Official Title: An Open-label, Single-dose, Parallel-group, Two-part Study to Evaluate the Pharmacokinetics and Safety of Risdiplam in Subjects with Mild or Moderate Hepatic Impairment Compared to Subjects with Normal Hepatic Function

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STATISTICAL ANALYSIS PLAN

An Open-label, Single-dose, Parallel-group, Two-part Study to Evaluate the Pharmacokinetics and Safety of Risdiplam in Subjects with Mild or Moderate Hepatic Impairment Compared to Subjects with Normal Hepatic Function

Statistical Analysis Plan Version: 2
Statistical Analysis Plan Status: Final
Statistical Analysis Plan Date: 18 October 2019

Study Drug: risdiplam

Sponsor Reference Number: BP40995
Covance Study Number: 8397571

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, and pharmacokinetic (PK) 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:

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Statistician

22 Oct 2019
Date

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22 Oct 2019
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8 Oct 2019
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2 TABLE OF CONTENTS

3 ABBREVIATIONS

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

ADaM	analysis data model
AE	adverse event(s)
ANOVA	analysis of variance
AUC	area under the plasma concentration-time curve
AUC_{inf}	area under the plasma concentration-time curve from time zero to infinity
$AUC_{inf,u}$	unbound AUC_{inf}
AUC_{last}	area under the plasma concentration-time curve from time zero to the last measurable concentration
$AUC_{last,u}$	unbound AUC_{last}
$\%AUC_{extrap}$	percentage of area under the plasma concentration-time curve due to extrapolation
BLQ	below the limit of quantification
BMI	body mass index
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence intervals
CL/F	apparent total plasma clearance
CL/F_u	unbound CL/F
C_{max}	maximum observed plasma concentration
$C_{max,u}$	unbound C_{max}
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV%	coefficient of variation
ECG	electrocardiogram
f_u	fraction unbound
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
LLOQ	lower limit of quantification
MR_{AUCinf}	metabolic ratio based on AUC_{inf}
$MR_{AUClast}$	metabolic ratio based on AUC_{last}
MR_{Cmax}	metabolic ratio based on C_{max}
NC	not calculated
NR	no result
PK	pharmacokinetic(s)
QTcF	QTc calculated using the Fridericia's correction
R^2-adjusted	adjusted coefficient of determination for exponential fit
SAE	serious adverse event(s)
SAP	Statistical Analysis Plan
$t_{1/2}$	apparent plasma terminal elimination half-life
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
T_{max}	time of the maximum observed plasma concentration

V_z/F	apparent volume of distribution during the terminal elimination phase
V_z/F_u	unbound V_z/F
λ_Z	apparent terminal elimination rate constant

4 INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 1 dated 08 January 2019).

This SAP describes the planned analysis of the safety, tolerability, and PK 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 safety data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between F. Hoffmann La Roche Ltd. and Covance. 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 finalized, 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 F. Hoffmann La Roche Ltd. and Covance 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 objective of the study is:

- to determine the effect of mild or moderate hepatic impairment on the plasma PK of a single oral dose of risdiplam compared to matched healthy subjects with normal hepatic function.

The secondary objective of the study is:

- to determine the effect of mild or moderate hepatic impairment on the safety and tolerability of a single oral dose of risdiplam compared to matched healthy subjects with normal hepatic function.

6 STUDY DESIGN

This is a Phase I, multi-center, open-label, non-randomized, parallel-group, 2-part study to evaluate the effect of hepatic impairment on the PK and safety and tolerability of a single oral dose of risdiplam compared to matched healthy subjects with normal hepatic function.

In Part 1, 8 subjects with mild hepatic impairment (per Child-Pugh Class A [score of 5 to 6] as assessed at Screening and Check-in [Day -1]) and 8 demographically matched healthy subjects with normal hepatic function will be enrolled. Preliminary PK and safety and tolerability data from a minimum of 4 subjects with mild hepatic impairment and 4 matched subjects with normal hepatic function will be reviewed prior to the start of Part 2.

