STATISTICAL ANALYSIS PLAN

GB1211 - A Randomised, Double-Blind, Placebo-Controlled, First-In-Human, Study of Orally Administered GB1211 to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses (SAD) and Multiple Ascending Doses (MAD) in Healthy Subjects and in Subjects with Suspected Nonalcoholic Steatohepatitis (NASH) and Liver Fibrosis

Statistical Analysis Plan Status: Final V1
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Study Drug: GB1211

Sponsor Reference Number: GB1211-001 (Parts A and B)

Covance Study Number: 8392356

Clinical Phase 1

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1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical, pharmacokinetic (PK), and biomarker analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

Covance approval:

[redacted]
Statistician

25JUL2019
Date

[redacted]
Pharmacokineticist

30 Jul 2019
Date

Sponsor approval:

[redacted]
Chief Medical Officer

25th - Jul - 2019.
Date

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3 ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

ADaM	analysis data model
A_e	Amount of drug excreted unchanged in urine
AE	adverse event
$AUC_{0-\tau}$	Area under the plasma concentration-time curve over a dosing interval (τ = 12 hours)
$AUC_{0-tlast}$	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
$\%AUC_{extrap}$	Area under the plasma concentration-time curve extrapolated from last quantifiable concentration to infinity as a percentage of total AUC
BID	twice daily
BLQ	below the level of quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CL/F	Apparent total plasma clearance
CL_R	Renal clearance
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV%	coefficient of variation
EC	Early Clinical
ECG	electrocardiogram
f_e	Percentage of dose excreted unchanged in urine
ICH	International Conference on Harmonisation
LLOQ	lower limit of quantification

MedDRA	Medical Dictionary for Regulatory Activities
NASH	Nonalcoholic Steatohepatitis
NC	Not calculated
NR	No result
PK	pharmacokinetic
QTc	QT correction; QT interval corrected for heart rate
QTcB	QTc calculated using the Bazett correction
QTcF	QTc calculated using the Fridericia correction
$RA_{AUC0-\tau}$	Observed accumulation ratio based on $AUC_{0-\tau}$
RA_{Cmax}	Observed accumulation ratio based on C_{max}
SAP	Statistical Analysis Plan
TBD	To be determined
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
$t_{1/2}$	Apparent plasma terminal elimination half-life
T_{max}	Time of the maximum observed plasma concentration
Vz/F	Apparent volume of distribution during the terminal elimination phase

4 INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 2.0 dated 05 November 2018).

This SAP describes the planned analysis of the safety, tolerability, PK, and biomarker data from this study. A detailed description of the planned TFLs to be presented in the Clinical Study Report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical analyses of PK and Biomarker data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Galecto Biotech and Covance Early Clinical (EC) Biometrics. A limited amount of information concerning this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalised prior to the lock of the clinical database for this study. When the SAP and TFL shells are agreed upon and finalised, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between Galecto Biotech and Covance EC Biometrics and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports."[1,2]

5 STUDY OBJECTIVES

The primary objectives of the study are:

- to evaluate the safety and tolerability of single and multiple doses of GB1211 administered to healthy subjects.
- to evaluate the safety and tolerability of multiple doses of GB1211 administered to subjects with suspected NASH and liver fibrosis.

The secondary objectives of the study are:

- to evaluate the PK of single doses of GB1211 in plasma and urine in healthy subjects and the PK of multiple doses of GB1211 in plasma of healthy subjects and subjects with suspected NASH and liver fibrosis.
- to determine the effect of food on the single oral dose PK of GB1211.

The exploratory objectives of the study are:

- to investigate biomarkers related to GB1211 activity at single and/or multiple doses in comparison to placebo in healthy subjects and subjects with suspected NASH and liver fibrosis.
- to investigate biomarkers of metabolism, inflammation, and fibrosis following multiple doses of GB1211 in healthy subjects and/or subjects with suspected NASH and liver fibrosis.
- to identify metabolites of GB1211 in plasma and urine.

6 STUDY DESIGN

6.1 Part A

Part A will comprise a single-dose, sequential-cohort study incorporating a single-cohort, randomised, 2-part arm to investigate the effect of food. Overall, 40 subjects will be studied in 5 cohorts (Cohorts A1 to A5), with each cohort consisting of 8 subjects.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only, residing at the Clinical Research Unit (CRU) from Day -1 (the day before dosing) to Day 3 (48 hours postdose), except for the food-effect cohort (planned to be Cohort A3), where each subject will participate in 2 treatment periods separated by a minimum of 7 days.

All subjects will return for a Follow-up visit 5 to 7 days after their final dose.

