Galápagos

STATISTICAL ANALYSIS PLAN

Project Number:	GLPG1690
Study Number:	GLPG1690-CL-202
Study Title:	Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multicenter, Exploratory Phase IIa Study to Assess Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Properties of GLPG1690 Administered for 12 Weeks in Subjects with Idiopathic Pulmonary Fibrosis (IPF).
Development Phase:	IIa
Status:	Final
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1.1. STUDY OBJECTIVES

1.1.1. Primary Objectives

- To evaluate the safety and tolerability of GLPG1690.
- To characterize the PK and PD properties of GLPG1690.

1.1.2. Secondary Objectives

- To evaluate the change from baseline in FVC.
- To explore the change in biomarkers in blood and BALF.
- To evaluate the change in FRI parameters.
- To evaluate the change in quality of life measures.

1.2. STUDY DESIGN

This study is a randomized, double-blind, parallel group, placebo-controlled, multicenter, exploratory phase IIa study to evaluate the safety, tolerability, PK, and PD of GLPG1690 in subjects with IPF. In addition, several exploratory assessments will be performed. Male and female subjects of non-child-bearing potential with a confirmed diagnosis of IPF aged 40 years or older will be screened to determine eligibility as per the inclusion and exclusion criteria. The screening period will be up to 4 weeks.

Written informed consent must be obtained before any study-related procedures take place. During the screening period, following signing of the informed consent form (ICF), the subject's historical HRCT and surgical lung biopsy (SLB; if available) will be sent to central review for the confirmation of the IPF diagnosis through a:

- central review of the chest HRCT,
- central review of the SLB (if available).

Note that both the chest HRCT and SLB need to be sent to central review at least 8 days prior to the baseline visit to allow for central reading and confirmation of IPF diagnosis.

At baseline, after the subject's eligibility for the study has been confirmed, subjects will be randomized in a 3:1 ratio to GLPG1690 600 mg q.d. or matching placebo administered for 12 weeks.

The subjects will visit the clinical study center at screening (Day -28 to Day -4), Day -1 (baseline), Week 1 (Day 7), Week 2 (Day 14), Week 4 (Day 28), Week 8 (Day 56), and Week 12 (Day 84) or the early discontinuation visit (EDV). In addition, a follow-up visit will be planned 2 weeks after the last administration of study drug (Week 14 [Day 98]). Each subject will be in the study for up to approximately 18 weeks (from screening to follow-up). The end of the study (EOS) will be defined as the last contact with the last subject in the study.

The assessments performed at each visit are detailed in the study flow chart.

To enhance the safety and integrity of the study data, an independent medical safety review will be implemented.

1.3. CLINICAL STUDY PROTOCOL (CSP) AND CSP AMENDMENTS

Protocol Versions	Date (ddMMMyyyy)
Final	16OCT2015

Protocol Amendments	Date (ddMMMyyyy)
Italy Country Specific Amendment	21APR2016
General Amendment I	19DEC2016

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

1.4. FLOWCHART

EVENT			DOSING PERIOD						EDV	FU
Visit	Visit 1 Screening	Visit 2 Baseline		Visit 3 [1] W1	Visit 4 [1] W2	Visit 5 [1] W4	Visit 6 [1] W8	Visit 7 [1] W12		Visit 8/ EOS W14
Study days (D)	D-28 to D-4	D-1	D1	D7 ±2 days	D14 ±2 days	D28 ±3 days	D56 ±3 days	D84 ±3 days		D98 ±3 days
Informed consent	X									
Historical HRCT sent to central review [2]	X									
SLB sent to central review [2, 3]	X									
Demographics	X									
Medical history/Concurrent illnesses	X									
Inclusion/exclusion criteria	X									
Serology	X									
FSH test [4]	X									
DLCO	X									
Confirm all eligibility criteria		X								
Randomization		X								
Dispense study drug		X		X	X	X	X			

[1] Subjects will be asked to come to the study center in the morning at approximately the same time on every visit.
[2] The HRCT and SLB need to be sent to central review at least 8 days prior to the baseline visit to allow for central reading and confirmation of diagnosis.
[3] If available.
[4] Only at screening in case there is doubt on whether a female subject is postmenopausal.

EVENT			DOSING PERIOD						EDV	FU
Visit	**Visit 1 Screening**	**Visit 2 Baseline**		**Visit 3 [1] W1**	**Visit 4 [1] W2**	**Visit 5 [1] W4**	**Visit 6 [1] W8**	**Visit 7 [1] W12**		**Visit 8/ EOS W14**
Study days (D)	**D-28 to D-4**	**D-1**	**D1**	**D7 ±2 days**	**D14 ±2 days**	**D28 ±3 days**	**D56 ±3 days**	**D84 ±3 days**		**D98 ±3 days**
Collect study drug				X	X	X	X	X	X	
Study drug intake [5]			*On a daily basis*							
Check study drug accountability and compliance				X	X	X	X	X	X	
Diary card dispensing		X		X	X	X	X			
Diary card collection				X	X	X	X	X	X	
Clinical laboratory tests [6]	X	X		X	X	X	X	X	X	X
Vital signs [7]	X	X		X	X	X	X	X	X	X
Physical examination [8]	X	X		X	X	X	X	X	X	X
12-Lead ECG [9]	X			X	X	X	X	X	X	X
PK blood samples[10]		X		X	X	X	X	X	X	X

[5] Subjects will begin to take treatment the morning following randomization (*i.e.*, on Day 1). Study drug intake at Visits 3, 4, 5, 6, and 7 will take place at the study center after all pre-dose assessments have been performed.
[6] Clinical laboratory tests include hematology, serum/plasma chemistry, coagulation, and urinalysis.
[7] Vital signs include blood pressure, respiratory rate, heart rate, and oral temperature.
[8] Height and weight will be measured at screening only.
[9] A 12-lead ECG will be performed after the subject has been in supine position for at least 5 minutes.
[10] All PK samples will be taken pre-dose. At Day 28, in addition to pre-dose, samples will be taken 1.5h, 4h, and 6h post-dose.

EVENT			DOSING PERIOD						EDV	FU
Visit	**Visit 1 Screening**	**Visit 2 Baseline**		**Visit 3 [1] W1**	**Visit 4 [1] W2**	**Visit 5 [1] W4**	**Visit 6 [1] W8**	**Visit 7 [1] W12**		**Visit 8/ EOS W14**
Study days (D)	**D-28 to D-4**	**D-1**	**D1**	**D7 ±2 days**	**D14 ±2 days**	**D28 ±3 days**	**D56 ±3 days**	**D84 ±3 days**		**D98 ±3 days**
PD blood samples [11] (LPA)		X				X		X	X	X
Biomarker blood samples [12]		X				X		X	X	X
BALF sample (bronchoscopy)		X						X	X [13]	
Spirometry [14]	X	X		X	X	X	X	X	X	X
Home-based spirometry		X	*On a daily basis*							
SGRQ		X				X		X	X	X
HRCT [15]		X						X	X	
(S)AE assessment	*Throughout the study*									
Concomitant medications	*Throughout the study*									

AE=adverse event; BALF=bronchoalveolar lavage fluid; D=day; DLCO= diffusing capacity for the lungs for carbon monoxide; ECG=electrocardiogram; EDV=early discontinuation visit; EOS=end of study; FU=follow-up; FRI=functional respiratory imaging; FSH=follicle stimulating hormone; HRCT=high-resolution computed tomography; LPA=lysophosphatidic acid; PD=pharmacodynamics; PK=pharmacokinetic; SAE=serious adverse event; SGRQ=St George's Respiratory Questionnaire; SLB=surgical lung biopsy; W=week.

[11] All PD samples will be taken pre-dose. At Day 28, in addition to pre-dose, samples will be taken 1.5h and 6h post-dose.
[12] All blood samples will be collected pre-dose.
[13] If feasible for the subject.
[14] All spirometry evaluations should be performed prior to administration of bronchodilator.
[15] To measure FRI parameters. During the baseline visit an additional scan of the upper airway will be taken.

2. ANALYSIS POPULATIONS

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

2.1. ALL SCREENED SUBJECTS

All subjects who signed an ICF.

2.2. ALL RANDOMIZED SUBJECTS

All subjects randomized into the study.

2.3. SAFETY ANALYSIS SET

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

In case a particular subject would be unblinded (e.g., in case of an SAE), all safety data of this subject recorded in the database will still be included in the safety analysis.

2.4. PHARMACOKINETICS ANALYSIS SET

All randomized subjects who received at least one dose of GLPG1690 and for whom evaluable PK data were available. Subjects with a protocol deviation that may impact the PK results will be excluded from this population.

2.5. PHARMACODYNAMICS ANALYSIS SET

All randomized subjects who have at least one dose of study drug and have at least one post-baseline assessment with PD data.

2.6. INTENT TO TREAT ANALYSIS SET

All randomized subjects who received at least one dose of study drug and have at least one post-baseline assessment with exploratory endpoint data.

In case a particular subject would be unblinded (e.g., in case of an SAE), all efficacy data of this subject up to the point of unblinding will still be included in the ITT analysis. Recorded efficacy data from the moment of unblinding onwards will be disqualified from the analysis. Such data will still be part of the listings, but will be labeled as use=no. Missing data after the moment of unblinding will be imputed using the same rules as used for other subjects.

3. TREATMENT GROUPS

3.1. RANDOMIZED VERSUS ACTUAL TREATMENT

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

For safety and PK parameters, the treatment that was actually used during most of the time (i.e., >50% of the duration of intakes) 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:

- Placebo q.d.
- GLPG1690 600 mg q.d.

3.3. TOTALS OVER GROUPS

A total over all groups will be presented for the general part of the analysis, but not for the other parts (PK, PD, efficacy and safety). Totals will only be shown on tables, but not on listings or 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 the first study drug intake date, 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, concomitant medication).

Analysis period	Start period	End Period
Screening	Date of signing the ICF	First treatment administration date - 1 day
Treatment	First treatment administration date	Study termination date

Note that the last analysis period in case of early termination will always be ended by the study termination date (date of last contact, as recorded in the eCRF).

