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Boehringer Ingelheim

1466-0002

Phase Ib trial to assess safety and tolerability of multiple subcutaneous doses of BI 3006337 in patients with overweight or obesity and hepatic steatosis

Statistical Analysis Plan

Version: 4.0

[redacted] **Project Number:** [redacted]

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TABLE OF CONTENTS

1 INTRODUCTION 15
2 STUDY OBJECTIVES 16
2.1 Main Objective 16
2.2 Primary Objective/Estimand(s) 16
2.3 Secondary Objective/Estimand(s) 16
3 INVESTIGATIONAL PLAN 17
3.1 Overall Study Design and Plan 17
3.2 Endpoints and Associated Variables 17
3.2.1 Efficacy Variables 17
3.2.2 Pharmacodynamic Variables 17
[redacted]
3.2.4 Pharmacokinetic Variables 18
3.2.5 Safety Variables 19
4 STATISTICAL METHODS 20
4.1 Data Quality Assurance 20
4.2 General Presentation Considerations 20
4.2.1 Treatment 21
4.2.2 Study Day 21
4.2.3 End of Study 21
4.2.4 Baseline 21
4.2.5 Controlled, Repeat, Retest, Scheduled and Unscheduled Assessment 21
4.2.6 Summary and Representation of Data 22
4.2.7 Missing Data 22
4.2.8 Missing Adverse Events Data 23
4.3 Software 23
4.4 Study Subjects 23
4.4.1 Analysis Sets 23
4.4.2 Disposition of Subjects 24
Table XX: Disposition (Treated Set) 24
Table XX: Screening failures (Enrolled Set) 24
4.4.3 Protocol Deviations 24
4.4.3.1 Protocol Deviations with Non-PK Implications 24
4.4.3.2 Protocol Deviations with PK Implications 24
Listing XX: Important protocol deviation (TS) 25
4.5 Demographics and Baseline Characteristics 25
Table XX Demographics (Treated Set) 25
Listing XX Demographics (Treated Set) 25
Table XX Baseline characteristics (Treated Set) 26
Listing XX Baseline characteristics (Treated Set) 26
4.6 Medical and Surgical History 26
Table XX Medical history (Treated Set) 26
Listing XX Medical history (Treated Set) 26
4.7 Prior and Concomitant Medications 26
Table XX Prior and concomitant medication (Treated Set) 26
Listing XX Prior and concomitant medication (Treated Set) 26

4.8 Treatment Exposure and Compliance....26
4.8.1 Treatment Exposure....26
Table XX Treatment exposure (Treated Set)....27
Table XX Skipped dose summary (Treated Set)....27
Listing XX Treatment exposure (Treated Set)....27
4.8.2 Compliance....27
Listing XX Treatment compliance (Treated Set)....27
4.9 Analysis Supporting Primary Objective(s)....27
4.9.1 Primary Endpoint(s)....27
4.9.2 Statistical Hypothesis, Model, and Method of Analysis....28
4.9.3 Handling of Intercurrent Events....28
4.9.4 Handling of Missing Values not Related to Intercurrent Event....28
[redacted]
4.10 Analysis Supporting Secondary Objective(s)....28
[redacted]
4.10.2 Statistical Hypothesis, Model, and Method of Analysis....29
4.10.3 Handling of Intercurrent Events....29
4.10.4 Handling of Missing Values not Related to Intercurrent Event....29
[redacted]
4.11 Efficacy Evaluation....30
Table XX Descriptive statistics of liver measurements change from baseline at week 12 (TS)....30
Listing XX Liver measurements (TS)....30
[redacted]
4.11.1 Analysis and Data Conventions....31
4.11.1.1 Handling of Dropouts or Missing Data....31
4.11.1.2 Examination of Subgroups....31
4.11.2 Primary Efficacy Variable(s)....31
4.11.3 Secondary Efficacy Variables....31
[redacted]
4.12 Pharmacokinetic Analysis, Concentration, and Parameter TFLs, and Statistical Analysis of Pharmacokinetic Parameters for Final Analysis....31
4.12.1 Pharmacokinetic Concentrations....31
Listing XX Pharmacokinetic BI 3006337 serum concentration (ug/L) summary (TS)....32
Table XX Pharmacokinetic BI 3006337 serum concentration (ug/L) summary (PKS)....32
Figure XX Individual subject profiles for BI 3006337 Serum Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (PKS)....33

Figure XX Individual subject profiles for BI 3006337 serum concentration at predose – (Linear Scale and Semi-Logarithmic Scale) (PKS) 33
Figure XX Overlaid individual subject profiles for BI 3006337 Serum Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (PKS) 33
Figure XX Overlaid individual subject profiles for BI 3006337 serum concentration at predose – (Linear Scale and Semi-Logarithmic Scale) (PKS) 33
Figure XX Mean (± SD) BI 3006337 Serum Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (PKS) 33
Figure XX Mean (± SD) BI 3006337 serum concentration at predose – (Linear Scale and Semi-Logarithmic Scale) (PKS) 33
Figure XX Geomean (± SD) BI 3006337 Serum Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (TS) 33
Figure XX Geomean (± SD) BI 3006337 serum concentration at predose – (Linear Scale and Semi-Logarithmic Scale) (TS) 33
4.12.2 Pharmacokinetic Parameters 33
Listing XX Pharmacokinetic parameters summary (PKS) 36
[redacted]
PK Parameter Summary Tables: 36
Table XX Pharmacokinetic parameters summary (PKS) 37
[redacted]
Figure XX Scatter plots of dose-adjusted PK parameters (PKS) 37

[redacted]

[redacted]

4.13 Safety Evaluation....44
4.13.1 Adverse Events....44
Table XX Summary of adverse events (TS)....47
Table XX Summary of drug-related adverse events (TS)....47
Table XX Adverse events by worst CTCAE grade, SOC, and PT (TS)....47
Table XX Drug-related adverse events by worst CTCAE grade, SOC, and PT (TS)....47
Table XX Adverse events by SOC, and PT (TS)....47
Table XX Drug-related adverse events by SOC, and PT (TS)....47
Table XX Serious adverse events by SOC, and PT (TS)....47
Table XX Drug-related serious adverse events by SOC, and PT (TS)....47
Table XX Adverse events of special interest (DILI or systemic hypersensitivity reaction) by SOC, and PT (TS)....47
Table XX Drug-related adverse events of special interest (DILI or systemic hypersensitivity reaction) by SOC, and PT (TS)....47
Table XX Adverse events leading to discontinuation by SOC, and PT (TS)....47
Table XX Drug-related adverse events leading to discontinuation by SOC, and PT (TS)....47
Table XX Potential DILI cases for subjects with normal ALT or AST at baseline (TS)....47
Table XX Potential DILI cases for subjects with abnormal ALT or AST at baseline (TS)....47
Figure XX Potential DILI cases with maximum ALT and Total Bilirubin on-treatment assessment (TS)....47
Figure XX Potential DILI cases with maximum AST and Total Bilirubin on-treatment assessment (TS)....47
Table XX Immune related adverse events by SOC, and PT (TS)....48

Table XX Drug-related and immune related adverse events by SOC, and PT (TS).....48
[redacted]
4.13.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events 48
Listing XX Adverse events (TS).....48
Listing XX Serious adverse events (TS).....48
Listing XX Adverse events of special interest including DILI or systemic hypersensitivity reaction (TS).....48
Listing XX Adverse events leading to discontinuation (TS).....48
Listing XX Drug related treatment emerged adverse events (TS).....48
4.13.3 Clinical Laboratory Evaluation.....48
Table XX Clinical laboratory evaluation (TS).....49
Table XX Clinically significant abnormal laboratory evaluation (TS).....49
Table XX Clinical laboratory evaluation by outside the reference range (TS).....49
Listing XX Clinical laboratory evaluation (TS).....49
Figure XX Glucose bedside mean linear plot (TS).....49
Figure XX Mean (+/- SD) clinical laboratory assessments (TS).....49
4.13.4 Vital Signs.....49
Table XX Vital signs (TS).....50
Table XX Vital signs shift from baseline (TS).....50
Figure XX Vital signs box plot (TS).....50
Figure XX Vital signs change from baseline box plot (TS).....50
Figure XX Vital signs change from baseline box plot per treatment (TS).....50
Listing XX Vital signs (TS).....50
4.13.5 ECG.....50
Table XX 12-lead ECG results (TS).....51
Table XX Frequency of subjects with notable on treatment ECG findings (TS).....51
Listing XX 12-lead ECG results (TS).....51
Listing XX 12-lead ECG abnormal results (TS).....51
Table XX New ECG findings between baseline and end of study (TS).....51
4.13.6 Physical Examination.....51
Listing XX Physical examination (TS).....51
4.13.7 Dose Escalation.....51
4.13.8 Other Analysis.....51
4.13.8.1 Assessment of Local Tolerability.....51
Table XX Local tolerability (TS).....52
Listing XX Local tolerability with severity (TS).....52
4.13.8.2 C-SSRS.....52
Table C-SSRS shift from baseline to maximum on-treatment value (TS).....52
Listing XX C-SSRS results (TS).....52
4.13.8.3 Death listing.....52
Listing XX Death (TS).....52
[redacted]

[redacted]

4.15 Handling of Dropouts or Missing Data 55
4.16 Determination of Sample Size 55
[redacted]
5 REFERENCES 55
6 APPENDICES 56
6.1 Schedule of Assessments 56
6.2 Imputation Rules for Partial Dates 58
6.3 Laboratory Test Parameters 62
6.4 Visit Names 65
6.5 ECG Notable Criteria 66
6.6 Liver Event and Laboratory Trigger Definitions 67
[redacted]