Dose Regimen:

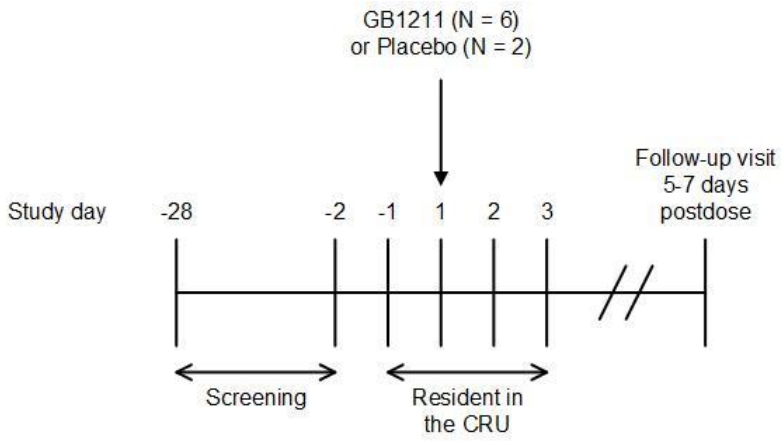
In each of Cohorts A1 to A5, 6 subjects will receive GB1211 and 2 will receive placebo. In all cohorts, except the food-effect cohort, all doses will be administered in the fasted state in accordance with a randomisation schedule on the morning of Day 1. For the food-effect cohort, which is planned to be Cohort A3, Treatment Period 1, Day 1 doses will be administered in the fasted state in accordance with the randomisation schedule and in Treatment Period 2, Day 1 doses will be given 30 minutes after the start of a high fat breakfast. Each subject in Cohorts A1 to A5 (except the food-effect cohort) will receive only a single dose of GB1211 or placebo during the study. In the food-effect cohort, subjects will receive the same treatment in both periods and will receive 2 single doses of GB1211 or placebo during the study.

In Cohorts A1 to A5 (except the fed period of the food-effect cohort), dosing will occur such that 2 subjects (1 active and 1 placebo) will be dosed at least 24 hours before the remaining subjects, where continuation to dose the remaining subjects will be at the Investigator's discretion.

Based on the ongoing review of the safety, tolerability, and PK results, additional nonresidential visits may be required. The number of additional visits per subject will not exceed 3 and will not extend beyond 28 days after each final dosing occasion.

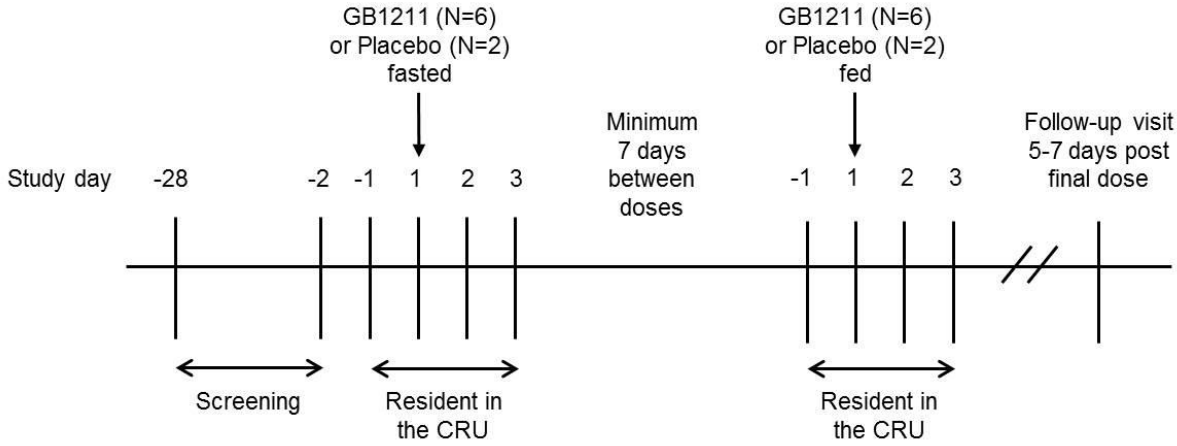
An overview of the study design is shown in Figure 1 and Figure 2 and the planned dose levels in Figure 3.

Figure 1: Study Schematic - Part A Cohorts (Except the Food-Effect Cohort)