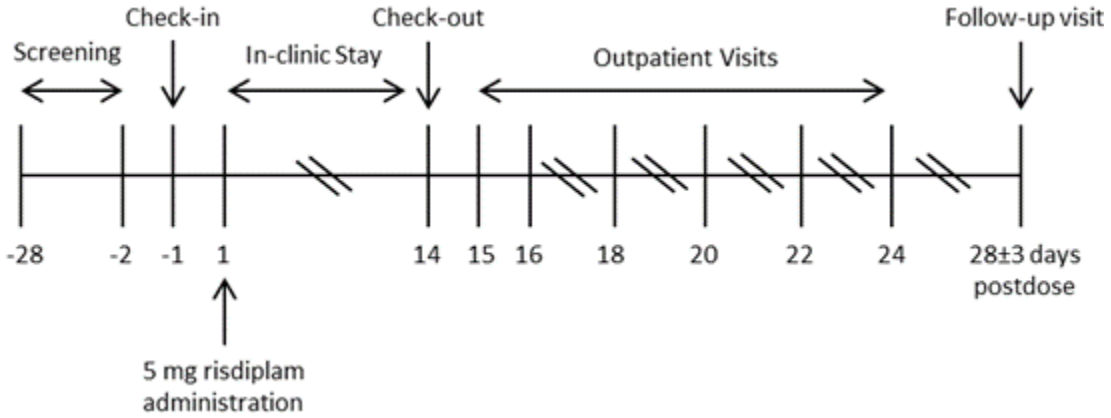
In Part 2, 8 subjects with moderate hepatic impairment (per Child-Pugh Class B [score of 7 to 9] as assessed at Screening and Check-in [Day -1]) and 8 demographically matched healthy subjects with normal hepatic function will be enrolled.

Hepatic function for subjects with hepatic impairment will be classified according to the Child-Pugh system.

In Parts 1 and 2, each subject with normal hepatic function (ie, matched control subject) will be enrolled following the completion of a mild or moderate hepatically impaired subject. Each subject with normal hepatic function will be demographically matched (1:1) by sex, age (±10 years), body mass index (BMI) (±15%), and smoking status to the completed hepatic impairment subject(s). Should another subject with hepatic impairment be identified with whom an already enrolled healthy subject is demographically matched, the healthy subject may also be matched with that impaired subject as long as the impaired subject is in a different hepatic group (ie, a subject with normal hepatic function may serve as a matched control across both Part 1 and Part 2 but may only serve as a matched control to a maximum of 1 hepatically impaired subject within either Part 1 or Part 2).

An overview of the study design is shown in Figure 1.

Figure 1: Study Schematic



Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to study drug administration. Subjects will be admitted into the Clinical Research Unit (CRU) on Day -1 and be confined to the CRU until discharge on Day 14. Subjects will return to the CRU for outpatient visits on Days 15, 16, 18, 20, 22, and 24, and a Follow-up visit 28±3 days postdose.

On the morning of Day 1, following a fast of at least 8 hours, a single oral dose of 5 mg risdiplam will be administered. No food will be allowed for at least 4 hours postdose. Pharmacokinetic samples will be obtained from predose through 552 hours postdose (Day 24).

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 8 weeks.

The start of the study is defined as the date the first subject who is subsequently enrolled signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

7 TREATMENT

The treatment administered will be 5 mg risdiplam.

8 HEPATIC FUNCTION GROUPS

The following is a list of the hepatic function groups and ordering that will be used in the TFLs:

Part	Hepatic Function	Order in TFLs
Part 1	Mild Hepatic Impairment	1
	Normal Hepatic Function	2
Part 2	Moderate Hepatic Impairment	3
	Normal Hepatic Function	4

Note: Subjects with mild hepatic impairment will be included Part 1 TFLs only; subjects with moderate hepatic impairment will be included Part 2 TFLs only; subjects with normal hepatic function will be included in Part 1 and/or Part 2 TFLs, based on matching, and regardless of enrolment time.

9 SAMPLE SIZE JUSTIFICATION

Up to 32 evaluable subjects will be enrolled in the study.