List of Tables

Table 4-1 Pharmacokinetic Parameter and Estimation 34
Table 4-4 Treatment-emergent markedly abnormal (TEMA)/ Potentially clinically significant (PCS) Criteria for Vital Signs 50
Table 6-1 Schedule of Assessments 56
Table 6-2 Algorithm for Treatment-Emergent Adverse Events: 59
Table 6-3 Algorithm for Prior/Concomitant Medications Categorization: 61

REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
Draft 0.1	29-Aug-23	New document
0.2	01-Sep-23	Updated after internal review
0.3	13-Sep-23	Updated after sponsor's comments and discussion
1.0	13-Sep-23	Signatures page updated
1.1	11-Oct-23	Updates after senior review.
1.2	23-Oct-23	Lab test parameters table updated.
1.3	31-Jan-2024	Updates after first DEC minor and major meetings
1.4	1-Mar-2024	1. After Sponsor review 2. And Internal review
1.5	29-Mar-2024	1) Chapter 5 - Added "Not Applicable" 2) Chapter 4.11 Efficacy evaluation - clarification was added 3) Chapter 4.14.1 Stat analysis of Biomarkers – was updated
1.6	8-Apr-2024	1) Chapter 4.14.1 – additional correlation analysis for biomarkers was added 2) Chapter 4.8.2 – Compliance chapter – clarification was added
2.0	11-Apr-2024	Finalization v2.0
2.1	31-Oct-2024	The following updates before Dry run #2: 1) Chapter 3.2.2, Chapter 4.11 – end of study and unscheduled visits were added 2) Chapter 4.1.1, Chapter 4.12.3 – total column is not displayed for pharmacodynamic variables 3) Chapter 4.4.2 – Table Subject information was removed 4) Chapter 4.10.5 – sensitivity part was added 5) Chapter 4.12.1 – Cthrough was removed 6) Chapter 4.13.1 – Immune related AE table was added
3.0	05-Nov-2024	Finalization v3.0
3.1	25-Nov-2024	Updates after Dry run 2. Added the following updates: [redacted] 2) Added output title name Table XX, Figures XX, Listings XX 3) Description for Immunogenicity Variables was added [redacted]

		[redacted] 7) Immune related AE derivation was added and additional outputs related with that 8) Editorial changes. 9) Chapter 4.17 was updated
3.2	28-Nov-2024	1) Chapter 4.13.3, 4.13.5 additional outputs were added
4.0	28-Nov-2024	Finalization v4.0 – before DBL

LIST OF ABBREVIATIONS

Abbreviation/Acronym	Definition/Expansion
$\%AUC_{tz\text{-}inf}$	Percentage of AUC_{inf} obtained by extrapolation
[redacted]	
AE	Adverse event
AESI	Adverse events of special interest
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
$AUC_{0\text{-}inf}$	AUC from time zero extrapolated to infinity
$AUC_{0\text{-}tz}$	AUC from time zero to the last quantifiable data point
$AUC_{\tau,1}$	AUC over the dosing interval tau after administration of the first dose
$AUC_{\tau,norm}$	Dose normalized AUC over the dosing interval tau after administration of the first dose
$AUC_{\tau,ss}$	AUC over the dosing interval tau at steady state
$AUC_{\tau,ss,norm}$	Dose normalized AUC over the dosing interval tau at steady state
$AUC_{t1\text{-}t2}$	AUC over the time interval t1 to t2
$AUC_{t1\text{-}t2,ss}$	AUCE over the time interval t1 to t2 at steady state
BLQ	Below the lower limit of quantification
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
C_{avg}	Average concentration at steady state
C_{max}	Maximum observed concentration after administration of the first dose
$C_{max,norm}$	Dose normalized C_{max}
$C_{max,ss,norm}$	Dose normalized C_{max} at steady state
$C_{\tau,1}$	Concentration taken at the end of the first dosing interval
$C_{max,ss}$	Maximum observed concentration in serum at steady state
$C_{pre,ss}$	Predose concentration before administration of the next dose at steady state
$C_{pre,N}$	Predose concentration before administration of the Nth dose after N-1 doses were administrated
C_{min}	Minimum observed concentration after administration of the first dose
$C_{min,ss}$	Minimum C_{min} at steady state
C_{trough}	Concentration at the end of a dosing interval [taken directly before next administration]

Abbreviation/Acronym	Definition/Expansion
Cτ	Concentration at dosing time plus tau (typically defined as the last dosing interval plus tau)
CI	Confidence interval
CL	Clearance
CL/F,ss	Apparent clearance following extravascular (non-intravenous) administration at steady state
CPMS	Clinical Pharmacology, Modeling, and Simulation
CRF	Case Report Form
CS	Clinically significant
CSR	Clinical Study Report
CTP	Clinical Trial Protocol
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DBP	Diastolic blood pressure
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
ES	Enrolled Set
EOS	End of study
ET	Early termination
FGF-21	Fibroblast growth factor
HR	Heart rate
GLP-1	Glucagon-like peptide
GMR	Geometric mean ratio
IMP	Investigational medicinal product
IV	Intravenous(ly)
LI	Linearity index
LLOQ	Lower limit of quantification
LOQ	Limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI-PDFF	Magnetic resonance imaging - estimated proton density fat fraction
$MRT_{ex,ss}$	Mean residence time of the analyte in the body at steady state after extravascular administration
NA	Not available

[redacted]

Abbreviation/Acronym	Definition/Expansion
NCS	Not clinically significant
NR	Not reportable
NS	No sample
PCS	Potentially clinically significant
PD	Pharmacodynamic(s)
PR	Pulse rate
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic analysis set
PoCP	Proof of clinical principle
PT	Preferred Term
QRS	Time between start of the Q-wave and the end of the S-wave in an electrocardiogram
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	corrected QT interval
QTcB	QT corrected using Bazett's formula
QTcF	QT corrected using Fridericia's formula
$R_{a,AUC}$	Accumulation ratio based on Cmax
$R_{a,Cmax}$	Accumulation ratio based on AUCo-tau
RR	Time between 2 R-waves in an electrocardiogram
RTF	Rich Text Format
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SI	Standard international
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
$t_{½}$	Apparent terminal elimination half-life
$t_{½,ss}$	Apparent terminal elimination half-life at steady state
$t_{min,ss}$	Time corresponding to occurrence of C_{min} at steady state
$t_{max,ss}$	Time corresponding to occurrence of C_{max} at steady state
TEAE	Treatment-emergent adverse event
TEMA	Treatment-emergent markedly abnormal
TQT	Through QT
V_z	Volume of distribution during terminal phase following intravenous dosing

Abbreviation/Acronym	Definition/Expansion
V_z/F,ss	Apparent volume of distribution during terminal phase following extravascular dosing at steady state
WHO-DD	World Health Organization - Drug Dictionary
λ_z	Terminal elimination rate constant

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of Study 1466-0002 [redacted] Phase Ib trial to assess safety and tolerability of multiple subcutaneous doses of BI 3006337 in subjects with overweight or obesity and hepatic steatosis.

The content of this SAP is based on the following study documents:

- Study 1466-0002 protocol v5.0 08-Feb-2024.
- Electronic Case Report Form (eCRF) 04-Jul-2023.

This SAP will be finalized prior to database lock. Any changes after the finalization of this SAP will be documented in Statistical Method Modification Form.

2 STUDY OBJECTIVES

2.1 Main Objective

The main objectives of this trial are to assess the safety, tolerability, PK, and PD of 3 dose levels: [redacted] over 12 weeks in comparison with placebo in trial participants with overweight/obesity and steatosis. The primary objective is to descriptively assess the frequency (N [%]) of trial participants with drug-related AEs. Secondary objectives are to descriptively assess the PK parameters for BI 3006337 and to explore superiority of clinical efficacy vs. placebo for BI 3006337 at the highest tolerated dose.

2.2 Primary Objective/Estimand(s)

The primary endpoint for the assessment of safety and tolerability of BI 3006337 is the occurrence of drug-related AEs between the first administration of trial medication (BI 3006337 or placebo) and end of study (EOS).

2.3 Secondary Objective/Estimand(s)

The following PK parameters of BI 3006337 will be determined, if feasible:

- AUCτ,ss (area under the concentration-time curve of the analyte in serum over the dosing interval tau at steady state) after the last dose in Week 12
- Cmax,ss (maximum measured concentration of the analyte in serum at steady state) after the last dose in Week 12
- tmax,ss (time from dosing to the maximum measured concentration of the analyte in serum at steady state) after the last dose in Week 12

The following efficacy endpoints will be assessed:

- Percentage change in liver steatosis as measured by Magnetic resonance imaging - estimated proton density fat fraction (MRI-PDFF) from baseline after 12 weeks of treatment.

Trial subjects who do not complete 12 weeks of treatment due to disruption related to COVID-19 will be replaced to achieve a 100% sample size in each dose group.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

Please refer to Section 3 of the Clinical Trial Protocol (CTP).

3.2 Endpoints and Associated Variables

3.2.1 Efficacy Variables

Percentage change in liver steatosis (as measured by MRI-PDFF) from baseline after 12 weeks of treatment.