In the analysis, the analysis periods will be replaced by the actual treatment taken during the period (see section 3.1).

4.3. ALGORITHM OF ALLOCATING VISITS TO TIME WINDOWS

All visits (including early termination visits and 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:

Time point label	Target day	Interval lower bound	Interval upper bound
Screening[3]	NA[4]	NA[4]	NA[4]
Baseline[1]	NA[4]	NA[4]	1
Week 1	7	2	10
Week 2	14	11	20
Week 4	28	21	41
Week 8	56	42	69
Week 12	84	70	97
>Week 12[2]	NA[4]	98	+∞
Follow-up[3]	2 weeks after last visit	NA[4]	NA[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. If the baseline is on the same day of the first study drug intake we assume that the assessments were done before.
[2] Visits falling really late in the study (relative day > 98; excluding the follow-up visit) will be allocated to a "> Week 12" interval, and will not be shown in tables or figures, but will only be listed.
[3] For the screening and follow-up visits, no time window is defined. The visit as recorded in the eCRF will be used.
[4] NA = Not applicable

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 non-selected 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 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 non-missing pre-dosing value will be used. This is normally the scheduled baseline itself. A missing scheduled baseline value will be imputed with the last non-missing value of a preceding pre-dosing visit. This can be a screening visit or an unscheduled visit prior to the first dose of study drug. 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 date 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 visit will be duplicated in the derived dataset. 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" in the derived dataset. The imputed baseline will be presented in the tables. In the listings, the original unscheduled data will be shown and flagged as "reference" visit.

5. HANDLING OF DATA

5.1. CALCULATION OF DESCRIPTIVE STATISTICS

For continuous parameters, descriptive statistics will be presented when N≥2. When N=1, the observation will not be shown in the table/figure but only in the listing(s). Same holds for summary graphs.

Descriptive statistics will include at least the following:

- The number of non-missing 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 and derived PK parameters, descriptive statistics will include:

- The number of non-missing data points (N)
- The number of data points above the limit of quantification (GLPG1690 plasma concentrations only)
- 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%)
  $= 100 \times \sqrt{e^{(standard\ deviation\ of\ ln-transformed\ data)^2} - 1}$

Notes:

- Since a high proportion of BLOQ (<LLOQ) values may affect the statistics; if more than 50% of values are imputed or non-missing results, then only the arithmetic mean will be calculated for that time point. The other descriptive statistics will be listed as "NC" (not calculated).
- If the calculated mean is less than LLOQ, then it will be presented as BLOQ. The minimum will be "BLOQ", and the maximum will be derived from the actual data.

- The plasma concentrations will be presented with 3 significant digits in the original concentration unit. PK 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.
- In listings, BLOQ will be presented for all values of <LLOQ and a value of LLOQ added to a footnote.

5.2. CALCULATION OF PERCENTAGES

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

Imputed missing values are no longer considered to be missing values.

5.3. CATEGORIZATION OF CONTINUOUS PARAMETERS

When a continuous parameter (eg age) is also categorized to be presented in a frequency table, discrepancies can arise because of rounding. To prevent this, the rounding will be done first on the continuous parameter. This rounded continuous parameter will be used for the descriptive statistics and will also be used for the categorization.

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

5.4.1. Safety and Efficacy 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".

5.4.2. PK Data

The lower limit of quantification (LLOQ) will be X.XX <unit>.

Concentration summaries:

- Prior to calculation of summary statistics: any individual values less than lower limit of quantification (<LLOQ) will be replaced with zero for the calculation of descriptive statistics except for geometric mean and geometric CV where it will be imputed by LLOQ/2 and listed as "BLOQ".

During calculation of PK parameters:

- Any BLOQ (<LLOQ) values that occur before the first quantifiable concentration will be replaced with zero for the calculation of descriptive statistics except for geometric mean and geometric CV where it will be imputed by LLOQ/2 and listed as "BLOQ".
- If a BLOQ (<LLOQ) value occurs after a quantifiable concentration in a profile and is followed by a value of LLOQ or above, the quantifiable time point will be treated as 'missing'.

- If two BLOQ (<LLOQ) values occur in succession, the profile will be deemed to have terminated at the final quantifiable concentration and subsequent LLOQ or above values will be treated as 'missing'.

For individual pharmacokinetic profiles/plots:

- A 'missing' value will be substituted for any BLOQ (<LLOQ) irrespective of where they are in the profile and the plasma concentration-time data will be plotted as such, except for the pre-dose were it should be replace by zero.

Mean concentration profiles/plots:

- When estimating the mean value for the concentration at a given time point (descriptive mean curve), the following guidelines should be considered: the mean value at a time with one or more BLOQ (<LLOQ) values will be calculated by assigning zero. If the calculated mean value is less than LLOQ of the assay, then that time point will be plotted as zero in the mean pharmacokinetic profiles.

5.4.3. PD Data

Values below the quantification limit will be imputed by 0 and listed as "BLOQ".

5.5. HANDLING OF MISSING DATA

5.5.1. Handling of Missing Values and Early Dropouts in the General, Safety and PK Analyses

No imputation is done of missing values or missing visits. The analysis will be observed-case only, except for the following PK analyses:

- Missing Week 4 pre-dose plasma concentrations will be imputed by the concentration values found at Week 2 pre-dose (assuming that steady state will be reached after 2 weeks dosing).
- Week 4 24h post-dose plasma concentrations will be imputed using the Week 4 pre-dose values, in order to complete the full dosing interval PK profile (of 24 hours).

5.5.2. Handling of Missing Values and Early Dropouts in the Exploratory Efficacy and PD Analyses

Missing visits as well as early dropouts will be imputed using the last observation carried forward (LOCF) algorithm. So to impute a missing value, the last preceding non-missing value will be used (which could even be a baseline value).

Note that for spirometry parameters, data excluded because of a poor quality grading (cf. section 9.1.1) will be imputed following the rules defined above.

And note that missing post-dose (week 4 1.5h and 6h) PD (LPA in blood) data won't be imputed.

For all parameters, an observed-case (OC) analysis will also be performed (i.e., without any imputation).

5.5.3. Handling of Missing Date or Partially Known Date

Unless specified otherwise, no imputation will be done of missing date fields, or of the missing parts of partially known date fields. When needed, a worst-case selection will be made. Such worst-case selection rules are elaborated in the specific sections.

5.6. HANDLING OF OUTLIERS

All measured values will be included in the analyses.

For the (specific) airway resistance at FRC and TLC in the FRI data (section 9.4), outliers can occur that are real values but affect the model estimates extremely. In these cases, values that are larger than the third quantile + 3 times the interquartile range may be removed. Infinite values for resistance are possible and these will be listed, but will be removed from the data before statistical analysis.

5.7. HANDLING OF SECONDS IN DATE(TIME) FIELDS

If a date(time) 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 9.2 (or higher) will be used for programming ([redacted]

Phoenix WinNonLin version 6.4 (or higher) will be used for PK derivations ([redacted]

The statistical analysis and visualization of the FRI parameters will be implemented in R version 3.2.5 (or higher) (The R Foundation for Statistical Computing, Vienna, Austria) ([redacted]

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)

The following [redacted] STAT SOPs will be followed:

- CI502: Preparation of Statistical Analysis Plan and Documentation of Statistical Methods
- CI503: Determination Of Analysis Sets
- CI504: Programming Specifications for Analysis Data Sets
- CI505: Verification Of Statistical Programs And Outputs
- CI510: Unblinding of Clinical Trials

The following [redacted] PK work instructions will be followed:

– WBS003: Creation and Verification of Data Sets for Pharmacokinetic Analysis

6.3. FORMATS

Because the locked data is in CDISC SDTM format, the derived data will be following CDISC ADaM version 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 be presented and will display the number of observations, mean, standard error (SE), median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data. In addition to tabulated descriptive statistics, graphical data displays may be used to summarize the data. Unless otherwise noted, inferential statistics will be interpreted at the 2-sided 5% level. Data will be pooled across centers and countries.

7.1.2. Analyses of Demographics and Baseline Characteristics

Subject disposition (including reasons for early discontinuation), protocol deviations, demographics, baseline characteristics, medical history, will be presented descriptively.

Use of study drug and concomitant medications will also be presented descriptively.

7.1.3. Exploratory Efficacy Assessments

Exploratory endpoint data at each post-dosing visit will be analyzed descriptively. Comparison between GLPG1690 and the placebo group will be done exploratively.

Analysis methods:

– Continuous parameters will be analyzed using descriptive statistics of actual values, changes from baseline, and percent changes from baseline. GLPG1690 and placebo will be compared using an ANCOVA model on the changes from baseline, with the following covariates: disease severity (baseline %FVC, screening %DLCO), age, gender, treatment group, country, and baseline value. Within-group comparisons of each visit versus baseline will be investigated using a paired t-test.

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

– Additional exploratory analyses and graphical presentations may be performed when deemed useful to better understand the data.

7.1.4. Pharmacokinetic Analyses

Descriptive statistics will be calculated for the plasma concentrations and PK parameters. Mean (± SE) concentration-time profile will be generated.

Individual subject GLPG1690 concentrations and PK parameters will be listed.

7.1.5. Pharmacodynamic Analyses

In blood, LPA C18:2 species peak area ratio will be used to calculate the percentage reduction versus baseline. Baseline will be the average of the pre-dosing duplicates (pre-dose sample from Day -1).

The percentage reduction from baseline will be calculated as follows:

% reduction = 100-(100 x visit/baseline)

PD data will be summarized descriptively per treatment and per time point.

Individual and mean absolute values, individual and mean % reduction from baseline over time plots will be generated.

The AUEC (area under the effective-time curve) as well as E_{max} (maximum % reduction from baseline) on Day 28 will be determined from individual effect time profiles.

Absolute values, % reduction from baseline, AUEC and E_{max} will be compared between the treatment groups using an analysis of covariance (ANCOVA) model with the following covariates: disease severity (baseline FVC, screening DLCO), age, gender, treatment group, country, and baseline value.