No formal sample size calculation has been performed. The sample size determination has been based on historical studies of a similar nature. Eight evaluable subjects per hepatic impairment function group (ie, mild and moderate) and 8 to 16 evaluable subjects with normal hepatic function are planned to complete the study. This is considered a sufficient sample size to evaluate the PK of risdiplam under various degrees of hepatic function.

10 DEFINITION OF ANALYSIS POPULATIONS

The **Safety Population** will consist of all subjects who received a dose of risdiplam.

The **PK Population** will consist of all subjects who received a dose of risdiplam and have evaluable PK data. A subject will be excluded from the PK descriptive statistics and statistical analysis if a subject has an adverse event (AE) of vomiting that occurs at or before 2 times median time of the maximum observed plasma concentration (T_{max}) or if they have any major protocol deviation(s) thought to impact PK analysis.

The **All Subjects Population** will consist of any subjects who signed informed consent.

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. Protocol deviations will be listed. Details of subject assignment to the analysis populations will be listed.

11 STATISTICAL METHODOLOGY

11.1 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).

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: area under the plasma concentration-time curve [AUCs] and maximum observed plasma 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 higher.

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.

11.1.1 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 11.1.2 for definitions of repeat and unscheduled readings). For ECGs taken in triplicate, baseline will be the mean of the last 3 values taken prior to dosing.

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.

11.1.2 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 11.1.1).

11.2 Demographics and Subject Disposition

The demographic variables age, sex, race, ethnicity, body weight, height, BMI, and smoking status will be listed and summarized (under Safety population) by part and hepatic function. Subject disposition will be listed and summarized (under Safety population) by part and hepatic function.

11.3 Pharmacokinetic Assessment

11.3.1 Pharmacokinetic Analysis

The following pharmacokinetic parameters will be determined where possible from the plasma concentrations of risdiplam and metabolite M1 using non-compartmental methods performed using Phoenix WinNonlin (Version 8.1 or higher):

Parameter	Definition
AUC_{last}	area under the plasma concentration-time curve from time zero to the last measurable concentration
AUC_{inf}	area under the plasma concentration-time curve from time zero to infinity
$\%AUC_{extrap}$	percentage of area under the plasma concentration-time curve due to extrapolation
C_{max}	maximum observed plasma concentration
T_{max}	time of the maximum observed plasma concentration
$t_{1/2}$	apparent plasma terminal elimination half-life (whenever possible)
CL/F	apparent total plasma clearance (risdiplam only)
λ_Z	apparent terminal elimination rate constant
MR_{AUCinf}	metabolic ratio based on AUC_{inf} (M1 only)
$MR_{AUClast}$	metabolic ratio based on AUC_{last} (M1 only)
MR_{Cmax}	metabolic ratio based on C_{max} (M1 only)

The fraction unbound (f_u) will be used to calculate the following unbound risdiplam PK parameters for each individual subject whenever possible:

Parameter	Definition
$AUC_{last,u}$	unbound AUC_{last}, calculated as $AUC_{last}*f_u$
$AUC_{inf,u}$	unbound AUC_{inf}, calculated as $AUC_{inf}*f_u$
$C_{max,u}$	unbound C_{max}, calculated as $C_{max}*f_u$
CL/F_u	unbound CL/F, calculated as dose/$AUC_{inf,u}$

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 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} 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.

The metabolic ratios (MR_{AUC} and MR_{Cmax}) will be calculated as follows:

$$MR_{AUC} = \frac{AUC\ metabolite}{AUC\ parent\ drug} \times \frac{MW\ (parent\ drug)}{MW\ (metabolite)}$$

$$MR_{C_{max}} = \frac{C_{max}\ metabolite}{C_{max}\ parent\ drug} \times \frac{MW\ (parent\ drug)}{MW\ (metabolite)}$$

MW (parent drug) = 401.46 g/mol

MW (metabolite) = 419.1946

MR_{AUC} refers to both MR_{AUCinf} and $MR_{AUClast}$.

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

- Concentration values that are below the limit 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 and graphical displays.
    - 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.
    - If a predose concentration is missing, these values may be set to zero by default.