3.2.2 Pharmacodynamic Variables

To assess the effect of BI 3006337 on pharmacodynamic (PD) variables, samples will be collected at the times specified in the Schedule of Assessments:

[redacted]

- Change and percentage change of liver fat content from baseline and at Week 12 assessed by MRI-PDFF (Visit 17 or unscheduled visits)

[redacted]

[redacted]

[redacted]

3.2.4 Pharmacokinetic Variables

[redacted]

After the third and last dose of BI 3006337

- [redacted]
- AUCτ,ss (area under the concentration-time curve of the analyte in serum over the dosing interval tau at steady state) after third dose
- Cmax,ss (maximum measured concentration of the analyte in serum at steady state after third dose
- tmax,ss (time from dosing to the maximum measured concentration of the analyte in serum at steady state) after third dose
- [redacted]

- [redacted]

3.2.5 Safety Variables

Safety variables will be:

- Physical examination including at minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.
- All available AE assessments, SAEs, AESIs including drug induced liver injury (DILI) with identification of subjects that discontinued trial treatment due to AEs (as in CTP section 3.3.4.1).
- Central laboratory data with identification of values outside the reference range as well as values defined as clinically relevant
- 12-lead electrocardiogram (ECG) (heart rate [HR], pulse rate [PR], the time between start of the Q-wave and the end of the S-wave [QRS], the time between 2 R-waves [RR], the time between start of the Q-wave and the end of the T-wave [QT], QT corrected using Bazett's formula [QTcB] and QT corrected using Fridericia's formula [QTcF] and others, if applicable)
- Vital signs, demographic and baseline characteristics including temperature, systolic and diastolic blood pressure, heart rate, weight, height and others, including medical history and concomitant medication, Columbia-Suicide Severity Rating Scale (C-SSRS).
- Local tolerability at the injection site ("swelling", "induration", "redness", "pain", or "other findings")
- Patient profiles

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures, and data listings to be included in the report will be independently checked for consistency, integrity, and in accordance with standard [redacted] procedures.

4.2 General Presentation Considerations

The below-mentioned general principles will be followed throughout the study:

- Baseline data will be presented by the actual assigned dose group of subjects while data collected after randomisation will be presented by different time points / time periods, if not stated otherwise.
- Change from baseline will be calculated as the visit value of interest minus the baseline value.

  The formula for calculating change from baseline is below:
  Change from baseline = value after 12 weeks – baseline value

- Percentage change from baseline will be calculated as the change from baseline value divided by the baseline value (i.e., [post-baseline value – baseline value] / baseline value x 100).

  The formula for calculating percent change from baseline is as below:
  Percentage Change = (value after 12 weeks – baseline value) / baseline value * 100%.

- Summary tables, in general, will be presented by each dose group as follows:

Table 2 Overview of summary design

[redacted]	Placebo N = xx	Total N = xx

"Total" column will be displayed for all Tables except for Pharmacodynamic variables, PK [redacted] ("BI Total" should still be displayed). More details will be in TLFs shells document. Percentages will be based on N (the number of subjects in each dose group), if not stated otherwise.

- All variables shown in summaries will also be included in subject data listings.
- Subject data listing will be presented and sorted by dose group, unique subject identifier and relevant visits or dates, if applicable.
- Dates will be formatted according to the International Standards Organization (ISO) 8601 standard. If time is part of a date, then it will be added as YYYY-MM-DDThh:mm (e.g., 2022-02-12T14:31 being February 12th, 2022, 2:31 p.m.).
- Rounding for all variables will occur only as the last step of a derivation, immediately prior to presentation in listings and tables. No intermediate rounding will be actively performed on derived variables.
- Every table, listing and figure will be produced with

  - client name and study ID
  - an electronic date stamp to document when it was produced
  - the name of the program used for creation
- Further formatting and presentation standards can be specified in the Tables Listings mock shell document.

4.2.1 Treatment

Outputs will be presented by each dose group, which refer to:

- [redacted]
- BI Total (for Tables): includes total data for all subjects receiving BI 3006337 at any dose.
- Placebo
- Total (for Tables): includes total data for all subjects receiving BI 3006337 or Placebo.

4.2.2 Study Day

Study days will be numbered relative to the first day of study drug administration.

- If the date of event is before the study drug administration, then:
  Study day = (Date of measurement – Date of study drug administration)
- If the date of event is on or after the study drug administration, then:
  Study day = (Date of measurement – Date of study drug administration) + 1

4.2.3 End of Study

End of study is defined as the last available post-treatment assessment. The last visit is expected to be at Day 99.

4.2.4 Baseline

Baseline is defined as the last non-missing measurement recorded before first dose of study drug administration. If assessment or measurement happened at the same day as first drug administration, consider time of both events to determine if measurement was taken before first dose.

In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment.
- Baseline evaluations (laboratory tests, physical measurements, vital signs etc.) will be defined as evaluations with a date on or prior to the day of first dose of study treatment.

No imputation will be done for missing baseline value for derivation of change from baseline or summary tables and shift tables.

4.2.5 Controlled, Repeat, Retest, Scheduled and Unscheduled Assessment

Repeat, retest, and unscheduled assessment will not be considered for the calculation of summary statistics and figures, unless the assessment qualifies as baseline.

Average of controlled and planned (scheduled) assessment will be considered for the calculation of summary statistics and figures, if more than one controlled/planned assessment will be performed at a specific time point.

4.2.6 Summary and Representation of Data

Continuous data will be summarized in terms of mean, standard deviation (SD), median, minimum, maximum, and number of observations, unless otherwise stated.

Categorical data will be summarized in terms of the number of participants providing data at the relevant time point (n), frequency counts, and percentages.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistics.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using N as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only. Percentage will be presented as whole number if count is 100.

If for any summary table, n is less than three then only n, minimum, and maximum should be presented, and other summary statistics will be left blank.

4.2.7 Missing Data

Missing information on the date of first administration of trial drug:

In the unlikely event that the date of first drug administration is missing but the subject was randomised and treated, the date of the first drug administration will be set to the date of randomisation. If the date of first administration is partially missing with the month and year present, the day will be set to the date of randomisation if randomisation was in the same month. If randomisation was in the month prior to the first drug administration the missing day will be imputed as the first day of the month.

A missing time of first drug administration will be imputed as 09:00 o'clock in the morning.

As a general rule, a missing drug stop date will be imputed according to the following principles:

- If an EOS visit is documented, it should be the date of the EOS visit.
- If the date is incomplete with only month and year and the EOS visit is missing, it should be the first day of the following month.
- If the subject is lost to follow-up it should be the date of the last visit + the longest treatment duration based on drug supply + 1 day.
- If a subject died during the course of the trial and no additional information about drug stop date are available, the date of death will be used as drug stop date assuming that the subject took the medication until the day of death.
- All other cases need to be assessed by the trial team on an individual basis, trying to use the points above as guidance.

For other incomplete date information, the midpoint of the possible interval will be used. If only the year is present, the day and month will be imputed as 01 July. If year and month is present, the day will be imputed as 15. If the month is missing only, the month will be imputed as July. If the year is missing, the date will be considered missing.

4.2.8 Missing Adverse Events Data

In case of missing or incomplete dates not directly allowing allocation to any of the categories of AEs, a worst-case allocation will be done according to the available parts of the start and the stop dates.

Completely missing AE start dates will be deemed treatment emergent if the AE end date does not indicate that the AE ended prior to study treatment start date. For more details, see Appendix 6.2

4.3 Software

All report outputs (tables, listings, figures) will be produced using [redacted] in a secure and validated environment.

PK analysis will be performed using [redacted].

All report outputs (tables, listings, figures) will be provided in portable document format (PDF) documents. The outputs will be categorized by type (tables, listings, figures, if applicable) and numbered logically.

A mock shell document will be created to define details of outputs as an MS Word document.

All tables and listings will be produced in landscape orientation as an MS Word document with a Rich Text Format (RTF).

4.4 Study Subjects

4.4.1 Analysis Sets

- **Enrolled set (ES)**
  This subject set includes all subjects who have signed informed consent given.
- **Randomised set (RS)**
  This subject set includes all subjects screened with informed consent given and who completed at least one screening procedure, and who were randomised to study drug, regardless of whether any study drug was taken.
- **Treated set (TS)**
  This subject set includes all subjects from the randomised set (RS) who are treated with at least one dose of study medication. The treatment assignment will be determined based on the first treatment the trial subjects received. The TS is the basis for safety analyses. Subject's data will be displayed by the actual treatment.
- **Pharmacokinetic analysis set (PKS)**
  This subject set includes all trial subjects in the treated set (TS) who provide at least one primary or secondary PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability. Thus, a trial subject will be included in the PKS, even if he contributes only one primary or secondary PK parameter value for one period to the statistical assessment.

- [redacted]

4.4.2 Disposition of Subjects

A clear accounting of the disposition of all subjects who enter the study will be provided, from screening to study completion, including screening failures subjects.

Disposition data will be presented based on the TS.

Disposition summaries will be presented by dose group (see section 4.2.1) and will include the following information:

- number and percentage of subjects started treatment, completed treatment, discontinued treatment (including reasons for discontinuing)
- number and percentage of subjects on follow-up
- number and percentage of subjects, completed study and the number and percentage of subjects who were withdrawn (including reasons for withdrawal).

Table XX: Disposition (Treated Set)

The separate table will be provided for:

- number of subjects screened and number of screen failures (including reasons for failing) based on the ES. ES includes re-screened subjects

Table XX: Screening failures (Enrolled Set)

4.4.3 Protocol Deviations

All protocol deviations are predefined in the Protocol Deviation Analysis Plan.

4.4.3.1 Protocol Deviations with Non-PK Implications

The defined protocol deviations will be collected during the study period by site monitor/clinical team and programming team. All deviations related to study inclusion or exclusion criteria, conduct of the study, participant management or participant assessment, and handling of the participant's rights will be described.