Within-group comparisons of PD marker level obtained (absolute values and % reduction from baseline) on Day 28 pre-dose, 1.5h and 6h post-dose, and on Day 84 pre-dose, versus baseline will be investigated using a paired t-test.

The analysis will be performed for the LPA C18:2 species. Other LPA species might be analyzed if deemed appropriate.

In BALF, data for all LPA species detectable will be used for the analysis. LPA species peak area ratio will be used to calculate the percentage reduction from baseline. Baseline will be the average of the pre-dosing duplicates (pre-dose sample from Day -1).

7.1.6. Pharmacokinetic / Pharmacodynamic and Pharmacokinetic / Exploratory Efficacy Correlations

Individual and/or mean ± SE, safety, PD, exploratory efficacy endpoint, and/or GLPG1690 plasma concentrations may be plotted against one another.

PK/PD, PK/exploratory efficacy endpoint and safety correlation will be explored between GLPG1690 concentrations or PK parameters and selected exploratory PD or safety endpoints, but only if the latter are significantly altered by the treatment.

Exploratory safety/PK/PD/exploratory efficacy endpoint analyses may be added when deemed useful to better understand the collected data.

7.1.7. Analyses of Safety Data

A descriptive analysis of the TEAEs, laboratory assessments, 12-lead ECG, and vital signs will be performed. Changes from baseline and shifts according to normal ranges will be presented as well.

Physical examination results will be listed only.

AEs will be fully described and coded according to the Medical Dictionary for Regulatory Activities Dictionary.

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

7.2.1. Changes before Database Lock

For FRI parameters, the comparison between GLPG1690 and the placebo group will only be done for 2 zones (lower lobes and upper lobes separately). These analyses will be performed using an ANCOVA model (like the other efficacy parameters) instead of a mixed effects ANCOVA model (the regional nature of the data being discarded).

And the FRI data being mostly not normally distributed and being measured on a regional scale, more complex additional exploratory analyses (models with extra covariates, nested random factors, interaction terms…) may be needed to better understand the data.

7.2.2. Changes after Database Lock

None

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, populations, country and site.

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

Population: all randomized subjects.

Table 14.1.1.1: Subject disposition: Tabulation by country and investigator

Tabulation per treatment group (and overall) of the number of subjects in each of the countries and sites.

Population: safety.

Table 14.1.1.2: 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 14.1.1.3: Subject disposition: No-treatment subjects: Tabulation of the reasons

Tabulation of discontinuations and the reasons for discontinuation.

Population: all screened subjects, minus the safety population (so selecting only subjects who were never exposed to the study drug: subjects either never randomized or randomized but not exposed).

Table 14.1.1.4: Subject disposition: Tabulation of the number of subjects at each time interval

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

Population: safety.

Listing 16.2.1.2: Subject disposition: Number of days in study

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

Population: safety.

Table 14.1.1.5: Subject disposition: First and last date in the study

List the following (overall, not per subject):

- Date of the first signature on study ICF.
- Date of first and last screening visit.
- 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 subjects.

Table 14.1.1.6: Subject disposition: Tabulation of the study termination reasons

Tabulation per treatment group (and overall) of completion/discontinuations and the reasons for discontinuation.

Population: safety.

Listing 16.2.1.3: 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 treatment administration at study termination. In case the discontinuation was due to AE, the AE verbatim 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.

8.2. PROTOCOL DEVIATIONS AND ELIGIBILITY

Protocol deviations are determined and recorded whilst the study is ongoing, and the list is finalized prior to database lock (and unblinding). All deviations are classified as either "major" or "minor". For more details, please refer to the Protocol Deviation Plan.

Table 14.1.2.1: Protocol deviations: Tabulation

Tabulation per treatment group (and overall) of the protocol deviations categories (each scored as major / minor).

Tabulation per treatment group (and overall) of the major protocol deviations.

Population: safety.

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. These are criteria as ticked by the investigator in the eCRF (not from the protocol deviations list, though eligibility violations will also be listed in the protocol deviations).

Population: safety.

8.3. SUBJECTS EXCLUDED FROM ANALYSIS

Listing 16.2.3.1: Subjects excluded from the safety analysis

Listing of all subjects that were randomized and/or 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, minus the safety population.

Listing 16.2.3.2: Subjects excluded from the 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, minus the ITT population.

Listing 16.2.3.3: Subjects excluded from the PD analysis

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

Population: safety, minus the PD population.

8.4. DEMOGRAPHICS AND BASELINE 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
- Age categories:
  [40,50[years
  [50,60[years
  [60,70[years
  ≥ 70 years
- Date of birth: only listed
- Date of signing the ICF: only listed
- Race
- "Other" race: only listed
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index BMI = (weight in kg) / (height in m)² (kg/m²): 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 categories:
  ≤ 18.5 kg/m²
  ]18.5,25.0] kg/m²
  ]25.0,30.0[kg/m²
  ≥ 30.0 kg/m²
- Alcohol status: never / current / former
- Smoking status: never / current / former
- Alcohol and smoking status details: only listed
- Female of child-bearing potential: yes / no, no: surgically sterile / post-menopausal
- Female of child-bearing potential: birth control methods details: 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).

Population: safety.

Listing 16.2.4.1: Demographic data

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

Population: safety.

Listing 16.2.4.2: Alcohol and smoking status

Listing per treatment group and per subject of all details on alcohol and smoking status.

Population: safety.

Listing 16.2.4.3: Birth control methods

Listing per treatment group and per subject of all details on birth control methods.

Population: safety, women of childbearing potential only.

Table 14.1.3.2: Baseline laboratory data: Tabulation of abnormalities

Frequency tabulation per lab test per treatment group (and overall) of the baseline result, categorized as low / normal / high according to the normal ranges (see section 13.2.5).

Population: safety.

Table 14.1.3.3: Baseline ECG data: Tabulation of abnormalities

Frequency tabulation per parameter (QT and QTcF) per treatment group (and overall) of the baseline result, categorized as (same as in section 13.3.5):

- $\leq$ 450 ms
-]450,480] ms
-]480,500] ms
- > 500 ms

Population: safety.

Table 14.1.3.4: Baseline vital signs data: Tabulation of abnormalities

Frequency tabulation per parameter and per treatment group (and overall) of the baseline result, categorized as low / normal / high according to the normal ranges (see section 13.4.4).

Population: safety.

Table 14.1.3.5: Baseline physical examination: Tabulation of abnormalities

Frequency tabulation per CRF body system and per treatment group (and overall) of the baseline result, categorized as normal / abnormal

Population: safety.

8.5. BASELINE DISEASE CHARACTERISTICS

8.5.1. Parameters

- Duration of IPF (years) = $\frac{\text{(date of signing the ICF)} - \text{(date of initial diagnosis of IPF)}}{365.25}$, rounded to the first decimal. 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
- Duration of IPF, categorized as:
  < 0.5 year
  [0.5,1[year
  [1,2[years
  ≥ 2 years
- Date of initial diagnosis: only listed
- Number of IPF exacerbations within 6 weeks prior to screening
- Absolute decline in FVC within the last 6 months:
  < 5%
  5-10%
  > 10%
  Unknown
- Relative decline in FVC > 10 within last 6 months:
  Yes
  No
  Unknown
- Absolute decline in DLCO within the last 6 months:
  ≤ 15%
  > 15%
  Unknown
- Screening DLCO, % predicted of normal
- Screening DLCO, corrected for hemoglobin
- Screening and baseline FVC
- Change in FVC: baseline - screening*
- Screening and baseline %FVC
- Screening and baseline %FVC, categorized as:
  < 50 %
  [50,70[%
  [70,90[%
  ≥ 90 %
- Change in %FVC: baseline - screening*

*only calculated if the baseline value has not been imputed by the screening value.

8.5.2. Analysis

Table 14.1.3.6: Screening and baseline disease characteristics

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

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

Population: safety.

Listing 16.2.4.4: Screening and baseline disease characteristics

Listing per treatment group and per subject of all disease characteristics.

Population: safety.

Table 14.1.3.7: Prior and concomitant allowed IPF treatment

Tabulation per treatment group and overall of prior IPF medications.

No formal comparison of the two treatment groups planned.

Population: safety.

Listing 16.2.4.5: Prior and concomitant allowed IPF treatment

Listing per treatment group and per subject.

Population: safety.

8.6. MEDICAL HISTORY AND CONCURRENT DISEASES

Table 14.1.3.8: Medical history: Tabulation

Frequency tabulation per treatment group (and overall) of the system organ classes and preferred terms, selecting only the medical history findings (i.e., condition no longer present at the start of the study).

Population: safety.

Table 14.1.3.9: Concurrent diseases: Tabulation

Frequency tabulation per treatment group (and overall) of the system organ classes and preferred terms.

Population: safety.

Listing 16.2.4.6: 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 16.2.4.7: 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 study drug intake in case the non-missing 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.

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 drug 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 drug.

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

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

Stop day

= (Therapy stop date) – (date of first study drug 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 drug.

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

= (Study termination date) – (date of first study drug 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. In the table(s), the generic term will be used. 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 14.1.3.10: Prior therapies: Frequency table

Frequency tabulation per treatment group (and overall) of the ATC classes (level 2) and generic terms, of "prior" and "prior+concomitant" therapies only.

These are all the therapies that were used before the first intake of study drug.

Population: safety.

Table 14.1.3.11: Concomitant therapies: Frequency table

Frequency tabulation per treatment group (and overall) of the ATC classes (level 2) and generic terms, selecting "concomitant" and "prior+concomitant" therapies only.

These are all the therapies that were used during the study, concomitantly to the study drug.

Population: safety.

Table 14.1.3.12: Post-treatment therapies: Frequency table

Frequency tabulation per treatment group (and overall) of the ATC classes (level 2) and generic terms, selecting "post-treatment" therapies only.

These are all the therapies that were used during the study, but started after the last dose of study drug.

Population: safety.

