censored result;

= missing when the AE start date is incomplete or unknown, or when the AE has resolved but with an incomplete or unknown end date.

These derived parameters will only be presented in the listings. Note that the start and stop times of the AE are not used; only the dates are used.

13.1.5. Calculation of Percentages

All percentages will be calculated against the total number of subjects that are still in the study in that particular analysis period.

13.1.6. Tables

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

Analysis periods will be replaced by their respective treatment via the data captured in the CRF (i.e, an as-treated allocation). All tabulations and listings will present treatments rather than analysis periods.

Table 14.3.1.1: Treatment-emergent adverse events: Summary table

Tabulation per treatment of the number and percentage of subjects with the following:

- Subjects with at least one treatment-emergent adverse event (TEAE)
- Subjects with at least one serious TEAE
- Subjects who died
- Subjects with at least one mild TEAE as worst intensity
- Subjects with at least one moderate TEAE as worst intensity
- Subjects with at least one severe TEAE
- Subjects with at least one TEAE that was considered treatment-related
- Subjects with at least one TEAE for which the study treatment was temporarily stopped
- Subjects with at least one TEAE for which the study treatment was permanently stopped.

Population: safety population.

Table 14.3.1.2: Treatment-emergent adverse events: Tabulation of all adverse events

Tabulation of TEAE preferred terms per body class, per treatment group.

With a frequency tabulation of the number of events (reportings).

Population: safety.

Table 14.3.1.3: Treatment-emergent adverse events: Tabulation per intensity

Cross-tabulation of TEAE preferred terms versus their intensity. Use the worst-case intensity per TEAE per subject. Per treatment group.

Population: safety.

Table 14.3.1.4: Treatment-emergent adverse events: Tabulation of all treatment-related events

Tabulation of TEAE preferred terms per body class, per treatment group. Selecting only the TEAEs that were treatment-related (see section 13.1.2).

Population: safety.

Table 14.3.1.5: Treatment-emergent adverse events: Tabulation of the intensity of treatment-related events

Cross-tabulation per analysis period of TEAE preferred terms versus their intensity; per body class and per treatment group. Use the worst-case intensity per TEAE per subject, selecting only the TEAEs that were treatment-related (see section 13.1.2).

Population: safety.

Table 14.3.1.6: Serious treatment-emergent adverse events: Tabulation for EudraCT reporting

Tabulation of the number of subjects and events per body class, preferred term and per treatment.

Population: Safety.

Table 14.3.1.7: Non-serious treatment-emergent adverse events: Tabulation for EudraCT reporting

Same as the previous table, but only selecting TEAEs that are not serious.

Population: Safety.

Table 14.3.1.8: Non-serious treatment-emergent adverse events: Tabulation for EudraCT reporting of TEAEs occurring in at least 5% in one of the treatment group

Same as the previous table, selecting all the lines from the table where there is at least 5% occurrence in one of the treatment group either at SOC or at preferred term level. If the SOC line is selected but none of the associated preferred terms, then the SOC line is still to be presented but without preferred term lines.

Population: Safety.

13.1.7. Listings

Listing 16.2.10.1: Treatment-emergent adverse events: Summary listing of all events

Listing per treatment group, per subject of the following:

Period start and end date(time)
- AE preferred term (flagging serious TEAEs with an asterisk *)
- AE start and end date(time)
- AE onset day in study
- AE duration
- AE intensity
- AE drug relatedness
- AE action taken
- Concomitant therapy started (yes/no)

In such a way that all information fits on one line for each AE.

Periods without an AE will be included as “no AE” records.

Population: safety.

Listing 16.2.10.2: Treatment-emergent adverse events: Full listing

Listing per treatment group, per subject of all AE details, including MedDRA coding. Only actual adverse events will be presented here: periods or subjects without a TEAE will be left out. If a ConMed was started due to the AE, then the listing will present the ConMed’s generic term.

Population: safety.