4.4.3.2 Protocol Deviations with PK Implications

Protocol deviations that may potentially impact PK parameter derivations include, but are not limited to:

- Administration deviations – interruption of administration, etc.
- Missed PK samples that impact estimation of PK parameter(s)
- Concomitant medications not authorized by protocol
- PK samples obtained out of allowance window that may impact the estimation of PK parameter(s)
- Food intake deviations (consumed food other that provided by the staff)

Protocol deviations (mentioned in Sections 4.4.3.1 and 4.4.3.2) and analysis sets will be reviewed in the Planned Analysis Review meeting to decide inclusion or exclusion of participant(s) from analyses

sets or to exclude participant data from the analysis. Decisions regarding the exclusion of participants and/or participant data from analysis will be made prior to database lock and will be documented and approved.

A by-participant listing of *major* protocol deviations will be provided including participant identifier; actual treatment; visit; start date\time of deviation; protocol deviation term; protocol deviation code; and exclusion from specific analysis sets.

Listing XX: Important protocol deviation (TS)

4.5 Demographics and Baseline Characteristics

Demographic and baseline characteristics obtained at the screening visit (visit 1) will be summarized and listed based on the TS and displayed by dose group (see 4.2.1)

- Age (years)
- Sex
- Ethnicity
- Childbearing Potential
- Race

Table XX Demographics (Treated Set)

Listing XX Demographics (Treated Set)

Baseline characteristics obtained at the screening visit (visit 1) will be summarized and listed based on the TS and displayed by dose group (see 4.2.1)

- Height (cm)
- Weight (kg)
- Waist circumference (cm)
- Body Mass Index (BMI, kg/m^2);
- C-SSRS Assessment (Type 1\Type 2 or 3\ Type 4 or 5, Not reported)
- ECG Interpretation (Abnormal\Normal\Unevaluable)
- Temperature (C)
- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (beats/min)
- Physical Exam Performed (Yes\No, Not reported)
- Liver Fat fraction Result (%)
- [redacted]
- [redacted]
- Serum Pregnancy Test (Positive, Negative, Not reported)

Baseline C-SSRS assessments are the most severe suicidal ideation in the past 12 months prior and at Visit 1. Subjects with any suicidal ideation of type 2 to 5 on the C-SSRS in the past 12 months prior to Visit 1 are not eligible for treatment.
Baseline for other characteristics is the last observed measurement prior to drug administration.

Table XX Baseline characteristics (Treated Set)

Listing XX Baseline characteristics (Treated Set)

4.6 Medical and Surgical History

Medical history is collected via the eCRF and then coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or higher.

All related medical history will be summarized and listed including MedDRA SOC, PT, start date and stop date (or ongoing, if applicable) and displayed by dose group (see 4.2.1).

Number of subjects with a history will be counted by SOC and PT and by dose group. Percentages will be based on the number of subjects in the TS.

Table XX Medical history (Treated Set)

Listing XX Medical history (Treated Set)

4.7 Prior and Concomitant Medications

Medication taken before and during the study are collected in the eCRF and coded according to Anatomical Therapeutic Chemical (ATC) classification of the World Health Organization - Drug Dictionary (WHO-DD) January 2022 or later.

The TS will be used for listing and summary of prior and concomitant medication. The subject data listing and summary table will include the anatomical main group (level 1), the therapeutic subgroup (level 2), preferred name and reported term. Counts and percentages of subjects taking medication for each of these levels will be based on the number of subjects in the TS.

Medications that start and stop prior to the date of Visit 2 will be classified as Prior only. If a medication starts before the date of Visit 2 and stops on or after the date of Visit 2, then the medication will be classified as Prior and Concomitant. Medications will be classified as Concomitant only if they have a start on or after the date of Visit 2, but not after the last dose of study medication.

Table XX Prior and concomitant medication (Treated Set)

Listing XX Prior and concomitant medication (Treated Set)

4.8 Treatment Exposure and Compliance

4.8.1 Treatment Exposure

A by -subject listing of subject exposure to study drug will be generated for all dose groups together.

The listing will include dose groups, subjects, treatment name, date and time first exposure to treatment, actual dose, unit, fasting status, and route. Listing will include information if dose was skipped as well.

The total number of doses received per subject and time of study treatment per subject will be summarized by dose group for the TS. Number of doses received per subject will be provided with descriptive statistics and categorical information (0, 1, 2-5, 6-7, 8-9, 10-11, >=12).

Skipped dose summary will contain the number of subjects with at least one skipped dose, number subjects with skipped dose by category (0, 1, 2, 3, >3, where ">3" will be provided as the check of compliance of trial medication), and ratio of total number of doses skipped to total number of doses received. A dose was considered as skipped dose if the planned dose visit is skipped or if the dose is not administered for a planned visit. If dose was taken outside of 2 days (48 hours window) according to planned dose visit, we should consider it as protocol deviation but still count it as dose taken.

Table XX Treatment exposure (Treated Set)

Table XX Skipped dose summary (Treated Set)

Listing XX Treatment exposure (Treated Set)

4.8.2 Compliance

Compliance will be defined as below:

Compliance(%) = 100 × Total volume delivered (mg)/Total volume planned (mg).

Total volume delivered will be counted as number of doses per subject which are received × size of dose in mg.

Total volume planned will be counted as number of doses per subject which are planned in Protocol × size of dose in mg.

Exposure duration = Last date of exposure – First date of exposure + 1

A by-participant listing of treatment compliance will be provided.

Listing XX Treatment compliance (Treated Set)

4.9 Analysis Supporting Primary Objective(s)

Occurrence of drug-related AEs between the first administration of trial medication (BI 3006337 or placebo) and end of study (EOS) will be derived according to BI standards. Inferential statistics is not planned here. The analysis will be based on the treated set (TS) and will be descriptive in nature.

Refer to Section 4.13 for a description of the analysis of safety and tolerability, which are the primary objectives of this trial.

4.9.1 Primary Endpoint(s)

Occurrence of drug-related adverse events occurring between first administration of trial medication (BI 3006337 or placebo) and end of study (EOS).

4.9.2 Statistical Hypothesis, Model, and Method of Analysis

Not applicable.

4.9.3 Handling of Intercurrent Events

The expected intercurrent events of interest in this trial are restricted to the Treatment Period and are defined as:

- Premature treatment discontinuation of BI 3006337

All intercurrent events will be handled according to the treatment policy approach as defined in ICH E9 (R1).

4.9.4 Handling of Missing Values not Related to Intercurrent Event

Missing values won't be imputed for Primary Endpoints. Missing dates will be imputed as described in Appendix 6.2.

[redacted]

4.10 Analysis Supporting Secondary Objective(s)

The secondary endpoints will be analysed descriptively.

Pharmacokinetic
The PK parameters listed in section 3.2.4 for BI 3006337 will be calculated using noncompartmental analysis. Noncompartmental PK parameters will be calculated based on actual sampling times using a validated PK software (e.g., Phoenix® WinNonlin®). For details see Section 4.12.

The following descriptive statistics will be calculated for analyte concentrations as well as for all PK parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation.

The data format for descriptive statistics of concentrations will be identical to the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

Efficacy
Efficacy endpoints will be assessed: relative reduction in liver steatosis (as measured by MRI-PDFF) after 12 weeks of treatment compared with baseline (i.e., percentage change from baseline). For details see Section 4.11. Efficacy results will be listed and summarized for the Treated Set.

Trial participants who do not complete 12 weeks of treatment due to disruption related to COVID-19 will be replaced to achieve up to 100% sample size in each dose group; the main PoCP efficacy

analysis will exclude these trial participants,

4.10.2 Statistical Hypothesis, Model, and Method of Analysis

Not applicable.

4.10.3 Handling of Intercurrent Events

The expected intercurrent events of interest in this trial are restricted to the Treatment Period and are defined as:

- Premature treatment discontinuation of BI 3006337

All intercurrent events will be handled according to the treatment policy approach as defined in ICH E9 (R1). The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the premature treatment discontinuation happened.

There is an exception for evaluating efficacy analysis. Trial participants who do not complete 12 weeks of treatment due to disruption related to COVID-19 will not be taken into efficacy analysis (they will be replaced to achieve up to 100% sample size in each dose group).

.

4.10.4 Handling of Missing Values not Related to Intercurrent Event

Missing values won't be imputed for Primary Endpoints.

[redacted]

4.11 Efficacy Evaluation

Liver measurements listing and summaries will be presented by dose group (see 4.2.1) using the TS and will include the following information: liver steatosis (as measured by MRI-PDFF), [redacted] at baseline and after 12 weeks and percentage change in liver steatosis from baseline after 12 weeks of treatment.

[redacted]

Measurements after 12 weeks of treatment will correspond to visit 17. In case there are no measurements at visit 17, then unscheduled visits will be taken as measurements after 12 weeks of treatment.

Table XX Descriptive statistics of liver measurements change from baseline at week 12 (TS)

Listing XX Liver measurements (TS)

[redacted]

[redacted]

4.11.1 Analysis and Data Conventions

No formal testing of hypotheses has been planned in this study.

4.11.1.1 Handling of Dropouts or Missing Data

No imputation of missing data will be performed except for partial dates imputation mention in Section 0. For efficacy analysis data for the subject discontinued treatment due to COVID-19 will be excluded, see Section 4.10.3. [redacted]

4.11.1.2 Examination of Subgroups

Not applicable.

4.11.2 Primary Efficacy Variable(s)

Not applicable.

4.11.3 Secondary Efficacy Variables

The primary variable for the assessment of efficacy is the percentage change in liver steatosis (as measured by MRI-PDFF) from baseline after 12 weeks of treatment.