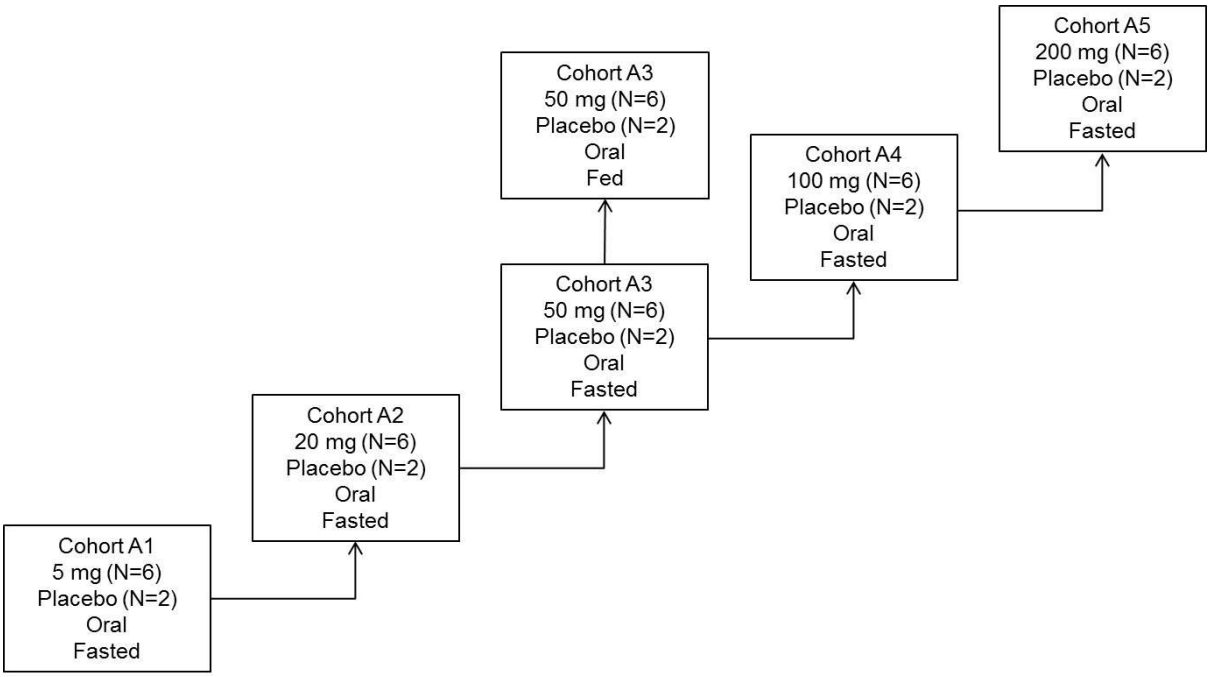
Abbreviation: CRU = Clinical Research Unit

Figure 2: Study Schematic - Part A Food-Effect Cohort (Planned to be Cohort A3)



Abbreviation: CRU = Clinical Research Unit

Figure 3: Planned Dose Levels (Part A)



The total duration of study participation for each subject (from Screening through Follow-up visit) for all Part A cohorts except the food-effect cohort is anticipated to be approximately 5 weeks. For each subject in the food-effect cohort (planned to be Cohort A3), the total duration is anticipated to be approximately 6 to 7 weeks.

6.2 Part B

Part B will comprise a multiple-dose, sequential-cohort study. Overall, 22 subjects will be studied in 2 cohorts (Cohorts B1 to B2), with each cohort consisting of 11 subjects. Dosing in Part B will start following review of safety, tolerability, and PK data from a single dose with exposure higher than the predicted steady-state exposure.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only and reside at the CRU from Day -1 (the day before dosing) until the morning of Day 11 (24 hours after the final dose on Day 10).

All subjects will return for a Follow-up visit 5 to 7 days after their final dose.

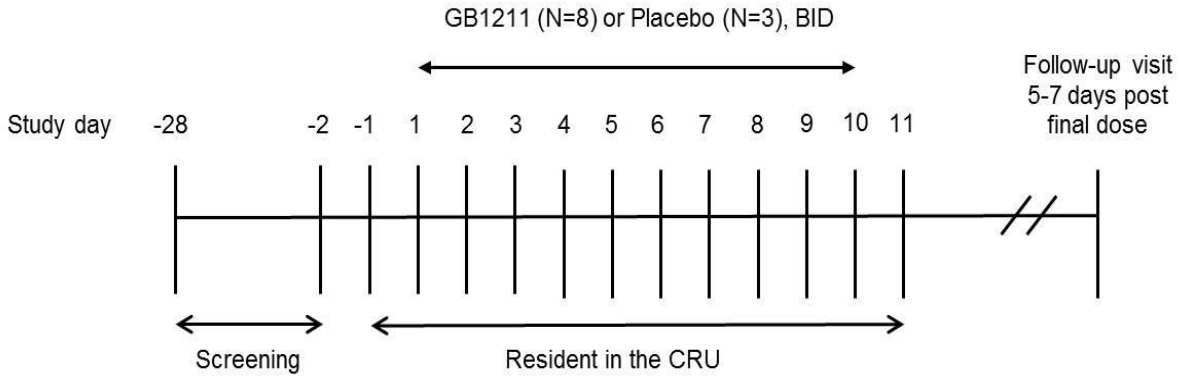
Dose Regimen:

In each of Cohorts B1 to B2, 8 subjects will receive GB1211 and 3 subjects will receive placebo. The dietary state for dosing in Part B will be fasted unless data from the food-effect cohort is

available and supports dosing in the fed state. For all subjects, the planned dosing will be BID on Days 1 to 9, inclusive, and a final single dose administration will occur in the morning of Day 10. The dosing interval/frequency and dosing duration in Part B may be changed following review of data from cohorts in Part A. The predicted total daily exposure will not exceed the highest exposure observed in Part A. There will be a minimum of 10 days between dose escalations for each cohort.