Listing 16.2.10.3: Pre-treatment adverse events: Full listing

Listing per treatment group and per subject of the screening period of all AE details, like in the previous listing.

Population: safety.

Listing 16.2.10.4: Adverse events: Full listing of the serious adverse events

Same as the previous listing, but only selecting SAEs (irrespective their treatment-emergence).

Population: safety.

Listing 16.2.10.5: Treatment-emergent adverse events: Full listing of the events leading to discontinuation

Same as the previous listing, but only selecting TEAEs that lead to a stop of study medication, or of the study itself.

Population: safety.

Listing 16.2.10.6: Adverse events: Coding information

Listing of all available coding steps between AE verbatim and AE system organ class, mentioning also the subjects who had this AE.

Population: safety.

13.2. LABORATORY SAFETY

13.2.1. Laboratory Units

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

Lab tests with only a very low sample size (N<3 overall) will not be presented in the tables, but only in the listings. Lab tests that are not part of the planned test panels according to the protocol will only be listed.

Urinalysis tests will be presented as part of the descriptive statistics and/or shift tables.

13.2.2. Number of Significant Digits

In tables and listings, the standardized results will be rounded to present only a relevant number of digits. The Mock TLFs contain tables on the expected number of significant digits per lab test. This rounding will be done prior to any parameter derivation.

Note that this table also contains the classification of lab tests into categories.

13.2.3. Baseline and Change from Baseline

The baseline is defined as the last sample prior to first dosing. Baseline will be determined per lab test individually. It is recognized that baseline tests may thus come from more than one lab sample.

The change from baseline will be calculated for all post-baseline time points as:

Change from baseline at time point t = value at time point t – baseline value.

13.2.4. Scoring of Laboratory Values and Urinalysis Results

All values will be compared to their matching normal ranges. The normal ranges provided by the laboratory will be used for this, as available in the database. Values are scored as abnormally low (L), normal (N) or abnormally high (H) by the central lab. The analysis will use this scoring (variable LBNRIND from SDTM.LB).

Tests without normal ranges will not be scored. Any clinical significance flags will be used in the listings.

13.2.5. Worst-Case Abnormality

Derived per parameter separately.

All nonmissing post-baseline values (including unscheduled measurements and follow-up measurements) will be used to derive the following worst-case:

- H = abnormally high:
  at least one post-baseline measurement is above the normal range, and there are no values below the normal range.
- L = abnormally low:
  at least one post-baseline measurement is below the normal range, and there are no values above the normal range.
- H+L = abnormally high and low:
  at least one post-baseline measurement is above the normal range, and at least one other post-baseline measurement is below the normal range.
- N = normal:
  all post-baseline measurements are within normal limits.

13.2.6. Tables

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

Table 14.3.2.1: Laboratory data: Descriptive statistics of the actual values per time point

Descriptive statistics of actual values per lab test category (hematology, biochemistry, urinalysis), lab test and unit, treatment group and time point.

Population: safety.

Table 14.3.2.2: Laboratory data: Descriptive statistics of the changes from baseline per time point

Descriptive statistics of changes from baseline (including 95% confidence interval of the mean change) per lab test category (hematology, biochemistry, urinalysis), lab test and unit, treatment group and time point. The actual value at baseline will also be presented in this table.

Population: safety.

Table 14.3.2.3: Laboratory data: Shift table according to the lab normal range per time point

Shift table per lab test category (hematology, biochemistry, urinalysis), lab test, treatment group and time point (including worst-case). The table will present the shift in abnormality (L/N/H) at each post-baseline time point versus the baseline abnormality (L/N/H). Tests without normal ranges will not be presented in this table.

Population: safety.

Table 14.3.2.4: Laboratory data: Treatment-emergent abnormalities per time point

Frequency table of the treatment-emergent lab abnormalities per lab test category (hematology, biochemistry, urinalysis), lab test, treatment group and time point (including worst-case). A post-baseline abnormality is considered treatment-emergent if it differs from the baseline result. Tests without normal ranges will not be presented in this table.