A plot showing the mean change from baseline and mean percentage change from baseline in liver steatosis over time within each dose group will be provided.

[redacted]

4.12 Pharmacokinetic Analysis, Concentration, and Parameter TFLs, and Statistical Analysis of Pharmacokinetic Parameters for Final Analysis

PK and [redacted] will not be analyzed for subjects allocated to Placebo (only for subjects allocated to treatment).

[redacted].

4.12.1 Pharmacokinetic Concentrations

Concentration Listings:

Pharmacokinetic and [redacted] data for BI 3006337 will be listed by subject for the PKS. Concentration listings will include nominal PK sampling time, actual sampling times relative to dose administration, deviation from nominal time, and percent deviation from nominal

time, and concentrations. Serum concentrations below the lower limit of quantification (LLOQ) will be presented as below the limit of quantification (BLQ) in the listings and the LLOQ value presented as a footnote. Missing PK samples will be reported as no sample (NS) or not reportable (NR) as appropriate and considered excluded from PK analysis.

Listing XX Pharmacokinetic BI 3006337 serum concentration (ug/L) summary (TS)

Concentration Summary Tables:

Source data as reported from the laboratory will be used for calculation of concentration summary statistics. Tabular summaries for concentration-time data will report N (number of subjects who received treatment), n (number of subjects with non-missing values), and n(BLQ) (the number of subjects with BLQ samples).

Concentration for BI 3006337 will be summarized by dose group and nominal timepoint for the PKS. The following descriptive statistics will be presented for serum concentrations obtained at each nominal time point: N, n, n(BLQ), arithmetic mean, SD, coefficient of variation (CV%), geometric mean, geometric CV% (calculated as: gCV% =SQRT(exp(s^2)-1)*100; where s is the SD of the log transformed values), median, minimum, and maximum values.

For summary tables, all BLQs will be considered zero, and the number of BLQs and non-BLQs at each scheduled time point will be reported. Summary Statistics will not be calculated if non-BLQ concentrations at a scheduled time point is <3 and will be reported as NC. In such case only n, minimum, and maximum should be presented.

The rules followed for calculation and presentation of concentration data with regards to the number of decimal places/significant digits for the listings of subject level concentrations and summary tables of concentration are as follows:

Concentration Listings and Tables	Rounding
Individual concentrations	*n* s.f. as supplied by bioanalytical laboratory
Minimum and Maximum	*n* s.f. capped at 4
Mean/SD/Median/Geomean	*n+1* s.f. capped at 4
CV%/gCV%	*1* d.p.
N/n	Whole number

s.f = significant figures, d.p. = decimal place

Table XX Pharmacokinetic BI 3006337 serum concentration (ug/L) summary (PKS)

Concentration Figures:

For each dose group, arithmetic mean linear/semi-logarithmic figures will be calculated by default when at least 2/3 of the individuals from that dose group have concentrations within the validated concentration range. The overall sample size to decide whether the "2/3 rule" is fulfilled is based on the total number of samples that were drawn at the specific time point (i.e., BLQ, NOR, NOA and NOS are included).

For each cohort, Geometric mean linear/ semi-logarithmic figures will be calculated by default when at least 2/3 of the individuals from that dose group have concentrations within the validated concentration range. The overall sample size to decide whether the "2/3 rule" is fulfilled is based on the total number of samples that were drawn at the specific time point (i.e., BLQ, NOR, NOA and NOS are included).

For individual linear/ semi-logarithmic figures all BLQ values will be substituted as follows:

BLQs at the beginning of a subject profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero. When using log/linear scale, these timepoints will be considered missing.

BLQs at the end of a subject profile (i.e., after the last incidence of a measurable concentration) will be set to missing.

Single BLQs which fall between two measurable concentrations will be set to missing.

Consecutive BLQs which fall between measurable concentrations will be set to missing. Measurable concentrations after consecutive BLQs will be set to missing.

To visualize subject-level concentrations and the comparison between groups for each dose group, the descriptive PK figures listed below will be generated. An LLOQ line in individual and summary plots will be included.

Figure XX Individual subject profiles for BI 3006337 Serum Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (PKS)

Figure XX Individual subject profiles for BI 3006337 serum concentration at predose – (Linear Scale and Semi-Logarithmic Scale) (PKS)

Figure XX Overlaid individual subject profiles for BI 3006337 Serum Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (PKS)

Figure XX Overlaid individual subject profiles for BI 3006337 serum concentration at predose – (Linear Scale and Semi-Logarithmic Scale) (PKS)

Figure XX Mean (± SD) BI 3006337 Serum Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (PKS)

Figure XX Mean (± SD) BI 3006337 serum concentration at predose – (Linear Scale and Semi-Logarithmic Scale) (PKS)

Figure XX Geomean (± SD) BI 3006337 Serum Concentration Time Data – (Linear Scale and Semi-Logarithmic Scale) (TS)

Figure XX Geomean (± SD) BI 3006337 serum concentration at predose – (Linear Scale and Semi-Logarithmic Scale) (TS)

Figures will be generated in black and white using unique line style and marker for each plot in the figure. For all PK concentration-time plots, linear scale will be used for x-axis (e.g., do not use an ordinal scale).
For BI 3006337 serum concentration at predose when using Ct1 at Visit 2 Day 01 in the figures assign the value to Visit 4 Day 8.

4.12.2 Pharmacokinetic Parameters

PK parameters will be provided by Clinical Pharmacology, Modeling, and Simulation (CPMS) group. PK parameters will be calculated by NCA methods from the concentration-time data using Phoenix® WinNonlin® Version 8.3 following these guidelines:

- Actual time from dose will be used in the calculation of all derived pharmacokinetic parameters, except when parameters are calculated for safety/dose escalation meetings when nominal times may be used to calculate PK parameters.
- There will be no imputation of missing data.
- Handling of BLQ samples for derivation of serum PK parameters after single dose administration
    - BLQs at the beginning of a subject profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero.
    - BLQs at the end of a subject profile (i.e., after the last incidence of a measurable concentration) will be set to missing.
    - Single BLQs which fall between two measurable concentrations will be set to missing.
    - Consecutive BLQs which fall between measurable concentrations will be set to missing. Measurable concentrations after consecutive BLQs will also be set to missing.
- Handling of BLQ samples for derivation of serum PK parameters after multiple dose administration
    - BLQs on subsequent dosing days and not separated by a washout: pre-dose values, BLQs in the absorption phase, and BLQs between evaluable concentrations will be set to missing
    - Terminal BLQs (at the end of subject profile) will be set to missing.

Pharmacokinetic parameters will be estimated according to the guidelines presented in Table 4-1. All parameters listed in Table 4.1 will be calculated for BI 3006337 whereas only $AUC_{0\text{-}10}$, C_{max}, and t_{max} will be calculated [redacted].

Table 4-1 Pharmacokinetic Parameter and Estimation

Parameter	Guideline for Derivation
C_{max}, $C_{max,ss}$, C_{min} (=$C_{min,ss}$), t_{max}, $t_{max,ss}$, t_{min} (=$t_{min,ss}$), C_{trough} (=$C_{pre,ss}$), $C_{\tau,1}$, $C_{pre,N}$	Obtained directly from the observed concentration-time data
[redacted]	
$AUC_{0\text{-}x}$ (=$AUC_{0\text{-}tz}$)	The AUC from zero time to the specific time x is the sum of areas up to the specific time x sample: $AUC_{0\text{-}x}$=$AUC_{0-x} = \int_0^x Cx * dx$

Parameter	Guideline for Derivation
$AUC_{0\text{-}tau}$ ($=AUC_{\tau,1}$)	The AUC over the dosing interval will be determined for multiple dose studies using the trapezoidal rule, as stated above.
[redacted]	
[redacted]	
[redacted]	

Parameter	Guideline for Derivation
[redacted]	
$AUC_{\tau,ss}$	The partial area (at steady state) from dosing time to dosing time plus Tau.
[redacted]	

PK Parameters Listings:

PK parameters will be listed by participant for the PKS. Additionally, $AUC_{0\text{-}10}$, C_{max}, and t_{max} for acetaminophen will be listed based on TS.

Listing XX Pharmacokinetic parameters summary (PKS)

[redacted]

PK Parameter Summary Tables:

Biostatistics group will consider the derived PK parameters as source data and will use this data without rounding for calculation of PK parameters summary statistics tables.

PK parameters will be summarized by dose group for the PKS. [redacted].

Tabular summaries for PK parameters will report N (number of subjects who received treatment) and n (number of subjects with non-missing values).

Descriptive statistics for calculated PK parameters will include N, n, arithmetic mean, SD, CV%, geometric mean, gCV%, median, minimum, and maximum values. For tmax, only N, n, median,

minimum, and maximum values will be presented. No descriptive statistics will be determined when fewer than three individual PK parameters are available.

Table XX Pharmacokinetic parameters summary (PKS)

[redacted]

The rules followed for presentation of PK parameters data with regards to the number of decimal places/significant digits for the listings of subject level PK parameters and summary tables of PK parameters are as follows:

Table 4-2 Layout of Pharmacokinetic Values

PK Parameter Listings and Tables	Rounding
Derived Individual parameters	3 s.f.
Directly Derived Individual parameters (C_{max}, C_{12}, C_{24})	*n* s.f. as supplied by the analytical laboratory but not more than 3 s.f.
Minimum and Maximum	3 s.f.
Mean/SD/Median/Geomean	3 s.f.
CV%/gCV%	1 d.p.
Comparative estimates (e.g., ratios)	3 d.p.
CI and other percentages	2 d.p.
p-values	4 d.p.
N/n	Whole number
Exceptions for PK Tables	
t_{max} individuals and min/max	2 d.p
t_{max} median only	2 d.p

s.f = significant figures, d.p. = decimal place

PK Parameter Figures:

Scatter plots of dose-adjusted PK parameters (Cmax,norm, AUCτ,norm, Cmax,ss, norm, AUCτ,ss, norm) versus dose (with symbols for geometric means) and versus subjects baseline weight will be created. Dose-adjusted value is observed value divided by the amount of planned dose (50, 100 or 150).