Listing 16.2.4.8: Prior and concomitant therapies

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

Population: safety.

8.8. EXPOSURE TO STUDY DRUG AND COMPLIANCE

8.8.1. Derivations

Derived parameters:

- Total treatment duration (days) = (last study drug intake date – first study drug intake 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 morning dose > 0 capsules.
- Percentage days with an intake = $100\% \times \left(\frac{\text{total treatment duration,excluding days off drug}}{\text{total duration}}\right)$
- Total compliant treatment duration (days): sum of all durations (last – first +1) in the drug log pages where there is a morning dose with exactly 3 capsules.
- Percentage compliance = $100\% \times \left(\frac{\text{total compliant treatment duration}}{\text{total duration}}\right)$

The "total duration" used as denominator in the above formulae equals: (date of Week 12 visit or early termination visit) – (date of first study drug intake) + 1.

8.8.2. Analysis

Table 14.1.4.1: Use of study drug: Descriptive statistics

Descriptive statistics per treatment group (and overall) of the total treatment duration (days) and the overall compliance (%).

Frequency tabulation per treatment group (and overall) of the two treatment duration parameters, categorized in weeks.

Frequency tabulation per treatment group (and overall) of the days with intake and compliance, categorized as:

- < 80%,
- [80%,100%[,
- 100%,
-]100%,120%],
- > 120%.

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 study drug.

Population: safety.

Listing 16.2.5.3: Dispensed kit numbers

Listing per treatment group and per subject of all dispensed placebo/GLPG1690 kit numbers, flagging any mistakes in dispensing.

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 EXPLORATORY EFFICACY TABLES, LISTINGS AND FIGURES

9.1. PULMONARY FUNCTION BY SPIROMETRY

9.1.1. Parameters

Pulmonary function will be assessed through spirometry both performed at the study center and at home. All spirometry evaluations should be performed pre-bronchodilator*. The values will be used as available via the data transfer from [redacted].

* pre-bronchodilator is defined as:

- short-acting more than (>) 6 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)

Note that spirometry data taken post-bronchodilator will be excluded from the analysis (not applicable for home spirometry).

Note that 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

The following parameters will be measured as part of the spirometry assessment:

- Forced Expiratory Volume in 1 second (FEV1) (L) and percent predicted FEV1*
- Forced Vital Capacity (FVC) (L) and percent predicted FVC*
- FEV1/FVC ratio
- Forced expiratory flow between 25 and 75% of exhaled volume (FEF_{25-75})*

* parameters not available for home spirometry.

Spirometry parameters and derived*:

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

* daily values and weekly averages for home spirometry.

Weekly averages for home spirometry are defined as the mean of the measurements taken during 7 day weekly intervals (starting from study day 1). If there are less than 5 days of data per weekly interval, the mean will be "missing". If there is more than one measurement per day, then the worst-case will be taken (the lowest value). For the calculation of change from baseline, the baseline measurement is the corresponding baseline at study center measurement. Weekly averages for LOCF should be computed after applying LOCF for days with missing measurements.

9.1.2. Tables

Table 14.2.1.1.1: Spirometry: Descriptive statistics per time point

Descriptive statistics per parameter, per treatment group and per time point of the actual values, the changes from baseline and the percent changes from baseline. Including a 95% confidence interval of the mean changes and mean percent changes.

Population: ITT, LOCF + OC.

Table 14.2.1.1.2: %FVC: Descriptive statistics per time point by sub-groups

Descriptive statistics per treatment group and per time point of the actual values, the changes from baseline and the percent changes from baseline but split up by:

- baseline %FVC: < 50 % / [50,70[% / [70,90[% / ≥ 90 %
- screening DLCO, % predicted of normal: < 30 % / [30,40[% / [40,50[% / [50,60[% / ≥ 60 %
- age: [40,50[years / [50,60[years / [60,70[years / ≥ 70 years
- gender: male / female
- country: Ukraine / UK

Population: ITT, LOCF+OC.

Table 14.2.1.1.3: %FVC: Statistical evaluation per time point

Between-group comparison of placebo and GLPG1690: ANCOVA model on the changes from baseline with disease severity (baseline %FVC, screening %DLCO), age, gender, treatment and country as covariates*. The table will present type III p-values, LS-means per group, LS-mean difference between the two groups and a 95% confidence interval of this LS-mean difference.

* if the model does not convergence, country will be dropped.

Within-group comparisons of each visit versus baseline: paired t-test.

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

Population: ITT, LOCF+OC.

Table 14.2.1.1.4: %FVC: Frequency tabulation of the categorized actual values per time point

Frequency tabulation of the categorized %FVC per treatment group and per time point.

Population: ITT, LOCF + OC.

Table 14.2.1.1.5: %FVC: Frequency tabulation of the categorized changes from baseline per time point

Frequency tabulation of the categorized change from baseline in %FVC per treatment group and per time point.

Population: ITT, LOCF + OC.

Table 14.2.1.1.6: Home spirometry - Weekly averages: Descriptive statistics per time point

Descriptive statistics per parameter, per treatment group and per time point of the actual values, the changes from baseline and the percent changes from baseline. Including a 95% confidence interval of the mean changes and mean percent changes.

Population: ITT, LOCF + OC.

9.1.3. Figures

Figure 14.2.1.1.1: Spirometry: Subject profile plots over time

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

Population: ITT, LOCF+OC.

Figure 14.2.1.1.2: Spirometry: Mean (+/- SE) plots of the actual values over time

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

Population: ITT, LOCF+OC.

Figure 14.2.1.1.3: Spirometry: Mean (+/- SE) plots of the changes from baseline over time

Mean (with SE) plots of the changes from baseline over time, 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: ITT, LOCF+OC.

Figure 14.2.1.1.4: Spirometry: Mean (+/- SE) plots of the percent changes from baseline over time

Mean (with SE) plots of the percent changes from baseline over time, 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: ITT, LOCF+OC.

Figure 14.2.1.1.5: Home spirometry - Daily values: Subject profile plots over time

Figure 14.2.1.1.6: Home spirometry - Daily values: Mean (+/- SE) plots of the actual values over time

Figure 14.2.1.1.7: Home spirometry - Weekly averages: Subject profile plots over time

Figure 14.2.1.1.8: Home spirometry - Weekly averages: Mean (+/- SE) plots of the actual values over time

Figure 14.2.1.1.9: Home spirometry - Weekly averages: Mean (+/- SE) plots of the changes from baseline over time

Figure 14.2.1.1.10: Home spirometry - Weekly averages: Mean (+/- SE) plots of the percent changes from baseline over time

For Figures 5 and 6, Population: ITT, OC.

For Figures 7 to 10, Population: ITT, LOCF + OC.

9.1.4. Listings

Listing 16.2.6.1: Spirometry: Full listing

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

Population: ITT.

Listing 16.2.6.2: Home spirometry - Daily values: Full listing

Listing per treatment group, per subject and per day of all data related to home spirometry: use of bronchodilator, actual daily values.

Population: ITT.

Listing 16.2.6.3: Home spirometry - Weekly averages: Full listing

Listing per treatment group, per subject and per week of weekly averages: actual values, changes from baseline and percent changes from baseline.

Population: ITT.

9.2. BIOMARKERS

9.2.1. Parameters

The following exploratory biomarkers will be evaluated in blood samples:

- KL-6/Muc1
- surfactant protein A and D
- CCL18
- ATX
- MMP1, MMP7
- markers of extracellular matrix (ECM) turnover (neoepitope assays): BGM, C1M, C3M, C6M, CRPM, EL-NE and VICM

The following additional biomarkers may be analyzed in blood samples if deemed appropriate after results of the above exploratory markers have become available:

- oxydative stress: ICAM-1 and VCAM-1
- neutrophil recruitment, activation: IL8, S100A12
- other biomarkers might be analyzed if deemed appropriate (*e.g.*, serique protein, serique miRNA)

ATX will be determined in the supernatant of the BALF. Bronchoalveolar lavage (BAL) cell count (total and differential cell count for alveolar macrophage, lymphocyte, neutrophil and eosinophil) will be performed.

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

Biomarkers parameters and derived:

- Actual values
- Change from baseline (Day -1):
  change at time point t = (time point t value) – (baseline value)
- Percent change from baseline (Day -1):
  %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: Biomarkers: Descriptive statistics per time point

Descriptive statistics per type of sample (blood or BALF), per biomarker, per treatment group and per time point of the actual values, the changes from baseline and the percent changes from baseline. Including a 95% confidence interval of the mean changes and mean percent changes.

Population: ITT, LOCF + OC.

Table 14.2.1.2.2: Biomarkers: Descriptive statistics per time point by sub-groups

Descriptive statistics per type of sample (blood or BALF), per biomarker, per treatment group and per time point of the actual values, the changes from baseline and the percent changes from baseline but split up by:

- baseline %FVC: < 50 % / [50,70[% / [70,90[% / ≥ 90 %
- screening DLCO, % predicted of normal: < 30 % / [30,40[% / [40,50[% / [50,60[% / ≥ 60 %
- age: [40,50[years / [50,60[years / [60,70[years / ≥ 70 years
- gender: male / female
- country: Ukraine / UK

Population: ITT, LOCF.

Table 14.2.1.2.3: Biomarkers: Statistical evaluation per time point

Between-group comparison of placebo and GLPG1690: ANCOVA model on the changes from baseline with disease severity (baseline %FVC, screening %DLCO), age, gender, treatment, country and baseline value as covariates*. The table will present type III p-values, LS-means per group, LS-mean difference between the two groups and a 95% confidence interval of this LS-mean difference.

* if the model does not convergence, country will be dropped.

Within-group comparisons of each visit versus baseline: paired t-test.

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

Population: ITT, LOCF.

9.2.3. Figures

Figure 14.2.1.2.1: Biomarkers (in blood): Subject profile plots over time

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

Population: ITT, LOCF.