11.3.1.2 Criteria for the Calculation of an Apparent Terminal Elimination Half-Life

10.3.1.2.1 Number of Data Points

- At least 3 data points will be included in the regression analysis and must not include C_{max}.

10.3.1.2.2 Goodness of Fit

- When assessing terminal elimination phases, the adjusted coefficient of determination for exponential fit (R^2-adjusted) will be used as a measure of the goodness of fit of the data points to the determined line.

- λ_z derived parameters ($t_{1/2}$, AUC_{inf}, and CL/F) will only be calculated if the R^2-adjusted value of the regression line is greater than or equal to 0.7.

10.3.1.2.3 Period of Estimation

- Apparent terminal elimination half-life will be calculated over a time period of at least 2 half-lives, where possible.

- Where $t_{1/2}$ is estimated over a time period of less than 2 half-lives, the $t_{1/2}$, AUC_{inf} and CL/F values will not be reported.

11.3.1.3 Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

- AUC values will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations.

- For any partial AUC determination (if required), nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals will be used for all other time points within a certain interval as appropriate.

- AUC_{inf} values where the percentage extrapolation is <20% will be reported. Where the percentage extrapolation exceeds 20% the $t_{1/2}$, AUC_{inf}, and CL/F values will not be derived.

11.3.1.4 Anomalous Values

- If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and study report.

- Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.

- PK parameter data associated with quantifiable predose value(s) greater than 5% of C_{max} may be excluded from the summary statistics of PK tables and statistical analysis at the discretion of the Pharmacokineticist.

11.3.2 Presentation of Pharmacokinetic Data

11.3.2.1 Presentation of 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 plasma or whole blood concentration data series to be summarized.
    - For the calculation of summary statistics, BLQ values will be set to missing.
    - 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 50% values in the data series have measurable concentrations (excluding BLQ values), only N will be presented. The other summary statistics will be denoted as not calculated (NC).
    - If all the values are BLQ, then all summary statistics will be denoted as NC.
    - If the value of the arithmetic mean or median is below the lower limit of quantification, mean and/or median, the SD, geometric mean and geometric CV% will be denoted as NC.

11.3.2.2 Presentation of Pharmacokinetic Parameters

- For the calculation of summary statistics of PK parameters, all NR and NC values in a data series will be set to missing.
- The AUC values will be set to NC if they have been calculated using fewer than three concentrations, and/or three concentrations if the last is C_{max}.

11.3.3 Pharmacokinetic Statistical Methodology

The PK parameters and concentrations of risdiplam and metabolite M1 will be listed and summarized by part and hepatic function.

Concentrations will be graphically represented with an arithmetic mean (+/- SD) plot and a concentration-time profile by subject and for all subjects (linear scale and semi-logarithmic scale). 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 graphical displays.

The primary analysis is the evaluation of the PK of risdiplam (and metabolite M1, as appropriate) following a single dose in subjects with mild or moderate hepatic impairment (‘Test’ groups), compared to subjects with normal hepatic function (‘Reference’ group). The PK

parameters in subjects with normal hepatic function will be used as 'Reference' and the PK parameters in subjects with hepatic impairment will be used as 'Test'.

The primary PK parameters are AUC_{inf} and C_{max} for risdiplam and metabolite M1; all other PK parameters will be regarded as secondary and will not be subject to inferential statistical analysis. Data from Part 1 and Part 2 will be analyzed separately. An analysis of variance[3] (ANOVA) will be used to estimate the effect of hepatic impairment on the primary PK parameters (AUC_{inf} [or AUC_{last} if appropriate] and C_{max}) including the factor 'hepatic impairment' (ie, mild, moderate, or none). The PK parameters will be log transformed prior to analysis. The data from subjects with mild or moderate hepatic impairment and their matched control subjects will be included in the analysis. Geometric mean ratios and the corresponding 90% confidence intervals (CIs) of AUC_{inf} (or AUC_{last}, as appropriate) and C_{max} of risdiplam between the groups of hepatically impaired subjects and healthy subjects with normal hepatic function will be calculated.