Figure XX Scatter plots of dose-adjusted PK parameters (PKS)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.13 Safety Evaluation

All safety summaries and analyses will be based upon the TS as defined in Section 4.4.1 unless otherwise specified in specific section.

4.13.1 Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

Adverse events will be coded using the MedDRA Version 24.1 or higher.

Listings showing adverse events will be based on the TS.

AE information will be listed per subject. The listing will include AE start/end date/time, relationship to study medication per the investigator's opinion, outcome, duration, leading to drop-out, action taken of the event, severity (intensity in Common Terminology Criteria for Adverse Events [CTCAE] grade), seriousness and concomitant medications or additional treatment given due to AE.

AE listings will be provided for all AEs, SAEs, AESI including DILI events by dose group, SOC and PT separately.

The following descriptive summaries will be produced for TEAEs with percentages based on the number of subjects in the TS and the same outputs for drug related TEAEs:

- A summary of the number and percentage of subjects reporting a TEAE by seriousness, relationship to study medication for each dose group
- A summary of the number and percentage of subjects reporting a TEAE by dose group, SOC and PT including the number of events.
- A summary of the number and percentage of subjects reporting a TE SAE by dose group, SOC and PT including the number of events.
- A summary of the number and percentage of subjects reporting a TE AESI (including DILI or systemic hypersensitivity reaction events) by dose group, SOC and PT including the number of events.
- A summary of the number and percentage of subjects reporting a TEAE leading to study discontinuation by dose group, SOC and PT including the number of events.
- A summary of the number and percentage of subjects reporting an immune related TEAE by dose group, SOC and PT including the number of events.

All Adverse Events (AEs)

All AEs will be listed including pretreatment AEs, SAEs, AESI including DILI or systemic hypersensitivity reaction events by dose group, SOC and PT separately.

Treatment-emergent Adverse Event

A TEAE will be defined as any AE that emerge during treatment (i.e., AE which started after study drug administration or pre-existed that worsened in severity after study drug administration) and those will be analyzed for the purpose of safety analysis.

TEAEs will be summarized by SOC and PT, including the number and percentage of subjects experiencing events, separately.

Severity Grade

TEAEs will be summarized by SOC, PT, and the worst grade (intensity in CTCAE) including the number and percentage of subjects experiencing events. If a participant reports the same TEAE more than once within that SOC and PT, the TEAE with the highest grade will be used in the corresponding summaries.

Relationship (Causality)

TEAEs will be summarized by SOC, PT, and causality, including the number and percentage of subjects experiencing events. Relationship to study drug will be tabulated respectively. If a participant reports the same TEAE more than once within that SOC and PT, the TEAE with the worst-case relationship to study drug will be in summaries including relationship to study treatment, the following relationships will be summarized: 'Not related', 'Related'. Subjects who experience the same event multiple times will be included in the most related category. Events with missing relationship will be considered as 'Related' to the last given study drug for summary purposes but recorded as missing in the listings.

Serious Adverse Events (SAE)

Serious Adverse Event is defined as any AE that fulfils at least one of the following criteria:

- Results in death
- Is life threatening;
- Requires hospitalization;
- Leads to disability or permanent damage;
- Is congenital anomaly or birth defect;
- Any other important medical event.

SAE will be summarized by SOC, and PT including the number and percentage of subjects experiencing events.

Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) will be summarized by SOC and PT, including the number and percentage of subjects experiencing events. Listing of AESI will be provided.

Potential Severe DILI events are considered as AESIs.

For participants with **abnormal** aminotransaminase at baseline (defined as ALT or AST >1.5x ULN), any of the following events will trigger the DILI Checklist:

- AST or ALT ≥2x baseline or ≥300 U/L (whichever occurs first); and concomitant TB >2x baseline;

- AST or ALT ≥2x baseline or ≥300 U/L (whichever occurs first); and concomitant INR >1.2x baseline;
- AST or ALT ≥2x baseline or ≥300 U/L (whichever occurs first) and any new or worsening signs and/or symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%);
- AST or ALT ≥3x baseline.

For participants with abnormal aminotransaminase at baseline the following events should lead to immediate discontinuation of trial treatment (active or comparator):

- Hepatic injury alerts number 1, 2 or 3
- AST or ALT >5x baseline or >500 U/L (whichever occurs first)
- Any magnitude of ALT or AST elevation above baseline and any new or worsening signs and/or symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

For participants with normal/near **normal levels** of ALT and AST at baseline (defined as ALT and AST <=1.5x ULN) any of the following events will trigger the DILI Checklist:

- AST (Aspartate Aminotransferase) or ALT (Alanine Aminotransferase) elevation ≥3x ULN combined with an elevation of TB (total bilirubin) ≥2x ULN measured at the same visit, or in samples drawn within 30 days of each other;
- Aminotransferase (ALT or AST) elevations ≥3x ULN and INR≥1.5x ULN measured at the same visit, or in samples drawn within 30 days of each other
- Aminotransferase (ALT or AST) elevations ≥3x ULN with new onset, or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%);
- Aminotransferase (ALT or AST) elevations ≥5x ULN.

The emergence of an isolated AST or ALT elevation between ≥3-fold and <5x ULN requires repeat testing within 72 h. DILI Checklist is not required unless repeat testing triggers alerts 1, 2, 3, or 4.

For participants with normal/near normal levels of ALT and AST at baseline, the following events should lead to immediate discontinuation of trial treatment (active or comparator):

- Hepatic injury alerts number 1, 2 or 3
- Hepatic injury alerts number 4, if persists >2 weeks
- AST or ALT elevation >8x ULN

For participants with normal/near normal or abnormal aminotransaminase at baseline, following completion of the DILI Checklist, if the BI investigational drug cannot be excluded as a possible cause of DILI event, then discontinuation should be made permanent without rechallenge. If an alternative causality, e.g., acute viral hepatitis, is confirmed by the DILI Checklist evaluation, then BI investigational drug may be re-started if warranted.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary, in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Table XX Summary of adverse events (TS)

Table XX Summary of drug-related adverse events (TS)

Table XX Adverse events by worst CTCAE grade, SOC, and PT (TS)

Table XX Drug-related adverse events by worst CTCAE grade, SOC, and PT (TS)

Table XX Adverse events by SOC, and PT (TS)

Table XX Drug-related adverse events by SOC, and PT (TS)

Table XX Serious adverse events by SOC, and PT (TS)

Table XX Drug-related serious adverse events by SOC, and PT (TS)

Table XX Adverse events of special interest (DILI or systemic hypersensitivity reaction) by SOC, and PT (TS)

Table XX Drug-related adverse events of special interest (DILI or systemic hypersensitivity reaction) by SOC, and PT (TS)

Table XX Adverse events leading to discontinuation by SOC, and PT (TS)

Table XX Drug-related adverse events leading to discontinuation by SOC, and PT (TS)

Table XX Potential DILI cases for subjects with normal ALT or AST at baseline (TS)

Table XX Potential DILI cases for subjects with abnormal ALT or AST at baseline (TS)

Figure XX Potential DILI cases with maximum ALT and Total Bilirubin on-treatment assessment (TS)

Figure XX Potential DILI cases with maximum AST and Total Bilirubin on-treatment assessment (TS)

[redacted]

[redacted]

4.13.2 Deaths, Serious Adverse Events, and Other Significant Adverse Events

The following listings will be provided:

- A by-subject listing of all deaths that occurred during the study
- A by-subject listing of all AEs.
- A by-subject listing of all AESI including DILI or systemic hypersensitivity reaction.
- A by-subject listing of all AEs leading to discontinuation of study treatment

Listings should follow the format described for AEs in Section 4.13.1 if appropriate.

Listing XX Adverse events (TS)

Listing XX Serious adverse events (TS)

Listing XX Adverse events of special interest including DILI or systemic hypersensitivity reaction (TS)

Listing XX Adverse events leading to discontinuation (TS)

Listing XX Drug related treatment emerged adverse events (TS)

4.13.3 Clinical Laboratory Evaluation

Clinical laboratory test results of hematology, biochemistry, urinalysis, urinary drug screening, coagulation and serology will be provided by participant. A list of current reference ranges of laboratory assessments is included in Section 6.3. Since laboratory ranges can depend on subject's age and sex, the reference ranges presented in Section 6.3 might differ from the ones used and presented on SDTM. For analysis purposes only the ranges present on the SDTM will be used.

All TLFs will display only the standard international (SI) units after conversion by means of standard conversion factors.

Quantitative clinical laboratory variables, i.e., hematology, biochemistry, and urinalysis will be summarized using descriptive statistics (n, mean, SD, minimum, maximum and median) by dose group and time-point. Additionally, a within-participant change will be calculated as the post-baseline measurement minus the baseline measurement and summarized in the same way.

Baseline definition will be defined in section 4.2.4.

Any quantitative laboratory parameters that are given as '<xx' or '>xx' in the database will be imputed with the numeric part of the value without the sign (e.g., <2.2 will be imputed as 2.2) for the calculation of the changes from baseline and for the descriptive statistics. In the listings, no imputations will be performed, and all data will be displayed as recorded in the database.