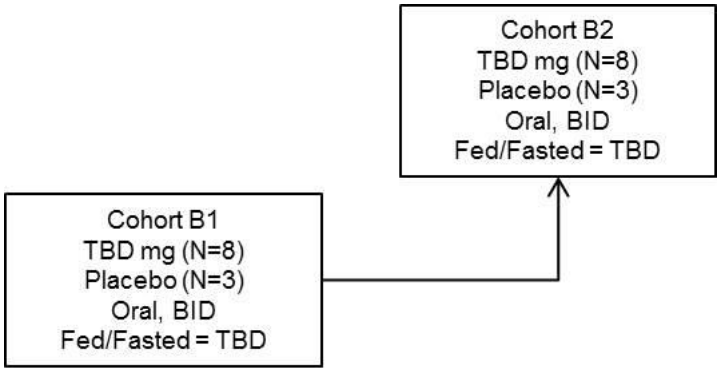
An overview of the study design is shown in Figure 4 and the planned dose levels in Figure 5.

Figure 4: Study Schematic (Part B)



Abbreviations: BID = twice-daily; CRU = Clinical Research Unit

Figure 5: Planned Dose Levels (Part B)



Abbreviations: BID = twice-daily; TBD = to be determined

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 6 to 7 weeks.

6.3 Part C (Optional)

Part C will comprise a multiple-dose cohort of 25 subjects with suspected NASH and liver fibrosis (Cohort C1). Part C may start following review of data from Part A and at least 1 Part B cohort.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Each subject will participate in 1 treatment period only and reside at the CRU from Day -1 (the day before dosing) until the morning of Day 2, returning for nonresidential visits on Days 7, 14, 21, 28, and 35. Subjects will then check back into the CRU on Day 41 until the morning of Day 43 (24 hours after the final dose on Day 42).

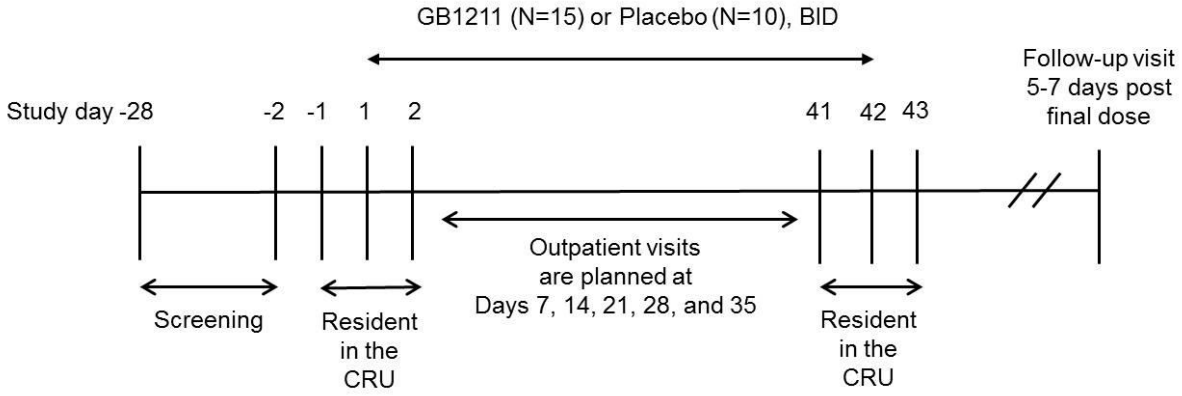
All subjects will return for a Follow-up visit 5 to 7 days after their final dose.

Dose Regimen:

For Part C, Cohort C1, 15 subjects will receive GB1211 and 10 subjects will receive placebo. The dietary state for dosing in Part C will be fasted unless data from the food-effect cohort is available and supports dosing in the fed state. For all subjects, the planned dosing will be BID on Days 1 to 41 inclusive, and a final single dose administration will occur in the morning of Day 42. The total daily dose administered, dose interval/frequency, and dosing duration will be based on review of data from Parts A and B.

An overview of the study design is shown in Figure 6.

Figure 6: Study Schematic (Part C)



Abbreviations: BID = twice-daily; CRU = Clinical Research Unit

The dose level of Part C is to be determined following completion of Part A and at least 1 cohort of Part B.

The total duration of study participation for each subject (from Screening through Follow-up visit) for Cohort C1 is anticipated to be approximately 11 weeks.