Population: safety.

Table 14.3.2.5: Laboratory data: Shift table of the categorical lab data per time point

Shift table per lab test category (hematology, biochemistry, urinalysis), lab test, treatment group and time point. Selecting only the tests with categorical data. The table will present the shift in value at each post-baseline time point versus the baseline value.

Population: safety.

13.2.7. Figures

Figure 14.3.2.1: Laboratory data: Subject profile plots over time

Subject profile plots over time, with each lab test and treatment group on a new page but with all subjects of one treatment group on the same plot. Any unscheduled results will also be part of this plot.

Population: safety.

Figure 14.3.2.2: Laboratory data: Mean (+/- SE) plots of the actual values over time

Mean (with SE) plots of the actual values over time, with each lab test on a new page but with all treatment groups on the same plot using different plot symbols. Unscheduled results will not be part of this plot.

Population: safety.

Figure 14.3.2.3: Laboratory data: Mean (+/- SE) plots of the changes from baseline over time

Mean (with SE) plots of the changes from baseline over time, with each lab test on a new page but with all treatment groups on the same plot using different plot symbols. Unscheduled results will not be part of this plot. With a horizontal reference line at zero, indicating no change. Plots will start with a zero mean at baseline.

Population: safety.

13.2.8. Listings

All listings will contain next to the actual data (raw and changes) the following parameters:

- an abnormality L/H flag
- the test's normal range
- a clinical relevance flag

Listing 16.2.11.1: Laboratory data: Full listing

Listing per treatment group, per subject and per time point of all data.

Population: safety.

Listing 16.2.11.2: Laboratory data: Abnormalities listing

Listing per treatment group, per subject and per time point of all post-baseline time points scored as out-of-normal-range or clinically significant, plus also the baseline reference time point.

Population: safety.

13.3. ECG

13.3.1. Available Data

Available parameters: HR (heart rate), RR, QRS, PR and QT (corrected QT).

13.3.2. Calculated Parameters

The QTc will always be derived during the statistical analysis, even when already available in the database. The value in the database will not be used in the analysis.

The QTc will be calculated using the following formulae:

- Fridericia's cube-root corrected QT (Fridericia, 1920):

  QTcF (ms) = QT (ms) x $\sqrt[3]{\frac{1000}{RR(ms)}}$

  QTcF (ms) = QT (ms) x $\sqrt[3]{\frac{HR(bpm)}{60}}$

The formula using RR is preferred. In case no RR is available, at a subject level, the formula using HR will be applied for all subjects. Derived QTc values will be rounded to the nearest first decimal before deriving changes from baseline and categories.

13.3.3. Baseline and Change from Baseline

The baseline is defined as the last nonmissing value prior to dosing. Baseline will be determined per ECG parameter individually. It is recognized that baseline parameters may thus come from more than one ECG reading.

The change from baseline will be calculated for all post-baseline time points as:

Change from baseline at time point t = value at time point t – baseline value.

13.3.4. Normal Ranges

QT and QTc parameters: first round the value as described above, and then apply the following categorizations:

- of the actual values:
  - <= 450 ms,
  -]450,480] ms,
  -]480,500] ms,
  - >500 ms;
- of the changes from baseline:
  - <= 30 ms (including all decreases in QT),
  -]30,60] ms,
  - >60 ms.

13.3.5. Worst-case Abnormality of QT and QTc

Derived per parameter separately.

All nonmissing postbaseline values (including unscheduled measurements and follow-up measurements) will be used to derive the following worst-case. The worst-case is the largest nonmissing post-baseline value and the largest non-missing change from baseline.

13.3.6. Tables

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

Table 14.3.3.1: ECG: Descriptive statistics of the actual values per time point

Descriptive statistics of the actual values per test and unit, treatment group and time point.

Population: safety.

Table 14.3.3.2: ECG: Descriptive statistics of the changes from baseline per time point

Descriptive statistics of the changes from baseline per test and unit, treatment group and time point. The actual value at baseline will also be presented in this table.