Figure 14.2.1.2.2: Biomarkers (in blood): Mean (+/- SE) plots of the actual values over time

Mean (with SE) plots of the actual values over time per biomarker, with all treatment groups on the same plot using different plot symbols. Unscheduled results will not be part of this plot.

Population: ITT, LOCF.

Figure 14.2.1.2.3: Biomarkers (in blood): Mean (+/- SE) plots of the changes from baseline over time

Mean (with SE) plots of the changes from baseline over time per biomarker, 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: ITT, LOCF.

Figure 14.2.1.2.4: Biomarkers (in blood): Mean (+/- SE) plots of the percent changes from baseline over time

Mean (with SE) plots of the percent changes from baseline over time per biomarker, 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: ITT, LOCF.

Figure 14.2.1.2.5: Biomarkers (in BALF): Distribution

Mean (with SE) per biomarker and treatment group at baseline and Week 12, with all individual results included as a scatterplot.

Population: ITT, LOCF.

Figure 14.2.1.2.6: Biomarkers: Boxplots over time

Boxplots per treatment group at baseline, weeks 4, 12 and follow-up for biomarkers in blood and at baseline and week 12 for biomarkers in BALF.

Population: ITT, LOCF.

9.2.4. Listings

Listing 16.2.6.4: Biomarkers in blood: Full listing

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

Population: ITT.

Listing 16.2.6.5: Biomarkers in BALF: Full listing

Listing per treatment group and per time point of all data related to biomarkers in BALF: actual values, changes from baseline, percent changes from baseline and also details about the lavage.

Population: ITT.

9.3. QUALITY OF LIFE: SGRQ

9.3.1. Parameters

The SGRQ is a 50-item questionnaire split into 3 domains: symptoms (assessing the frequency and severity of respiratory symptoms), activity (assessing the effects of breathlessness on mobility and physical activity), and impacts (assessing the psychosocial impact of the disease). Scores are weighted such that every domain score and the total score range from 0 to 100, with higher scores indicating a poorer health-related quality of life.

Note that before completing the questionnaire the patient will have to answer a question on his/her present health. This info will be tabulated.

The questions/items and their weights (from 0 to 100) are:

Part 1				
Q#	**I#**	**Question**	**Answer**	**Weight**
1	1	Over the past 4 weeks, I have coughed:	Most days a week	80.6
			Several days a week	63.2
			A few days a month	29.3
			Only with chest infections	28.1
			Not at all	0.0
2	2	Over the past 4 weeks, I have brought up phlegm (sputum):	Most days a week	76.8
			Several days a week	60.0
			A few days a month	34.0
			Only with chest infections	30.2

			Not at all	0.0
3	3	Over the past 4 weeks, I have had shortness of breath:	Most days a week	87.2
			Several days a week	71.4
			A few days a month	43.7
			Only with chest infections	35.7
			Not at all	0.0
4	4	Over the past 4 weeks, I have had attacks of wheezing:	Most days a week	86.2
			Several days a week	71.0
			A few days a month	45.6
			Only with chest infections	36.4
			Not at all	0.0
5	5	During the last year, how many severe or very bad unpleasant attacks of chest trouble have you had?	More than 3 attacks	86.7
			3 attacks	73.5
			2 attacks	60.3
			1 attack	44.2
			No attacks	0.0
6	6	How long did the worst attack of chest trouble last?	A week or more	89.7
			3 days or more	73.5
			1 or 2 days	58.8
			Less than a day	41.9
7	7	Over the past 4 weeks, in an average week, how many good days (with little chest trouble) have you had?	No good days	93.3
			1 or 2 good days	76.6
			3 or 4 good days	61.5
			Nearly every day was good	15.4
			Every day was good	0.0
8	8	If you have a wheeze, is it worse in the morning?	No	0.0
			Yes	62.0
Part 2				
Q#	**I#**	**Question**	**Answer**	**Weight**
9	9	How would you describe your chest condition?	The most important problem I have	83.2
			Causes me quite a lot of problems	82.5
			Causes me a few problems	34.6
			Causes me no problem	0.0
10	10	If you have ever had paid employment.	My chest trouble made me stop work altogether	88.9
			My chest trouble interferes with my work or made me change my work	77.6
			My chest trouble does not affect my work	0.0

11	11	Sitting or lying still.	False	0.0
			True	90.6
	12	Getting washed or dressed.	False	0.0
			True	82.8
	13	Walking around at home.	False	0.0
			True	80.2
	14	Walking outside on the level.	False	0.0
			True	81.4
	15	Climbing up a flight of stairs.	False	0.0
			True	76.1
	16	Climbing hills.	False	0.0
			True	75.1
	17	Playing sports or games.	False	0.0
			True	72.1
12	18	My cough hurts.	False	0.0
			True	81.1
	19	My cough makes me tired.	False	0.0
			True	79.1
	20	I get breathless when I talk.	False	0.0
			True	84.5
	21	I get breathless when I bend over.	False	0.0
			True	76.8
	22	My cough or breathing disturbs my sleep.	False	0.0
			True	87.9
	23	I get exhausted easily.	False	0.0
			True	84.0
13	24	My cough or breathing is embarrassing in public.	False	0.0
			True	74.1
	25	My chest trouble is a nuisance to my family, friends or neighbours.	False	0.0
			True	79.1
	26	I get afraid or panic when I cannot get my breath.	False	0.0
			True	87.7
	27	I feel that I am not in control of my chest problem.	False	0.0
			True	90.1
	28	I do not expect my chest to get any better.	False	0.0
			True	82.3
	29	I have become frail or an invalid because of my chest.	False	0.0
			True	89.9

	30	Exercise is not safe for me.	False	0.0
			True	75.7
	31	Everything seems too much of an effort.	False	0.0
			True	84.5
14	32	My medication does not help me very much.	False	0.0
			True	88.2
	33	I get embarrassed using my medication in public.	False	0.0
			True	53.9
	34	I have unpleasant side effects from my medication.	False	0.0
			True	81.1
	35	My medication interferes with my life a lot.	False	0.0
			True	70.3
15	36	I take a long time to get washed or dressed.	False	0.0
			True	74.2
	37	I cannot take a bath or shower, or I take a long time.	False	0.0
			True	81.0
	38	I walk slower than other people, or I stop for rests.	False	0.0
			True	71.7
	39	Jobs such as housework take a long time, or I have to stop for rests.	False	0.0
			True	70.6
	40	If I walk up one flight of stairs, I have to go slowly or stop.	False	0.0
			True	71.6
	41	If I hurry or walk fast, I have to stop or slow down.	False	0.0
			True	72.3
	42	My breathing makes it difficult to do things such as climbing up hills, carrying things upstairs, light gardening such as weeding, dancing, playing bowls or golf.	False	0.0
			True	74.5
	43	My breathing makes it difficult to do things such as carrying heavy loads, digging the garden or shovelling snow, jogging or walking at 5 miles per hour, playing tennis or swimming.	False	0.0
			True	71.4
	44	My breathing makes it difficult to do things such as very heavy manual work, running, cycling, swimming fast or playing competitive sports.	False	0.0
			True	63.5
16	45	I cannot play sports or games.	False	0.0
			True	64.8
	46	I cannot go out for entertainment or recreation.	False	0.0
			True	79.8
	47	I cannot go out of the house to do the groceries.	False	0.0
			True	81.0

	48	I cannot do housework.	False	0.0
			True	79.1
	49	I cannot move far from my bed or chair.	False	0.0
			True	94.0
17	50	Tick the statement which you think best describes how your chest affects you:	It does not stop me doing anything I would like to do	0.0
			It stops me doing one or two things I would like to do	42.0
			It stops me doing most of the things I would like to do	84.2
			It stops me doing everything I would like to do	96.7

Domain scores and total score:

- Symptoms score: questions 1-8.
- Activity score: questions 11 and 15.
- Impacts score: questions 9-10, 12-14 and 16-17.
- Total score: all questions.

Each domain score is calculated separately in three steps:

- The weights for all items with positive responses are summed.
- The weights for missed items are deducted from the maximum possible weight for each component. The weights for all missed items are deducted from the maximum possible weight for the total score.
- The score is calculated by dividing the summed weights by the adjusted maximum possible weight for that component and expressing the result as a percentage:

$$\text{Score} = 100 \text{ x} \frac{\text{summed weights from positive items in that component}}{\text{sum of maximum weights for all non-missing items in that component}}$$

The total score is calculated in similar way:

$$\text{Score} = 100 \text{ x} \frac{\text{summed weights from positive items in the questionnaire}}{\text{sum of maximum weights for all non-missing items in the questionnaire}}$$

Sum of maximum possible weights for each score:

- Symptoms: 662.5
- Activity: 1209.1
- Impacts: 2117.8
- Total: 3989.4

Note that the questionnaire requests a single response to questions 1-7, 9-10 and 17. If multiple responses are given to one of these questions then the weights for the positive responses for that question will be averaged.

In case of missing items, the following rules will be applied:

- The symptoms score will only be calculated when no more than 2 items are missing.
- The activity score will only be calculated when no more than 4 items are missing.

- The impacts score will only be calculated when no more than 6 items are missing.
- The total score will only be calculated when the 3 domain scores could be calculated.

Note that no imputation of individual missing items will be done, only the missing domain/total scores will be imputed.

SGRQ parameters and derived:

- Actual values
- Change from baseline (Day -1):
  change at time point t = (time point t value) – (baseline value)
- Percent change from baseline (Day -1):
  %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: SGRQ: Present health per time point

Frequency tabulation per treatment group.

Population: ITT, LOCF + OC.

Table 14.2.1.3.2: SGRQ: Shift table of the present health per time point

Shift table per treatment group and time point. The table will present the shift in present heath at each post-baseline time point versus the baseline.

Population: ITT, LOCF + OC.

Table 14.2.1.3.3: SGRQ: Descriptive statistics per time point

Descriptive statistics per score, per treatment group and per time point of the actual values, the changes from baseline and the percent changes from baseline. Including a 95% confidence interval of the mean changes and mean percent changes.

Population: ITT, LOCF + OC.