Each laboratory result will be classified as low (L), normal (N), or high (H) at each time point according to the laboratory supplied reference ranges. For hematology and biochemistry, shift tables will be presented showing the number and percentage of participants with shifts from baseline to each post-dose time point. Tabulations will be presented by dose group.

Measurements obtained at Screening and EOS will not be included in the shift tables.

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented by dose group and time-point.

All laboratory data will be displayed in listings.

A plot showing the mean change from baseline and mean percentage change from baseline in all clinical laboratory test results over time within each dose group will be provided.

Laboratory abnormalities that are considered clinically significant (CS) are recorded by investigator in the database as AEs. Therefore, no tabulation of laboratory values meeting any CS criteria (except liver chemistry) will be presented as all relevant information will be presented in the AE summaries. Laboratory assessments that are not marked as clinically significant but exceed normal ranges will be marked as potentially clinically significant.

Results of pregnancy tests (females only), serology, drugs of abuse and alcohol tests will be listed only.

Table XX Clinical laboratory evaluation (TS)

Table XX Clinically significant abnormal laboratory evaluation (TS)

Table XX Clinical laboratory evaluation by outside the reference range (TS)

Listing XX Clinical laboratory evaluation (TS)

Figure XX Glucose bedside mean linear plot (TS)

Figure XX Mean (+/- SD) clinical laboratory assessments (TS)

4.13.4 Vital Signs

The following vital signs parameters will be listed and summarized based on the TS:

- temperature
- systolic blood pressure (mmHg)
- diastolic blood pressure (mmHg)
- heart rate (beats/min)
- weight (kg)

A by-participant listing of all vital sign measurements and change from baseline will be presented.

Baseline will be defined in section 4.2.4.

Measured (observed) values including changes from baseline will be summarized by dose group and time point and by vital sign parameter (BP, pulse rate, respiratory rate, and temperature).

Measurements obtained at Screening and EOS will not be included in the shift tables or in the tabulations of descriptive statistics.

Table 4-2 Treatment-emergent markedly abnormal (TEMA)/ Potentially clinically significant (PCS) Criteria for Vital Signs

Variable	Unit	Criterion	
		Low	High
Systolic blood pressure	mmHg	≤ 80 and ≥ 20 decrease from Baseline	≥ 140 and ≥ 20 increase from Baseline
Diastolic blood pressure	mmHg	Value ≤ 60 and ≥ 15 decrease from Baseline	Value ≥ 90 and ≥ 15 increase from Baseline
Pulse rate	bpm	Value ≤ 40 and ≥ 15 decrease from Baseline	Value ≥90 and ≥15 increase from Baseline

Note: The change in measurement (increase or decrease) will be calculated relative to the value obtained at baseline. Both conditions must be satisfied for a measurement to be considered potentially clinically significant; bpm = Beats per minute.

For all vital sign parameters, shift tables will be presented showing the number and percentage of participants with shifts from baseline to each postdose time point.

Box plot of vital sign parameters over time and vital signs change from baseline will be presented for (systolic BP, diastolic BP, and pulse rate).

In addition, box plot of vital signs change from baseline per treatment will be presented for (systolic BP, diastolic BP, and pulse rate).

Table XX Vital signs (TS)

Table XX Vital signs shift from baseline (TS)

Figure XX Vital signs box plot (TS)

Figure XX Vital signs change from baseline box plot (TS)

Figure XX Vital signs change from baseline box plot per treatment (TS)

Listing XX Vital signs (TS)

4.13.5 ECG

Standard safety 12-lead ECGs will be performed as shown in the section 6.1.

The ECG will be evaluated by the Investigator as ‘Normal’, ‘Abnormal, NCS’ or ‘Abnormal, CS’.

All ECG parameters will be listed by participant including changes from baseline.

Baseline is defined in section 4.2.4.

Descriptive statistics for observed values and changes from baseline will be presented by dose group. A categorical QTc analysis will also be performed.

Measurements obtained at Screening and EOS will not be included in the shift tables.

Measurements obtained prior to dosing in each period will be included in the tabulations for the treatment received in that specific treatment period.

The listing of ECG abnormality will be presented separately.

Table XX 12-lead ECG results (TS)

Table XX Frequency of subjects with notable on treatment ECG findings (TS)

Listing XX 12-lead ECG results (TS)

Listing XX 12-lead ECG abnormal results (TS)

Table XX New ECG findings between baseline and end of study (TS)

4.13.6 Physical Examination

Physical examinations will be performed as shown in the section 6.1.

The full physical examination includes an assessment of general appearance and a review of systems (general appearance, neck, respiratory system, cardiovascular system, abdomen, extremities, and skin).

Clinically significant physical examination findings will be listed.

Listing XX Physical examination (TS)

4.13.7 Dose Escalation

Closed sessions of Dose Escalation Committee (DEC) will be conducted during this study. For more information see DEC SAP.

4.13.8 Other Analysis

4.13.8.1 Assessment of Local Tolerability

Local Tolerability will be summarized by dose group and by type (“swelling/induration”, “erythema/redness”, “pruritus”, “injection site pain”, or “other findings”) on the TS. Tabulations will include the site reaction along with the severity (mild, moderate, and severe) and a count of the number of times a participant had a mild, moderate, or severe reaction.

Clinically significant, moderate or severe injection site reactions are reported as adverse events.

Local tolerability with just not missing severity will be listed on the TS for all analysis timepoints and visits, including start date, study date, injection site reaction, severity, clinically significant assessment.

Table XX Local tolerability (TS)

Listing XX Local tolerability with severity (TS)

4.13.8.2 C-SSRS

C-SSRS will be summarized by dose group and presented in form of shift tables to reflect changes from baseline to maximum on-treatment value for types 1, 2\3 and 4\5 based on TS.

C-SSRS will be listed based on the TS for all timepoints and displayed by dose group (see 4.2.1).

Table C-SSRS shift from baseline to maximum on-treatment value (TS)

Listing XX C-SSRS results (TS)

4.13.8.3 Death listing

Death information, including any additional details recorded on the eCRF and randomised, first and last dose dates, will be listed based on TS, if data is available.

If no data available for subject, please, display in the output: “There are no observations for this study”.

Listing XX Death (TS)

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

4.15 Handling of Dropouts or Missing Data

No imputation of missing data will be performed except for partial dates imputation mention in Section 0.

4.16 Determination of Sample Size

It is planned to enroll 56 trial participants in total in this trial: the size of 14 trial participants per dose group (10 on BI 3006337 and 4 on placebo) is generally considered reasonable for the exploratory evaluation of multiple dose safety and PK.

[redacted]

Trial participants who cannot complete 12 weeks of treatment due to disruption related to COVID-19 will be replaced to achieve up to 100% sample size in each dose group.

No formal testing of hypotheses has been planned for this study. Therefore, no formal sample size calculations were performed. 36 subjects are considered to be adequate to analyze the study objectives.

[redacted]

5 REFERENCES

Not applicable.

6 APPENDICES

6.1 Schedule of Assessments

Table 6-1 Schedule of Assessments

Trial Period	**SCR**	**Treatment Period**															**EOS**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
Days	-48 to -4	-1 to 3	4	8	15-17	18	22	29	36	43	50	57	64	71	78-80	81	85	99
Informed consent	X																	
Randomisation		X																
BW & waist circumference	X	X			X	X											X	X
Height	X																	
Demographics	X																	
Relevant medical history	X																	
Concomitant therapy	X																	X
Review of inclusion and exclusion criteria	X																	
Drug administration		X		X	X		X	X	X	X	X	X	X	X	X			
Local tolerability at injection site[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
AE collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
C-SSRS completion[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
[redacted]																		
BI 3006337 in serum (PK)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																		
Glucose bedside test		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG	X	X			X	X	X	X	X	X	X				X			X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X																	X
MR imaging[2]	X																X	
[redacted]																		
Pregnancy testing[3]	X	X					X					X			X			X

1. Including SARS-CoV-2, hepatitis B and C testing

[redacted]

3. Serum pregnancy test at screening visit (test performed at central lab), and urine pregnancy test at the study site for other visits. Menstrual cycle status (not delayed or missed period) should be checked before the first dose (Visit 2). Applicable to only women of childbearing potential.

4. Local tolerability: see Section 5.2.5.1, Protocol.
5. C-SSRS, Columbia-Suicide Severity Rating Scale questionnaires will be administered at Visit 1 using the "baseline/screening" version. The "since last visit" version will be used at the following visits. Paper forms will be used for the assessment of C-SSRS (refer to Section 5.2.5.3, Protocol).
6. Blood sample should be collected before administration of trial medication.

[redacted]

6.2 Imputation Rules for Partial Dates

Imputed dates and time will NOT be presented in the listings.

Table 6-2 and Table 6-3 present algorithm for imputing partial dates for TEAE and prior/concomitant medication respectively.

Table 6-2 Algorithm for Treatment-Emergent Adverse Events:

Start/Increase Severity Date	Stop Date	Action
Known	Known	Considered as a treatment-emergent adverse event (TEAE) if start date on or after the date of the first dose of investigational product (IP)
	Partial	Considered as a TEAE if start date on or after the date of the first dose of IP. The last day of the month and the last month (ie, December) will be used if the stop day/month is missing.
	Missing	Considered as a TEAE if start date on or after the date of the first dose of IP
Partial, but known components show that it cannot be on or after first IP taken date	Known	Not a TEAE. The first day of the month and January will be used if the start day/month is missing.
	Partial	Not a TEAE. The first day of the month and January will be used if the start day/month is missing. The last day of the month and the last month (ie, December) will be used if the stop day/month is missing.
	Missing	Not a TEAE. The first day of the month and January will be used if the start day/month is missing.
Partial, could be on or after first IP taken date	Known	Considered as TEAE, if stop date is after first IP taken date. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date Considered as not TEAE, if stop date is prior to first IP taken date. The first day of the month and January will be used if the start day/month is missing.
	Partial	Considered as TEAE. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date. The last day of the month and the last month (ie, December) will be used if the stop day/month is missing.