Additional statistical analyses, on primary and/or on secondary PK parameters, may be conducted as appropriate.

Forest plot of the results from statistical analysis will be produced. Additionally, scatterplot of PK parameters versus Child-Pugh total score, and its individual components will be produced.

11.4 Safety and Tolerability Assessments

11.4.1 Adverse Events

A baseline sign and symptom is defined as an 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. As per the protocol, the only baseline sign and symptoms recorded should be serious adverse events (SAEs) caused by a protocol-mandated intervention (eg, SAEs related to invasive procedures such as biopsies). A treatment-emergent AE (TEAE) is defined as an AE that occurs postdose or that is present predose and becomes more severe postdose.

Each AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

All AEs will be listed. In the overall summary table, the TEAEs will be summarized by part, hepatic function, severity, and relationship to the study treatment. 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 summarized by part, hepatic function, MedDRA system organ class, and preferred term. The frequency TEAE tables will be presented for all causalities and for TEAEs considered related to the study treatment. Serious TEAEs will be tabulated separately. For any AEs that change severity ratings the AE will be included only once under the maximum severity rating in the summaries.

11.4.2 Clinical Laboratory Parameters

All clinical laboratory data will be listed and values outside the clinical reference ranges will be flagged.

Clinical chemistry, hematology, and coagulation data, together with changes from baseline, will be summarized by part, hepatic function, and timepoint.

In addition, all clinical chemistry, hematology, coagulation, and urinalysis data outside the clinical reference ranges will be listed by part, hepatic function, parameter and timepoint.

Shift from baseline tables will be provided for clinical chemistry, hematology, and coagulation data. Additionally, subjects with elevated post-baseline AST or ALT levels will be summarized.

11.4.3 Vital Signs

All vital signs will be listed and values outside the clinical reference ranges will be flagged. The following reference ranges will be used for vital signs data:

- Systolic Blood Pressure: 90 – 140 mmHg
- Diastolic Blood Pressure: 60 – 90 mmHg
- Pulse Rate: 40 – 100 bpm
- Body Temperature: 35.5 – 37.5 ºC

The vital signs data, together with changes from baseline, will be summarized by part, hepatic function, parameter and timepoint. Figures of mean vital signs profiles will be presented by part, and hepatic function.

11.4.4 Electrocardiogram

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

Where ECGs are measured in triplicate (at approximately 1-minute intervals), the mean value will be used in all subsequent calculations.

All ECG data will be listed and values outside the clinical reference ranges will be flagged. The following reference ranges will be used for ECG data:

- PR Interval: 120 – 200 ms
- QRS Duration: 80 – 120 ms
- QT Interval: 200 – 500 ms
- QTcF Interval: 300 – 450 ms
- RR Interval: 600 – 1500 ms
- Heart Rate: 40 – 100 bpm

The ECG data, together with changes from baseline, will be summarized by part, hepatic function, and timepoint. Figures of mean ECG profiles will be presented by part, and hepatic function.

11.4.5 Previous and Concomitant Medications

Previous medication will be defined as medication that ends prior to the first dose. Concomitant medication will be defined as medication that starts after the first dose or starts but does not end prior to the first dose.

Previous and concomitant medications will be coded using WHODrug.

Previous and concomitant medications will be listed.

11.4.6 Other Assessments

A listing of subjects with hepatic impairment and their matched subject with normal hepatic function will be provided.

Medical history data will be listed.

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

11.4.7 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

12 INTERIM ANALYSES

Preliminary PK and safety and tolerability data from a minimum of 4 subjects with mild hepatic impairment and 4 matched subjects with normal hepatic function will be reviewed prior to the start of Part 2.

Listings of individual data will be created for purposes of submitting FDA 3-months safety follow-up (see TFL shells for more details).

No other interim analyses are planned for this study.

13 CHANGES FROM THE PROTOCOL-SPECIFIED STATISTICAL ANALYSES

Listings of individual data will be created for purposes of submitting FDA 3-months safety follow-up. There were no other changes from the protocol-specified statistical analyses.

14 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.”

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