Table 14.2.1.3.4: SGRQ: Descriptive statistics per time point by sub-groups

Descriptive statistics per score, per treatment group and per time point of the actual values, the changes from baseline and the percent changes from baseline but split up by:

- baseline %FVC: < 50 % / [50,70[% / [70,90[% / ≥ 90 %
- screening DLCO, % predicted of normal: < 30 % / [30,40[% / [40,50[% / [50,60[% / ≥ 60 %
- age: [40,50[years / [50,60[years / [60,70[years / ≥ 70 years
- gender: male / female
- country: Ukraine / UK

Population: ITT, LOCF.

Table 14.2.1.3.5: SGRQ: Statistical evaluation per time point

Between-group comparison of placebo and GLPG1690: ANCOVA model on the changes from baseline with disease severity (baseline %FVC, screening %DLCO), age, gender, treatment, country and baseline value as covariates*. The table will present type III p-values, LS-means per group, LS-mean difference between the two groups and a 95% confidence interval of this LS-mean difference.

* if the model does not convergence, country will be dropped.

Within-group comparisons of each visit versus baseline: paired t-test.

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

Population: ITT, LOCF.

9.3.3. Figures

Figure 14.2.1.3.1: SGRQ: Subject profile plots over time

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

Population: ITT, LOCF.

Figure 14.2.1.3.2: SGRQ: Mean (+/- SE) plots of the actual values over time

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

Population: ITT, LOCF.

Figure 14.2.1.3.3: SGRQ: Mean (+/- SE) plots of the changes from baseline over time

Mean (with SE) plots of the changes from baseline over time, 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: ITT, LOCF.

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

Mean (with SE) plots of the percent changes from baseline over time, 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: ITT, LOCF.

9.3.4. Listings

Listing 16.2.6.6: SGRQ: Original items

Listing per treatment group, per subject and per time point of the raw individual 50 items.

Population: ITT.

Listing 16.2.6.7: SGRQ: Scores

Listing per treatment group, per subject and per time point of the total score and the 3 domain scores (raw, change, %change).

Population: ITT.

9.4. FUNCTIONAL RESPIRATORY IMAGING

9.4.1. Parameters

High-Resolution Computed Tomography (HRCT) scans will be used to generate Functional Respiratory Imaging (FRI) measurements. In case the subject is on bronchodilators, he/she can use the bronchodilator after the spirometry but prior to HRCT for FRI parameters. The values will be used as available via the data transfer from [redacted] (and will be analyzed [TLFs] by [redacted]

The following FRI parameters will be evaluated:

- (Predicted) lobar volumes at Functional Residual Capacity (FRC) and Total Lung Capacity (TLC)
- Trimmed and untrimmed (specific) airway volumes at FRC and TLC
- (Specific) airway resistance at FRC and TLC
- Low attenuation or emphysema score at TLC
- Blood vessel density or fibrosis score at TLC
- (Specific) airway wall thickness at TLC
- Air trapping at FRC
- Mass of deposited particles per defined airway section

In different zones:

- Right upper lobe (RUL)
- Right middle lobe (RML)
- Right lower lobe (RLL)
- Left upper lobe (LUL)
- Left lower lobe (LLL)
- Upper lobes (UL = combination of RUL, RML and LUL)
- Lower lobes (LL = combination of RLL and LLL)
- Central region (for airway related parameters)
- Distal region (for airway related parameters)
- Peripheral region (for particle related parameters)

– Total region

For the deposited particles, the 7 first zones instead of being splitted in a distal and peripheral region are considered combined.

FRI parameters and derived:

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

9.4.2. Tables

Table 14.2.1.4.1: FRI: Descriptive statistics per time point

Descriptive statistics per parameter, per zone, per treatment group and per time point of the actual values, the changes from baseline and the percent changes from baseline. Including a 95% confidence interval of the mean changes and mean percent changes.

Population: ITT, LOCF + OC.

Table 14.2.1.4.2: FRI: Descriptive statistics per time point by sub-groups

Descriptive statistics per parameter, per zone (lower and upper lobes only), per treatment group and per time point of the actual values, the changes from baseline and the percent changes from baseline but split up by:

– baseline %FVC: < 50 % / [50,70[% / [70,90[% / ≥ 90 %
– screening DLCO, % predicted of normal: < 30 % / [30,40[% / [40,50[% / [50,60[% / ≥ 60 %
– age: [40,50[years / [50,60[years / [60,70[years / ≥ 70 years
– gender: male / female
– country: Ukraine / UK

Population: ITT, LOCF.

Table 14.2.1.4.3: FRI: Statistical evaluation per time point

Between-group comparison of placebo and GLPG1690: ANCOVA model on the changes from baseline with disease severity (baseline %FVC, screening %DLCO), age, gender, treatment, country and baseline value as covariates*. The table will present type III p-values, LS-means per group, LS-mean difference between the two groups and a 95% confidence interval of this LS-mean difference.

* if the model does not convergence, country will be dropped.

Within-group comparisons of each visit versus baseline: paired t-test.

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

Population: ITT, LOCF.

Note: to be done for the lower and upper lobes only (and separately).

9.4.3. Figures

Figure 14.2.1.4.1: FRI: Mean plots

Mean (with SE) bar chart per treatment group at baseline and Week 12. For each parameter and zone.

Population: ITT population, LOCF.

9.4.4. Listings

Listing 16.2.6.8: FRI: Full listing

Listing per treatment group, per subject and per time point of all data related to FRI: use of bronchodilator, zone, actual values, changes from baseline and percent changes from baseline.

Population: ITT.

10. DEFINITIONS OF PHARMACOKINETICS ANALYSIS TABLES, LISTINGS AND FIGURES

10.1. PARAMETERS

Compound:

– GLPG1690

Time points:

– PK pre-dose samples are collected at each visit – i.e. Weeks 1, 2, 4, 8 and 12
– At Week 4, PK samples are collected at pre-dose and 1.5h, 4h, 6h post-dose

Derived PK parameters:

– C_{max}^{*}, C_{τ}, $AUC_{0-\tau}^{*}$, t_{max}^{*}

* week 4 only

Parameter name	Definition	Units
C_{max}	Maximum observed plasma concentration	µg/mL
C_{τ}	Trough plasma concentration (just before the next dosing i.e. pre-dose sample)	µg/mL
$AUC_{0-\tau}$	Area under the plasma concentration-time curve from time 0 to time τ over a dosing interval, where τ is the length of the dosing interval	µg h/mL
t_{max}	Time of maximum observed plasma concentration	h

Note: for $AUC_{0-\tau}$, τ represents the dosing interval, which in this study is 24h.

PK parameters derivation rules:

- Concentration BLOQ will be imputed according to the rules mentioned in section 5.4.2.
- Subjects with less than 3 concentrations > BLOQ will be reviewed to assess whether their PK results can still be included in the statistical analysis.
- PK parameters will be calculated according to linear up/log down trapezoidal method using the theoretical sampling time.
- 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.
- Day 1 pre-dose values exceeding 5% of the C_{max} will be flagged in the listing. Analysis will be repeated, excluding such subjects.

Excluded data will be flagged in the TLFs.

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

Note that [redacted] will derive the PK parameters, define the PK population and produce the TLFs.

10.2. TABLES

Table 14.2.2.1: GLPG1690 plasma concentrations (ng/mL): Individual data and descriptive statistics per day and time point

Subject data with descriptive statistics per day and planned time point of the plasma concentrations.

Population: PK.

Table 14.2.2.2: GLPG1690 PK parameters: Individual data and descriptive statistics – Week 4

Subject data with descriptive statistics at week 4 of the derived PK parameters (C_{max}, C_{τ}, $AUC_{0-\tau}$, t_{max}).

Population: PK.

10.3. FIGURES

Figure 14.2.2.1: GLPG1690 pre-dose plasma concentrations (ng/mL): Subject profile plots (linear-linear scale)

Subject profile plots of the GLPG1690 pre-dose plasma concentrations over time.

Population: PK.

Figure 14.2.2.2: GLPG1690 pre-dose plasma concentrations (ng/mL): Mean (+/- SE) concentration over time (linear-linear scale)

Arithmetic mean with SE of the GLPG1690 pre-dose plasma concentrations over time.

Population: PK.

Figure 14.2.2.3: GLPG1690 plasma concentrations (ng/mL): Subject profile plots – Week 4 (linear-linear scale)

Subject profile plots of the GLPG1690 plasma concentrations over time.

Population: PK.

Figure 14.2.2.4: GLPG1690 plasma concentrations (ng/mL): Subject profile plots – Week 4 (log-linear scale)

Same as previous plot, but with a log10-scaled vertical concentration axis.

Population: PK.

Figure 14.2.2.5: GLPG1690 plasma concentrations (ng/mL): Mean (+/- SE) concentration over time – Week 4 (linear-linear scale)

Arithmetic mean with SE of the GLPG1690 plasma concentrations over time.

Population: PK.

Figure 14.2.2.6: GLPG1690 plasma concentrations (ng/mL): Mean (+/- SE) concentration over time – Week 4 (log-linear scale)

Same as previous plot, but with a log10-scaled vertical concentration axis.

Population: PK.

10.4. LISTINGS

Listing 16.2.7.1: PK data handling

Listing per subject 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 day and 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-dosing.

Population: PK.

11. DEFINITIONS OF PHARMACODYNAMICS ANALYSIS TABLES, LISTINGS AND FIGURES

11.1. PARAMETERS

Parameters:

- LPA 18:2 species peak area ratio, in blood (other LPA species might be analyzed if deemed appropriate).
- All detectable LPA species peak area ratio, in BALF.

The percent reduction from baseline is derived as:

% reduction from baseline = 100-(100 × visit/baseline)

The baseline is the average of the pre-dosing duplicates (Day -1 pre-dose).

Further derived parameters (for LPA in blood only):

- E_{max} at Week 4 = maximum % reduction value over all time points, starting from the Week 4 pre-dose value and ending at the 6h value.
- AUEC at Week 4 = area under the % reduction curve using the trapezoidal summation rule, starting from the % reduction at the Week 4 pre-dose value and ending at the 6h value. The summation will use the scheduled time points rather than the actual times.