Population: safety.

Table 14.3.3.3: ECG: Shift table according to the QT normal range per time point

Shift table per test, treatment group and time point. The table will present the shift in abnormality at each post-baseline time point (including worst-case) versus the baseline abnormality. Parameters: QT, QTcF.

Population: safety.

Table 14.3.3.4: ECG: Treatment-emergent QT abnormalities per time point

Frequency table of the treatment-emergent abnormalities per parameter, treatment group and time point (including worst-case). A post-baseline abnormality is considered treatment-emergent if it is higher than the baseline result. Parameters: QT, QTcF.

Population: safety.

Table 14.3.3.5: ECG: Treatment-emergent abnormal change in QT per time point

Frequency table per test, treatment group and time point (including worst-case). The table will present the abnormality of the changes at each post-baseline time point according to the classifications of section 13.3.4 Parameters: QT, QTcF.

Population: safety.

Table 14.3.3.6: ECG: Frequency table of the eCRF ECG interpretation per time point

Frequency table per treatment group and time point of the ECG interpretation scores as recorded in the eCRF. Interpretation scores are:

- Cardiac conduction disorders;
- Rate and rhythm disorders;
- Supraventricular arrhythmias;
- Ventricular arrhythmias.

Note that more than one of these items can be ticked.

Population: safety.

13.3.7. Figures

No figures planned.

13.3.8. Listings

Listing 16.2.12.1: ECG: Full listing

Listing per treatment group, per subject and per time point of the ECG parameters (raw values as well as changes from baseline), flagging abnormal results. Includes ECG interpretation and morphology findings.

Population: safety.

Listing 16.2.12.2: ECG: Abnormalities listing

Listing per treatment group, per subject and per time point of all post-baseline data scored as out-of-normal-range (i.e., a QT or QTcF value > 450 ms or a QT or QTcF change > 30 ms) or post-baseline clinically significant, plus also the baseline reference time point.

Population: safety.

13.4. VITAL SIGNS

13.4.1. Available Data

Available parameters: heart rate, respiratory rate, diastolic and systolic blood pressure, temperature and weight.

13.4.2. Baseline and Change from Baseline

The baseline value will be the last nonmissing value prior to first dosing. Baseline will be determined per vital signs parameter individually. It is recognized that baseline parameters may thus come from more than one vital signs reading.

The change from baseline will be calculated for all post-baseline time points as:

Change from baseline at time point t = value at time point t – baseline value.

13.4.3. Normal Ranges

Parameter (unit)	Normal range	
	Lower limit	Upper limit
Pulse (bpm)	40	100
DBP (mmHg)	45	90
SBP (mmHg)	90	150
Temperature (°C)	35.5	37.5
Respiratory rate, breaths/min	12	16

Values equal to the boundaries are still considered normal (N). A value is classified as abnormally low (L) when the value < lower limit of the normal range. A value is classified as abnormally high (H) when the value > upper limit of the normal range.

13.4.4. Worst-Case Abnormality

Derived per parameter separately.

All nonmissing post-baseline values (including unscheduled measurements and follow-up measurements) will be used to derive the following worst-case:

- H = abnormally high:
  at least one post-baseline measurement is above the normal range, and there are no values below the normal range.
- L = abnormally low:
  at least one post-baseline measurement is below the normal range, and there are no values above the normal range.
- H+L = abnormally high and low:

at least one post-baseline measurement is above the normal range, and at least one other post-baseline measurement is below the normal range.

– N = normal:
all post-baseline measurements are within or equal to normal limits.

13.4.5. Tables

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

Table 14.3.4.1: Vital signs: Descriptive statistics of the actual values per time point

Descriptive statistics of the actual values per test and unit, treatment group and time point.

Population: safety.

Table 14.3.4.2: Vital signs: Descriptive statistics of the changes from baseline per time point

Descriptive statistics of the changes from baseline per test and unit, treatment group and time point. The actual value at baseline will also be presented in this table.