Start/Increase Severity Date	Stop Date	Action
	Missing	Considered as TEAE. The first IP taken date will be used if start date is in the same month/year with first IP taken date, or the first day of the month and January will be used if the start day/month is after first IP taken date.
Missing	Known	Considered as TEAE if stop date is on or after the date of the first dose of IP.
	Partial	The last day of the month and the last month (ie, December) will be used if the stop day/month is missing. If the imputed stop date is on or after the first dose of IP considered as a TEAE; if the year is missing, considered as a TEAE
	Missing	Considered as a TEAE

Table 6-3 Algorithm for Prior/Concomitant Medications Categorization:

Start Date	Stop Date	Action
Known	Known	If stop date is prior to the date for the first dose of IP, considered as prior; if stop date is on or after the date for the first dose of IP, considered as concomitant.
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if the imputed stop date is on or after the date for the first dose of IP, considered as concomitant.
	Missing	Considered as concomitant.
Partial	Known	If stop date is prior to the date for the first dose of IP, considered as prior; If stop date is on or after the date for the first dose of IP, considered as concomitant. The first day of the month and January will be used if the start day/month is missing.
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if the imputed stop date is on or after the date for the first dose of IP, considered as concomitant. The first day of the month and January will be used if the start day/month is missing.
	Missing	Considered as concomitant. The first day of the month and January will be used if the start day/month is missing.
Missing	Known	If stop date is prior to the date for the first dose of IP, considered as prior; if stop date is on or after the date for the first dose of IP, considered as concomitant.
	Partial	The last day of the month and the last month (ie, December) will be used if the day/month of stop date is missing. If the impuated stop date is prior to the date for the first dose of IP, considered as prior; if he imputed stop date is on or after the date for the first dose of IP, considered as concomitant.
	Missing	Considered as concomitant.

6.3 Laboratory Test Parameters

Category	Lab Parameter	Age group	Sex	Normal Range	SI Units
Haematology	Haematocrit				
	Haemoglobin				
	RBC Count/Erythrocytes				
	Reticulocytes, absol.				
	WNC/Leucocytes				
	Platelet Count/Thrombocytes (quant)				
Automatic WBC differential (relative and absolute)	Neutrophils			1.96 – 7.23	GI/L
	Eosinophils			0.00 – 0.57	GI/L
	Basophils			0.0 – 2.0	%
	Monocytes			0.12 – 0.92	GI/L
	Lymphocytes	18 - 59	F	0.91 - 4.28	GI/L
		18 – 59	M	0.91 - 4.28	GI/L
		59+	F	0.80 - 3.00	GI/L
		59+	M	0.80 - 3.00	GI/L
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), relat.;				
	Neutrophils Bands; Neutrophils Bands, relat.;				
	Eosinophils/Leukocytes; Eosinophils, relat.;				
	Basophils/Leukocytes; Basophils, relat.;				
	Monocytes/Leukocytes; Monocytes, relat.;				
	Lymphocytes/Leukocytes; Lymphocytes, relat.				
Coagulation	Activated partial thromboplastin time				
	Prothrombin time – (Quick and INR)				
Enzymes	AST/GOT, SGOT			8 - 40	U/L
	ALT/GPT, SGPT		F	4 - 43	U/L
	ALT/GPT, SGPT		M	5 - 48	U/L
	ALP				
	GGT	18 - 59	F	4 - 49	U/L
		18 – 59	M	10 - 61	U/L
		59+	F	5 - 50	U/L
		59+	M	10 - 50	U/L
	CK		F	26 – 192	U/L
			M	39 – 308	U/L
	CK Isoenzyme MB [only if CK is elevated]				
	Lactate Dehydrogenase			53 - 234	U/L
	Lipase	18 - 50		0 – 100	U/L
		50 - 60		0 – 100	U/L
		60 - 70		0 – 120	U/L
		70 - 80		0 - 130	U/L
	Amylase	18 - 50		28 - 100	U/L
		50 - 60		28 - 120	U/L
		60 - 70		28 - 150	U/L
		70 - 83		50 - 252	U/L
	Calcitonin				
Hormones	TSH				

Category	Lab Parameter	Age group	Sex	Normal Range	SI Units
Urinalysis (Stix)	Urine Nitrite (qual)				
	Urine Protein (qual)				
	Urine Glucose (qual)				
	Urine Ketone (qual)				
	Urobilinogen (qual)				
	Urine Bilirubin (qual)				
	Urine RBC/Erythrocytes (qual)		F	0 – 8	/HPF
			M	0 – 3	/HPF
	Urine WBC/Leucocytes (qual)		F	0 – 12	/HPF
			M	0 – 5	/HPF
	Urine pH			5.0 – 8.0	
Substrates	Glucose (NaF plasma)				
	Insulin			1.90 – 23.00	uIU/mL
	HbA1c				
	Creatinine	18 – 50	F	31 – 101	umol/L
		18 – 50	M	40 – 110	umol/L
		50 – 70	F	31 – 101	umol/L
		50 – 70	M	40 – 119	umol/L
		70 – 80	F	31 – 110	umol/L
		70 – 80	M	40 – 137	umol/L
	Bilirubin, Total			3 – 21	umol/L
	Bilirubin, Direct			0 – 7	umol/L
	C-Peptide				
	Protein, Total	18 – 59		61 – 84	g/L
	Protein, Total	59+		60 – 80	g/L
	C-Reactive Protein (Quant)				
	Uric Acid	18 – 50	F	125 – 428	umol/L
		18 – 50	M	125 – 488	umol/L
		50 – 70	F	149 – 446	umol/L
		50 – 70	M	149 – 494	umol/L
		70+	F	149 – 446	umol/L
		70+	M	149 – 494	umol/L
	Cholesterol, total	20 – 30	F	3.31 – 5.64	mmol/L
		20 – 30	M	3.31 – 6.10	mmol/L
		30 – 40	F	3.65 – 6.21	mmol/L
		30 – 40	M	3.88 – 6.83	mmol/L
		40 – 50	F	4.01 – 6.85	mmol/L
		40 – 50	M	4.19 – 7.24	mmol/L
		50 – 60	F	4.42 – 7.53	mmol/L
		50 – 60	M	4.40 – 7.53	mmol/L
		60 – 70	F	4.86 – 8.28	mmol/L
		60 – 70	M	4.53 – 7.71	mmol/L
		70+	F	5.35 – 9.10	mmol/L
		70+	M	4.58 – 7.76	mmol/L
	Triglyceride				
	High density lipoprotein (HDL) cholesterol				
	Low density lipoprotein (LDL) cholesterol				

Category	Lab Parameter	Age group	Sex	Normal Range	SI Units
Electrolytes	Calcium			2.07 – 2.64	mmol/L
	Sodium	18 – 59		132 – 147	mmol/L
		59+		135 – 145	mmol/L
	Potassium			3.5 – 5.2	mmol/L
	Inorganic phosphate				
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)				
PCR Test	SARS-CoV-2				
Serum pregnancy test (only for female participants of childbearing potential at Visit 1 and if urine pregnancy test is positive at other visits	Human Serum Chorionic Gonadotropin				
Urine pregnancy test	Urine Chorionic Gonadotropin				

6.4 Visit Names

Time Point	Visit Long Name	Short Name
Screening	Screening	SCR
Treatment Period	Baseline	BSL
	Visit 2	V02
	Visit 3	V03
	Visit 4	V04
	Visit 5	V05
	Visit 6	V06
	Visit 7	V07
	Visit 8	V08
	Visit 9	V09
	Visit 10	V10
	Visit 11	V11
	Visit 12	V12
	Visit 13	V13
	Visit 14	V14
	Visit 15	V15
	Visit 16	V16
	Visit 17	V17
Follow-up	End of Study	EOS
	Early Termination	ET[a]
	Unscheduled	UNSCH

[a] In case of participant withdrawal the procedures planned at the end-of-study (EOS) visit will be performed at early termination (ET).

6.5 ECG Notable Criteria

ECG Parameters	**Definition/threshold**
QTcF	New onset of QTcF > 500 msec, or increase from baseline in QTcF > 60 msec.
QT	New onset of QT > 500 msec.
HR	Increase from baseline in HR >= 25%, when corresponding on treatment HR > 100 beats/min or decrease from baseline in HR >= 25%, when corresponding on treatment HR < 50 beats/min.
PR	Increase from baseline in PR >= 25%, when corresponding on treatment PR > 200 msec.
QRS	Increase from baseline in QRS >= 10%, when corresponding on treatment QRS is > 100 msec.

ECG = electrocardiogram; bpm = beats per minute; QTcF = QT corrected using Fridericia's formula

6.6 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
Liver laboratory triggers	3 × ULN < ALT/AST ≤ 5 × ULN
	1.5 × ULN < TBL ≤ 2 × ULN
Liver event	ALT or AST > 5 × ULN
	ALP > 2 × ULN (in the absence of known bone pathology)
	TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	ALT or AST > 3 × ULN and INR > 1.5
	Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN
	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any AE potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms.

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

[redacted]

[redacted]

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