11.2. TABLES

Table 14.2.3.1: LPA species peak area ratio: Descriptive statistics per time point

Descriptive statistics of the absolute values and the changes from baseline per type of sample (blood or BALF), LPA species, treatment group and time point.

Population: PD, LOCF + OC.

Table 14.2.3.2: LPA species peak area ratio: Statistical evaluation per time point

Between-group comparison of placebo and GLPG1690: ANCOVA model on the changes from baseline with disease severity (baseline %FVC, screening %DLCO), age, gender, treatment, country and baseline value as covariates*. The table will present type III p-values, LS-means per group, LS-mean difference between the two groups and a 95% confidence interval of this LS-mean difference.

* if the model does not convergence, country will be dropped.

Within-group comparisons of each visit versus baseline: paired t-test.

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

Population: PD, LOCF.

Table 14.2.3.3: LPA species % reduction from baseline: Descriptive statistics per time point

Descriptive statistics of the % reduction values per type of sample (blood or BALF), LPA species, treatment group and time point.

Population: PD, LOCF + OC.

Table 14.2.3.4: LPA species % reduction from baseline: Descriptive statistics per time point by sub-groups

Descriptive statistics of the % reduction values per type of sample (blood or BALF), LPA species, treatment group and time point but split up by:

- baseline %FVC: < 50 % / [50,70[% / [70,90[% / ≥ 90 %
- screening DLCO, % predicted of normal: < 30 % / [30,40[% / [40,50[% / [50,60[% / ≥ 60 %
- age: [40,50[years / [50,60[years / [60,70[years / ≥ 70 years
- gender: male / female
- country: Ukraine / UK

Population: PD, LOCF.

Table 14.2.3.5: LPA species % reduction from baseline: Frequency tabulation per time point

Frequency table per type of sample (blood or BALF), LPA species, treatment group and time point, showing the % reduction in the following categories: <50%, [50,60[%, [60,70[%, [70,80[%, [80,90[%, [90,100]%.

Population: PD, LOCF + OC.

Table 14.2.3.6: LPA species % reduction from baseline: Statistical evaluation per time point

Between-group comparison of placebo and GLPG1690: ANCOVA model with disease severity (baseline %FVC, screening %DLCO), age, gender, treatment, country and baseline value as covariates*. The table will present type III p-values, LS-means per group, LS-mean difference between the two groups and a 95% confidence interval of this LS-mean difference.

* if the model does not convergence, country will be dropped.

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

Population: PD, LOCF.

Table 14.2.3.7: LPA species maximum % reduction from baseline E_{max}: Descriptive statistics

Descriptive statistics of the E_{max} values per treatment group at Week 4 (for blood samples only so for LPA 18:2 species only).

Population: PD, LOCF + OC.

Table 14.2.3.8: LPA species maximum % reduction from baseline E_{max}: Frequency tabulation

Frequency table per treatment group at Week 4 (for blood samples only so for LPA 18:2 species only), showing the E_{max} in the following categories: <50%, [50,60[%, [60,70[%, [70,80[%, [80,90[%, [90,100]%.

Population: PD, LOCF + OC.

Table 14.2.3.9: LPA species maximum % reduction from baseline E_{max}: Statistical evaluation

Between-group comparison of placebo and GLPG1690: ANCOVA model with disease severity (baseline %FVC, screening %DLCO), age, gender, treatment, country and baseline value as covariates*. The table will present type III p-values, LS-means per group, LS-mean difference between the two groups and a 95% confidence interval of this LS-mean difference.

* if the model does not convergence, country will be dropped.

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

Population: PD, LOCF.

Table 14.2.3.10: LPA species area under the % reduction curve AUEC: Descriptive statistics

Descriptive statistics of the AUEC values per treatment group at Week 4 (for blood samples only so for LPA 18:2 species only).

Population: PD, LOCF + OC.

Table 14.2.3.11: LPA species area under the % reduction curve AUEC: Statistical evaluation

Between-group comparison of placebo and GLPG1690: ANCOVA model with disease severity (baseline %FVC, screening %DLCO), age, gender, treatment, country and baseline value as covariates*. The table will present type III p-values, LS-means per group, LS-mean difference between the two groups and a 95% confidence interval of this LS-mean difference.

* if the model does not convergence, country will be dropped.

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

Population: PD, LOCF.

11.3. FIGURES

Figure 14.2.3.1: LPA 18:2 species peak area ratio (in blood): Subject profile plots over time

Subject profile plots over time of the actual values, with a new plot per treatment group and all subjects within a treatment group on the same plot. Any unscheduled results will also be part of this plot.

Population: PD, LOCF.

Figure 14.2.3.2: LPA 18:2 species peak area ratio (in blood): Mean (+/- SE) plot over time

Mean (with SE) plot over time with all treatment groups on one plot using different plot symbols. Unscheduled results will not be part of this plot.

Population: PD, LOCF.

Figure 14.2.3.3: LPA 18:2 species % reduction from baseline (in blood): Subject profile plots over time

Subject profile plots over time, with a new plot per treatment group and all subjects within a treatment group on the same plot. Any unscheduled results will also be part of this plot.

Population: PD, LOCF.

Figure 14.2.3.4: LPA 18:2 species % reduction from baseline (in blood): Mean (+/- SE) plot over time

Mean (with SE) plot over time with all treatment groups on one plot using different plot symbols. Unscheduled results will not be part of this plot.

Population: PD, LOCF.

Figure 14.2.3.5: LPA species peak area ratio (in BALF): Mean plots

Mean (with SE) bar chart per LPA species and treatment group at baseline and Week 12.

Population: PD, LOCF.

11.4. LISTINGS

Listing 16.2.8.1: PD: Full listing

Listing per type of sample (blood or BALF), LPA species, treatment group, subject, and planned time point of the actual sampling times relative to drug administration. The actually measured LPA species peak area ratios, the mean of the pre-dosing duplicates values (Day -1 pre-dose), the derived % reduction versus baseline, the E_{max} and AUEC will also be presented in this listing.

Population: PD.

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

No tables or listings are planned. These plots will only be produced in case there is an effect observed on PD / efficacy parameters.

Figure 14.2.4.1: Correlation between GLPG1690 plasma concentration and LPA species % reduction from baseline (linear-linear plot)

Scatterplot of the GLPG1690 plasma concentration versus the LPA species % reduction from baseline (in blood and in BALF). Overall and per time point. With all treatment groups on the same graph, in a different symbol. Placebos will be added as a zero plasma concentration.

Population: PD, LOCF.

Figure 14.2.4.2: Correlation between GLPG1690 plasma concentration and LPA species % reduction from baseline (log-linear plot)

Same plot as the previous one, but with a log10 scaled GLPG1690 plasma concentration axis. Placebos will not be on this plot.

Population: PD, LOCF.

Figure 14.2.4.3: Correlation between GLPG1690 C_{max} and LPA species maximum % reduction from baseline E_{max}

Scatterplot (linear-linear scale), like above.

Population: PD, LOCF.

Figure 14.2.4.4: Correlation between GLPG1690 C_{max} and LPA species area under the % reduction curve AUEC

Scatterplot (linear-linear scale), like above.

Population: PD, LOCF.

Figure 14.2.4.5: Correlation between GLPG1690 $AUC_{0-\tau}$ and LPA species area under the % reduction curve AUEC

Scatterplot (linear-linear scale), like above.

Population: PD, LOCF.

Figure 14.2.4.6: Correlation between GLPG1690 plasma concentration and %FVC (linear-linear plot)

Scatterplot of the GLPG1690 plasma concentration versus %FVC. Overall and per time point. With all treatment groups on the same graph, in a different symbol. Placebos will be added as a zero plasma concentration.

Population: ITT, LOCF.

Figure 14.2.4.7: Correlation between GLPG1690 plasma concentration and %FVC (log-linear plot)

Same plot as the previous one, but with a log10 scaled GLPG1690 plasma concentration axis. Placebos will not be on this plot.

Population: ITT, LOCF.

Figure 14.2.4.8: Correlation between GLPG1690 plasma concentration and change from baseline in %FVC (linear-linear plot)

Scatterplot of the GLPG1690 plasma concentration versus change from baseline in %FVC. Overall and per time point. With all treatment groups on the same graph, in a different symbol. Placebos will be added as a zero plasma concentration.

Population: ITT, LOCF.

Figure 14.2.4.9: Correlation between GLPG1690 plasma concentration and change from baseline in %FVC (log-linear plot)

Same plot as the previous one, but with a log10 scaled GLPG1690 plasma concentration axis. Placebos will not be on this plot.

Population: ITT, LOCF.

Figure 14.2.4.10: Correlation between the LPA species % reduction from baseline and efficacy

Scatterplots between the LPA species % reduction from baseline (in blood and in BALF) and the change from baseline of the following parameters: %FVC, biomarkers (in blood), FRI parameters (zones: lower and upper lobes).

Population: ITT, LOCF.

Figure 14.2.4.11: Correlation between the LPA species % reduction from baseline (in blood) and LPA species % reduction from baseline (in BALF)

Scatterplots between the LPA species % reduction from baseline (in blood) and the LPA species % reduction from baseline (in BALF).

Population: ITT, LOCF.

Figure 14.2.4.12: Correlation between change from baseline in %FVC and biomarkers

Scatterplots between the change from baseline in %FVC and biomarkers (in blood).

Population: ITT, LOCF.

Figure 14.2.4.13: Correlation between change from baseline in %FVC and FRI parameters

Scatterplots between the change from baseline in %FVC and FRI parameters (zones: lower and upper lobes).

Population: ITT, LOCF.

Figure 14.2.4.14: Correlation between change from baseline in biomarkers and FRI parameters

Scatterplots between the change from baseline in biomarkers and FRI parameters (zones: lower and upper lobes).

Population: ITT, LOCF.