This SAP and the accompanying shells are related to the analysis of Parts A and B only.

7 TREATMENTS

The following is a list of the study treatment abbreviations and ordering that will be used in the TFLs.

Part	Study Treatment Name	Treatment Order on TFLs
A	Placebo (fasted)	1
	Placebo (fed)	2
	5 mg GB1211 (fasted)	3
	20 mg GB1211 (fasted)	4
	50 mg (10 x 5 mg) GB1211 (fasted)	5
	50 mg (1 x 50 mg) GB1211 (fasted)	6
	50 mg (1 x 50 mg) GB1211 (fed)	7
	100 mg GB1211 (fasted)	8
	200 mg GB1211 (fasted)	9
	400 mg GB1211 (fasted)	10
B	Placebo bid	11
	50 mg GB1211 bid	12
	100 mg GB1211 bid	13

8 SAMPLE SIZE JUSTIFICATION

No formal statistical assessment, in terms of sample size, has been conducted as this is the first time GB1211 is being administered to humans. However, the number of subjects in each part of the present study is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study.

9 DEFINITION OF ANALYSIS POPULATIONS

The **Safety Population** will consist of all subjects who received at least 1 dose of study drug (GB1211 or placebo).

The **PK population** will include all subjects who received at least 1 dose of GB1211 and have evaluable PK data. A subject may be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2-times median time to maximum concentration.

The **Biomarker Population** will include all subjects who received at least 1 dose of study treatment (GB1211 or placebo) and have at least 1 postdose biomarker assessment.

All protocol deviations that occur during the study will be considered prior to database lock for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations. Details of subject assignment to the analysis populations will be listed.

The **All Subjects Population** will consist of any subjects who signed informed consent and had study assessments recorded on the database as per the protocol.

10 STATISTICAL METHODOLOGY

10.1 General

Data listings will be provided for the All Subjects Population. Summary statistics and statistical analyses will be performed for subjects included in the relevant analysis populations (Safety/PK/Biomarker).

For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation, median, minimum, maximum, and number. For log-normal data (eg, the PK parameters: areas under the concentration-time curve [AUCs] and maximum observed concentration [C_{max}]), the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency counts and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Missing values will not be imputed.

Data analysis will be performed using SAS® Version 9.4 or later.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1, and CDISC ADaM Implementation Guide Version 1.1. Pinnacle 21 Community Validator Version 2.2.0 will be utilised to ensure compliance with CDISC standards.

10.1.1 Definition of Baseline and Change from Baseline

Baseline for each parameter is defined as the last value measured prior to dosing, including repeat (vital signs and electrocardiograms [ECGs]) and unscheduled (clinical laboratory parameters) readings (see Section 10.1.2 for definitions of repeat and unscheduled readings). For vital signs taken in triplicate, baseline will be the median of the last 3 values taken prior to dosing (pre-am dosing for multiple dose parts). For ECGs taken in triplicate, baseline will be the mean of the last 3 values taken prior to dosing (pre-am dosing for multiple dose parts).

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

10.1.2 Repeat and Unscheduled Readings

Repeat readings occur when the original vital signs or ECG result requires confirmation. Repeat readings are labelled as 'Repeat' in the listings and replace the original readings in all summaries and changes from baseline presentations and calculations. Prior to dosing, all readings taken in addition to the original reading are defined as predose repeats. Postdose repeat readings are defined as readings collected within 15 minutes of the actual time of the original reading. Where results are taken in triplicate and repeated, the last 3 readings are used in all subsequent calculations**.**

With the exception of predose results described above, unscheduled readings for vital signs or ECGs are defined as readings collected >15 minutes from the actual time of the original reading. Where results are taken in triplicate, the original reading is defined as the first reading of the triplicate. All results not taken at a scheduled timepoint for other data types (eg, clinical laboratory parameters) are unscheduled. Unscheduled readings are labelled as 'Unscheduled' in the listings. Because unscheduled readings are not associated with any scheduled timepoint, they are excluded from all summaries (with the exception that they may be used as baseline, as stated in Section 10.1.1).

10.2 Demographics and Subject Disposition

The demographic variables age, sex, race, ethnicity, body weight, height, and body mass index will be summarised and listed. Subject disposition will be summarised and listed.