Population: safety.

Table 14.3.4.3: Vital signs: Shift table according to the normal range per time point

Shift table per test, treatment group and time point. The table will present the shift in abnormality (L/N/H) at each post-baseline time point (including worst-case) versus the normal range at baseline (L/N/H).

Population: safety.

Table 14.3.4.4: Vital signs: Treatment-emergent abnormalities per time point

Frequency table of the treatment-emergent abnormalities per parameter, treatment group and time point (including the worst-case). A post-baseline abnormality is considered treatment-emergent if it is different from the baseline result.

Population: safety.

13.4.6. Figures

No figures are planned.

13.4.7. Listings

Listing 16.2.13.1: Vital signs: Full listing

Listing per treatment, per subject and per time point of all parameters: raw values, changes from baseline, and flagging abnormal results.

Population: safety.

Listing 16.2.13.2: Vital signs: Abnormalities listing

Listing per treatment group, per subject and per time point of all treatment emergent time points scored as out-of-normal-range or clinically significant, plus also the baseline reference time point.

Population: safety.

13.5. PULSE OXIMETRY

13.5.1. Available Data

Available parameter: arterial oxygen saturation level.

13.5.2. Baseline and Change from Baseline

The baseline is defined as the last non-missing value prior to dosing. This will normally be Day 1 (pre-dose).

The change from baseline will be calculated for all post-baseline time points as:

Change from baseline at time point t = value at time point t – baseline value.

13.5.3. Normal Ranges

Normal range applicable in seated or supine position (after 5 min):

Parameter	Lower limit of normal
Arterial Oxygen Saturation Level, SpO2	95%

Values equal to the boundary are still considered normal (N). A value is classified as abnormally low (L) when the value < lower limit of the normal range.

13.5.4. Worst-Case Abnormality

All non-missing post-baseline values (including post-baseline unscheduled measurements) will be used to derive the overall worst-case:

– L = abnormally low: at least one post-baseline measurement is below the normal range.
– N = normal: all post-baseline measurements are within normal limits.

13.5.5. Tables

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

Table 14.3.5.1: Pulse oximetry (%): Descriptive statistics of the actual values per time point

Descriptive statistics of the actual values per time point.

Population: safety.

Table 14.3.5.2: Pulse oximetry (%): Descriptive statistics of the changes from baseline per time point

Descriptive statistics of the changes from baseline (including 95% confidence interval of the mean change) per time point. The actual value at baseline (Day 1 pre-dose) will also be presented in this table.

Population: Safety.

Table 14.3.5.3: Pulse oximetry (%): Shift table according to the normal range per time point

Shift table per time point. The table will present the shift in abnormality (L/N) at each post-baseline time point (including the worst-case) versus the normal range at baseline (L/N).

Population: Safety.

Table 14.3.5.4: Pulse oximetry (%): Treatment-emergent abnormalities per time point

Frequency table of the treatment-emergent abnormalities per time point (including the worst-case). A post-baseline abnormality is considered treatment-emergent if it is different from the baseline result.

Population: Safety.

13.5.6. Figures

No figures planned.

13.5.7. Listings

Listing 16.2.14.1: Pulse oximetry (%): Full listing

Listing per treatment group, per subject and per time point of the arterial oxygen saturation level (raw values as well as changes from baseline), flagging abnormal results.

Population: Safety.

Listing 16.2.14.2: Pulse oximetry (%): Abnormalities listing

Listing per treatment group, per subject and per time point of all post-baseline time points scored as out-of-normal-range, plus also the baseline reference time point.

Population: Safety.

13.6. PHYSICAL EXAMINATIONS

Listing 16.2.15.1: Physical examinations: Abnormalities listing

Listing per treatment group, per subject and per time point of the selection of all abnormal findings.

Population: safety.

14. REFERENCES

Fridericia, L. (1920). Die systolendauer im elektrokardiogramm bei normalen menschen und bei herzkranken. 53:469-486.

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