Figure 14.2.4.15: Correlation between change from baseline in spirometry at the study center and spirometry at home

Scatterplots between the change from baseline in spirometry at the study center (FEV1, FVC and FEV1/FVC ratio) and spirometry at home (FEV1, FVC and FEV1/FVC ratio - weekly averages).

Population: ITT, LOCF.

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. Analysis periods: see section 4.2. The AE will only be presented in the analysis period during which it started. Rule: period start date $\leq$ AE start date $\leq$ period stop date.

In case the AE start date is incomplete, a worst-case allocation will be done according to the available parts of the AE start date. When too much of the AE start date is missing to apply the above selection rule, 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, 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 no 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 and is on or after the date of first study drug administration

= (AE start date) – (date of first study drug administration), when the AE start date is completely known and is before the date of first study drug administration

= 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.

13.1.5. Calculation of Percentages

All percentages will be calculated against the total number of subjects who 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 group 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 as worst intensity
- 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.

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

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

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 and 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 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: Treatment-emergent adverse events: Tabulation of serious events

Tabulation of TEAE preferred terms per body class and per treatment group. Selecting only the treatment-emergent serious adverse events.

Population: safety.

Table 14.3.1.7: Treatment-emergent adverse events: Tabulation of events leading to a permanent stop

Tabulation of TEAE preferred terms per body class and per treatment group. Selecting only the TEAEs for which the study treatment was permanently discontinued (AE page), or for which the study was discontinued (study termination page).

Population: safety.

Table 14.3.1.8: Treatment-emergent serious adverse events: Tabulation for EudraCT reporting

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

Population: safety.

Table 14.3.1.9: Treatment-emergent non-serious adverse events: Tabulation for EudraCT reporting

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

Population: safety.

Table 14.3.1.10: Treatment-emergent non-serious adverse events: Tabulation for EudraCT reporting of TEAEs occurring in at least 5% in either treatment group

Same as the previous table, selecting all the lines from the table where there is at least 5% occurrence in either treatment group. 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 16.2.9.1: Treatment-emergent adverse events: Full listing

Listing per treatment group, per subject and per analysis period (excluding screening) of the following:

- Period start and end date
- AE preferred term

- AE start and end date
- AE onset day in study
- AE onset day in period
- AE duration
- AE intensity
- AE drug relatedness
- AE outcome
- AE action taken
- Concomitant therapy started (yes/no)

Population: safety.

Listing 16.2.9.2: 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 16.2.9.3: Serious adverse events: Full listing

Same as the previous listing, but only selecting SAEs (irrespective their treatment-emergence, so also showing any SAEs during the screening analysis period).

Population: safety.

Listing 16.2.9.4: 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 permanent stop of study drug (on the AE CRF page), or of the study itself (on the Study Termination CRF page).

Population: safety.

Listing 16.2.9.5: Treatment-emergent adverse events: Full listing of the events leading to a temporary stop

Same as the previous listing, but only selecting TEAEs that lead to a temporary stop of study drug.

Population: safety.

Listing 16.2.9.6: 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.

Listing 16.2.9.7: Adverse events: Listing of subjects for whom a narrative is required

Listing and flagging subjects who:

- Died
- Had an SAE
- Had an AE leading to study discontinuation
- Had an AE leading to a permanent stop of study drug.

Population: all screened subjects.

The clinical study report will add subject case narratives in the body of the report and/or in section 14.3.1. No standard programming is planned for this.

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.

Laboratory tests with only a very low sample size (N<3 overall) will not be presented in the tables, but only in the listings. Laboratory 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.

The parameters from the PD section will not be repeated in this section.

13.2.2. Number of Significant Digits

In tables and listings, the original 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 laboratory test. This rounding will be done prior to any parameter derivation.

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

13.2.3. Baseline and Change from Baseline

The baseline is defined as the last sample prior to dosing. Baseline will be determined per laboratory test individually. It is recognized that baseline tests may thus come from more than one laboratory sample and not just from the "baseline visit" 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. Screening and Follow-up Visits

Screening and follow-up visits will be shown for each treatment group; not pooled.

13.2.5. Scoring of Laboratory Values

All original 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 will be scored as abnormally low (L), normal (N) or abnormally high (H): the variable LBNRIND in SDTM.LB dataset will be used in the analysis.

Any clinical significance flags will be used in the listings.

13.2.6. Worst-Case Abnormality

Derived per parameter separately.

All non-missing post-baseline values (including post-baseline unscheduled measurements, retests 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.
- L+H = 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.

13.2.7. Tables

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

Table 14.3.2.1: Laboratory data: Descriptive statistics per time point

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

Population: safety.

Table 14.3.2.2: Laboratory data: Shift table of the laboratory abnormalities per time point

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

Population: safety.

Table 14.3.2.3: Laboratory data: Treatment-emergent laboratory abnormalities per time point

Frequency table of the treatment-emergent laboratory abnormalities per laboratory test category (hematology, biochemistry, urinalysis), laboratory test, treatment group and time point (including the 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 14.3.2.4: Laboratory data: Shift table of the categorical laboratory data per time point

Shift table per laboratory test category (hematology, biochemistry, urinalysis), laboratory 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.

13.2.8. Figures

Figure 14.3.2.1: Laboratory data: Subject profile plots over time for subjects with a treatment-emergent abnormality

Subject profile plots over time, with each laboratory 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, selecting subjects with a treatment-emergent abnormality.

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 laboratory 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 laboratory 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.

13.2.9. Listings

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

- A fasted Y/N flag
- An abnormality L/H flag
- The test's normal range
- A clinical relevance flag

Listing 16.2.10.1: Laboratory data: Full listing

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

Population: safety.

Listing 16.2.10.2: Laboratory data: Abnormalities listing

Listing per treatment group, per subject and per time point of all post-baseline time points scored as treatment-emergent 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: PR, HR, RR, QRS and 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):

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

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

The formula using RR is preferred. In case no RR is available, the formula using HR will be applied. Derived QTcF values will first 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 non-missing 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 and not just from the "baseline visit" 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. Screening and Follow-up Visits

Screening and follow-up visits will be shown for each treatment group; not pooled.

13.3.5. Normal Ranges

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

- of the actual values (a value > 450 ms is considered as abnormal):
  - ≤ 450 ms
  -]450,480] ms
  -]480,500] ms
  - > 500 ms
- of the changes from baseline (a change > 30 ms is considered as abnormal):
  - ≤ 30 ms (including all decreases in QT)
  -]30,60] ms
  - > 60 ms

13.3.6. Worst-case Abnormality of QT and QTcF

Derived per parameter separately.

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

13.3.7. Tables

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

Table 14.3.3.1: ECG: Descriptive statistics per time point

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

Population: safety.

Table 14.3.3.2: ECG: Shift table of the QT abnormalities 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 the worst-case) versus the baseline abnormality. Parameters: QT and QTcF.

Population: safety.

Table 14.3.3.3: ECG: Treatment-emergent QT 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 higher than the baseline result. Parameters: QT and QTcF.

Population: safety.

Table 14.3.3.4: ECG: Treatment-emergent abnormal change in QT per time point

Frequency table per test, treatment group and time point (including the worst-case). The table will present the abnormality of the changes at each post-baseline time point according to the classifications of section 13.3.5. Parameters: QT and QTcF.

Population: safety.

13.3.8. Listings

Listing 16.2.11.1: 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 16.2.11.2: ECG: Abnormalities listing

Listing per treatment group, per subject and per time point of all post-baseline data scored as treatment-emergent 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.

13.4.2. Baseline and Change from Baseline

The baseline value will be the last non-missing 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 and not just from the "baseline visit" 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. Screening and Follow-up Visits

Screening and follow-up visits will be shown for each treatment group; not pooled.

13.4.4. Normal Ranges

Parameter, unit	Normal range	
	Lower limit	Upper limit
HR, bpm	40	100
RR, breaths/min	12	16
DBP, mmHg	45	90
SBP, mmHg	90	150
Temperature, °C	35.5	37.5

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.

13.4.5. Worst-Case Abnormality

Derived per parameter separately.

All non-missing post-baseline values (including unscheduled measurements, retests 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.
- L+H = 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.

13.4.6. Tables

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

Table 14.3.4.1: Vital signs: Descriptive statistics per time point

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

Population: safety.

Table 14.3.4.2: Vital signs: Shift table of the abnormalities per time point

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

Population: safety.

Table 14.3.4.3: 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.

13.4.7. Listings

Listing 16.2.12.1: Vital signs: Full listing

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

Population: safety.

Listing 16.2.12.2: Vital signs: Abnormalities listing

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

Population: safety.

13.5. PHYSICAL EXAMINATIONS

Listing 16.2.13.1: 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.

ICH-E3. (December 1995). *Structure and content of clinical study reports. Step 4 Guideline.*

ICH-E6. (17 July 1996). *Guideline for good clinical practice. Step 5 Guideline.*

ICH-E9. (5 February 1998). *Statistical principles for clincal trials. Step 4 guideline.*

Miller, M., Hankinson, J., & Brusasco, V. e. (2005). Standardisation of spirometry. *Eur Respir J, 26*, 319-338.

Quanjer, P., Stanojevic, S., Cole, T., Baur, X., Hall, G., Culver, B., . . . Stocks, J. (2012). Multi-ethnic reference values for spirometry for the 3-95 year age range: the global lung function2012 equations: Report of the Global Lung Function Initiative (GLI), ERS Task Force to established imrpoved Lung Function Reference Values. *Eur Respir J 40 (6)*, 1324-43.

USNRC. (2014, Dec 12). *United States Nuclear Refulatory Commission. Fact sheet on biological effects of radiation.* Opgeroepen op Jun 05, 2015, van http://www.nrc.gov/reading-rm/doc-collections/fact-sheets/bio-effects-radiation.html

WNA. (2015, May 22). *World Nuclear Association.* Opgeroepen op Jun 05, 2015, van Nuclear radiation and health effects: http://www.world-nuclear.org/info/safety-and-security/radiation-and-health/nuclear-radiation-and-health-effects/