10.3 Pharmacokinetic Assessment

The following pharmacokinetic parameters will be determined where possible from the concentrations of GB1211 using non-compartmental methods performed using Phoenix WinNonlin (Certara, Inc., Version 8.1 or higher):

Part A (Single Dose)

Plasma

Parameter	Definition
$AUC_{0\text{-}tlast}$	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
$AUC_{0\text{-}\infty}$	Area under the plasma concentration-time curve from time zero to infinity
$\%AUC_{extrap}$	Area under the plasma concentration-time curve extrapolated from last quantifiable concentration to infinity as a percentage of total AUC
C_{max}	Maximum observed plasma concentration
T_{max}	Time of the maximum observed plasma concentration
$t_{1/2}$	Apparent plasma terminal elimination half-life
CL/F	Apparent total plasma clearance
V_z/F	Apparent volume of distribution during the terminal elimination phase

Urine

Parameter	Definition
A_e	Amount of drug excreted unchanged in urine (and cumulative A_e)
f_e	Percentage of dose excreted unchanged in urine (and cumulative f_e)
CL_R	Renal clearance

Parts B and C (Multiple Dose)

Plasma

Parameter	Definition
$AUC_{0\text{-}\tau}$	Area under the plasma concentration-time curve over a dosing interval (τ = 12 hours)
$AUC_{0\text{-}\infty}$	Area under the plasma concentration-time curve from time zero to infinity (Day 1 only)
$\%AUC_{extrap}$	Area under the plasma concentration-time curve extrapolated from last quantifiable concentration to infinity as a percentage of total AUC (Day 1 only)
C_{max}	Maximum observed plasma concentration
C_{min}	Minimum observed plasma concentration
T_{max}	Time of the maximum observed plasma concentration
$t_{1/2}$	Apparent plasma terminal elimination half-life
CL/F	Apparent total plasma clearance
V_z/F	Apparent volume of distribution during the terminal elimination phase
$RA_{AUC0\text{-}\tau}$	Observed accumulation ratio based on $AUC_{0\text{-}\tau}$
RA_{Cmax}	Observed accumulation ratio based on C_{max}

In addition, dose and body weight normalised values (norm) for $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\tau}$, $AUC_{0\text{-}\infty}$ and C_{max} will be determined by dividing the original PK parameter by mg/kg.

Additional pharmacokinetic parameters may be determined where appropriate.

Pharmacokinetic analysis will, where possible, be carried out using actual postdose times recorded in the raw data. If actual sampling times are missing, nominal times may be used.

Concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

C_{max}, C_{min} and T_{max} will be obtained directly from the plasma concentration-time profiles.

For multiple peaks, the highest postdose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest T_{max} will be reported.

AUC will be calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing (linear up/log down rule).

The parameters based on observed C_{last} will be reported.

The amount excreted in urine (A_e) for each urine collection interval will be calculated as the product of urine concentration and urine volume; Cumulative A_e will be calculated by summing the Ae values for each collection interval over the 0-48 h period.

The percent of the dose excreted (f_e) will be calculated for each urine collection interval (i) and cumulatively over 0-48 h according to the following formula:

$$\text{fe(i)} = \frac{\text{Ae(i)}}{\text{dose}} \times 100$$

CL_R will be calculated according to the following formula:

$$CL_{R\,0-x\,h} = \frac{Ae_{0-x\,h}}{AUC_{0-x\,h}}$$

where 0-x h represents a common cumulative time interval (eg, 0 to 48 hours after dosing).

10.3.1 Criteria for Handling Concentrations Below the Limit of Quantification in Pharmacokinetic Analysis

- Concentration values that are below the level of quantification (BLQ) will be set to zero, with defined exceptions as follows;
    - Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.

- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.

- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.

10.3.2 Criteria for the Calculation of an Apparent Terminal Elimination Half-Life Number of Data Points

- At least three data points will be included in the regression analysis and preferably should not include C_{max}.

10.3.2.1 Goodness of Fit

- When assessing terminal elimination phases, the R^2 adjusted value will be used as a measure of the goodness of fit of the data points to the determined line.

- An elimination half-life will only be calculated if the R^2 adjusted value of the regression line is greater than or equal to 0.7.

10.3.2.2 Period of Estimation

- Time period used for the estimation of apparent plasma terminal elimination half-lives, where possible, will be over at least two half-lives.

- Where an apparent plasma terminal elimination half-life is estimated over a time period of less than twice their resultant half-lifethe robustness of the value should be discussed in the study report.

10.3.2.3 Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

- For any partial AUC determination (i.e. AUC over a dosing interval), nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals may be used at the discretion of the Pharmacokineticist.

- $AUC_{0-\infty}$ values where the percentage extrapolation is less than 20% will be reported. $AUC_{0-\infty}$ values where the percentage extrapolation is greater than 20% may be excluded from descriptive statistics as discretion of pharmacokineticist

10.3.2.4 Anomalous Values

- If a value is considered to be anomalous due to being inconsistent with the expected pharmacokinetic profile, it may be appropriate to exclude this point from the

pharmacokinetic analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and study report.

10.4 Presentation of Pharmacokinetic Data

10.4.1 Presentation Pharmacokinetic Concentration Data

- The following rules will be applied if there are values that are BLQ or if there are missing values (e.g., no result [NR]) in a concentration data series to be summarised.
    - For the calculation of summary statistics, BLQ values will be set to zero.
    - If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.
    - Where there is NR, these will be set to missing.
    - If there are less than three values in the data series, only the min, max and N will be presented. The other summary statistics will be denoted as not calculated (NC). BLQ is considered a value.
    - If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, min and max will be presented as zero, and the geometric mean and geometric CV% will be denoted as NC.
    - If the value of the arithmetic mean or median is below the lower limit of quantification, these values will be presented as zero and the geometric mean and geometric CV% will be denoted as NC.

10.4.2 Pharmacokinetic Statistical Methodology

All investigational product plasma concentration data and derived PK parameters will be listed and summarised.

Dose proportionality for Part A

$AUC_{0-\infty}$, $AUC_{0-tlast}$ and C_{max} will be assessed for dose proportionality on Day 1 for Part A (fasted doses only). Data will be analysed over 2 dose ranges: 50 mg to 400 mg (50 mg capsule formulation) and 5 to 50 mg (5 mg capsule formulation). Data will be presented graphically to display the PK of the treatments.

To investigate dose proportionality[3] a statistical analysis using the power model[3] will be conducted. The power model will have the form:

$$Y = a*(dose)^b$$

where Y is the PK parameter, and a and b are the coefficient and exponent, respectively, of the power equation.

By taking logarithms, the power model can be analysed using linear regression and has the form:

$$\ln(Y) = b*\ln(dose) + error$$

For dose proportionality the slope of the regression line (b) = 1 and for dose independence b = 0.

An additional classification term for treatment will be added to the above model to assess departure from linearity. Linearity, and hence the power model, will be assumed appropriate if the treatment term is not significant at the 5% significance level and the diagnostic plots seem reasonable. The assessment of linearity may also be determined visually from plots by the pharmacokineticist. This assessment may over-ride the statistical assessment, where this occurs it will be detailed in the CSR.

If the assumption of linearity is considered acceptable and the 95% confidence interval (CI) for b is close to unity, the relationship between dose and the PK parameter will be concluded to be dose proportional for the dose range studied. Caution should be used when interpreting results since this study is not based on power calculations.

If the assumption of linearity is considered unacceptable then log-transformed[4], dose-normalised PK parameters will be analysed using an analysis of variance[5] (ANOVA) model. The model will include treatment as a fixed effect.

Least squares (LS) mean for each dose level will be calculated. P-values for overall and pairwise treatment comparisons will be presented.

Residual plots will be produced to assess the adequacy of the model.

An example of the SAS code that will be used is as follows:

```
/* Lack of fit test */
proc mixed data=<indata>;
  class trtmnt;
  model l_pk = logdose trtmnt / htype=1;
  ods output tests1=tests;
  run;
```

```
/* Exponent parameters */
proc mixed data=<indata>;
  model l_pk = logdose / solution cl alpha=0.1;
  ods output solutionf=estimate;
 run;

/* Dose normalised parameters */
proc mixed data=<indata>;
  class trtmnt;
  model l_pk = trtmnt;
  lsmeans trtmnt / pdiff alpha=.05 cl;
run;
```

where l_pk is the log-transformed (base e) PK parameter.

Statistical analysis will be used to determine pooled estimates (across the dose levels analysed) of the between-subject variability in the PK parameters.

Dose proportionality for Part B

$AUC_{0-\tau}$ and C_{max} will be assessed for dose proportionality on Day 10 for Part B. Data will be presented graphically to display the PK of the treatments.

Log-transformed, dose-normalised PK parameters will be analysed using an ANOVA model. The model will include treatment as a fixed effect.

Least squares (LS) mean for each dose level will be calculated. P-values for overall and pairwise treatment comparisons will be presented.

Residual plots will be produced to assess the adequacy of the model.

Statistical analysis will be used to determine pooled estimates (across the dose levels analysed) of the between-subject variability in the PK parameters.

Food effect

The PK parameters $AUC_{0-\infty}$, $AUC_{0-tlast}$ and C_{max} will be log-transformed (base e) prior to analysis and will be analysed using a mixed model[6]. The model will include treatment as a fixed effect and subject as a random effect. An example of the SAS code that will be used (assuming TRTMNT coding is 1= fed state, 2= fasted state) is as follows:

```
proc mixed data=xxx;
class subject trtmnt;
model l_pk = trtmnt / ddfm=kr;
random intercept / subject=subject;
estimate 'Test - Ref' trtmnt 1 -1 / cl alpha=0.1;
lsmeans trtmnt;
run;
```

where l_pk is the log-transformed (base e) PK parameter.

Least squares means will be calculated for the fed and fasted treatments. Mean differences between the fed and fasted treatments will be calculated. The residual variance from the mixed model will be used to calculate 90 and 95% CIs for the difference between the fed and fasted treatments. These values will be back-transformed to give geometric least squares means, a point estimate and 90 and 95% CIs for the ratio of the fed treatment relative to the fasted treatment. Within-subject coefficients of variation (CV_W) will be calculated for based on the log-normal distribution using the following formula:

$$CV_W(\%) = [\exp(mse) - 1]^{½} \times 100$$

where mse is the residual error from the mixed model.

Residual plots will be produced to assess the adequacy of the model.

10.5 Biomarker Assessment

Exploratory biomarker data will be listed and summarised using descriptive statistics. No formal statistical analysis of exploratory biomarker data is planned. Changes from baseline will be listed and summarised. Boxplots of changes from baseline will also be presented by treatment.

10.6 Safety and Tolerability Assessments

10.6.1 Adverse Events

A baseline sign and symptom is defined as an adverse event (AE) that starts after the subject has provided written informed consent and that resolves prior to the first dosing occasion, or an AE that starts prior to the first dosing occasion and does not increase in severity after dosing. A treatment-emergent AE (TEAE) is defined as an AE that occurs postdose or that is present predose and becomes more severe postdose.

All AEs will be listed. The TEAEs will be summarised by treatment, severity, and relationship to the study drug. The frequency (the number of TEAEs, the number of subjects experiencing a TEAE, and the percentage of subjects experiencing a TEAE) of TEAEs will be summarised by treatment, and by Medical Dictionary for Regulatory Activities system organ class and preferred term. A frequency summary will be presented by day of onset across the multiple-dosing period. The summary and frequency TEAE tables will be presented for all causalities and for those TEAEs considered related to the study drug (those that have a relationship of possibly related or

related). Any severe or serious AEs will be tabulated. For any AEs that change severity ratings the AE will be included only once under the maximum severity rating in the summaries.

For multiple dose parts onset times postdose are calculated from the last dose administered.

10.6.2 Clinical Laboratory Parameters

Serum biochemistry and haematology data will be summarised by treatment. Changes from baseline will be calculated. In addition, all serum biochemistry, haematology, and urinalysis data outside the clinical reference ranges will be listed by parameter and treatment.

Values for any serum biochemistry, haematology, and urinalysis values outside the clinical reference ranges will be flagged on the individual subject data listings.

10.6.3 Vital Signs

Where vital signs are measured in triplicate (at approximately 2-minute intervals), the median value will be used in all subsequent calculations. Changes from baseline will be calculated.

Vital signs values outside the clinical reference ranges will be flagged on the individual subject data listings.

The vital signs data will be summarised by treatment, together with changes from baseline. Figures of mean vital signs and mean change from baseline profiles will be presented by treatment.

10.6.4 Electrocardiogram

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the QT interval calculated using the Bazett correction (QTcB), the QT interval calculated using the Fridericia correction (QTcF), the PR and QT intervals, the QRS duration, and heart rate.

Where ECGs are measured in triplicate (at approximately 2-minute intervals), the mean value will be used in all subsequent calculations. Changes from baseline will be calculated.

Values for ECG parameters outside the clinical reference ranges will be flagged on the individual subject data listings.

The ECG data will be summarised by treatment, together with changes from baseline. Figures of mean ECG data and mean change from baseline profiles will be presented by treatment.

An outlier analysis will be performed including all individual postdose measurements (not the mean data), including all repeat and unscheduled readings. The frequency of subjects with a maximum increase from baseline in QTcB and QTcF intervals will be summarised for each treatment according to the following categories: >30, >60, and ≤30 ms. All incidences of >30 and >60 ms will be flagged on the listing. In addition, the frequency of subjects with QTcB and QTcF postdose values will be summarised for each treatment, according to the following

categories: >450, >480, >500, and ≤450 ms. All incidences of >450, >480, and >500 ms will be flagged on the listing.

10.6.5 Other Assessments

All other safety assessments not detailed in this section will be listed but not summarised or statistically analysed.

Medical history data will not be presented.

10.6.6 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11 INTERIM ANALYSES

No interim statistical analyses are planned.

12 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol-specified statistical analyses.

13 DATA PRESENTATION

13.1 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, "No serious adverse events occurred for this study."

14 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

3. Gough K, Hutchinson M, Keene O, Byrom B, Ellis S, Lacey L et al. Assessment of dose proportionality: Report from the Statisticians in the Pharmaceutical Industry/Pharmacokinetics UK joint working party. Drug Information Journal 1995; 29: 1039-1048.

4. Keene ON. The log transformation is special. Statistics in Medicine 1995; 14: 811-819.

5. Snedecor GW, Cochran WG. Statistical Methods (8th edition). Iowa: Iowa State Univ Press, 1989: 217-253.

6. Brown H, Prescott R. Applied Mixed Models in Medicine. Wiley, 1999; Ch 7.