Official Title: A Phase I, 2-Part, Open-Label Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Multiple Doses of Risdiplam and the Effect of Risdiplam on the Pharmacokinetics of Midazolam Following Oral Administration in Healthy Participants

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STATISTICAL ANALYSIS PLAN

A PHASE I, 2-PART, OPEN-LABEL STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF MULTIPLE DOSES OF RISDIPLAM AND THE EFFECT OF RISDIPLAM ON THE PHARMACOKINETICS OF MIDAZOLAM FOLLOWING ORAL ADMINISTRATION IN HEALTHY PARTICIPANTS

Statistical Analysis Plan Version: 1
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Study Drug: Risdiplam (RO7034067)

Sponsor Reference Number: BP41361
Covance Study Number: 8406533

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:

[redacted] BSc, CStat
Statistician

7 Oct 2019
Date

[redacted] PharmD, PhD
Pharmacokineticist

07-Oct-2019
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Sponsor approval:

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2 Oct 2019
Date

2 TABLE OF CONTENTS

3 ABBREVIATIONS

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

λ_z	apparent terminal elimination rate constant
ADaM	analysis data model
AE	adverse event(s)
AR_{AUC}	accumulation ratio for AUC
AR_{Cmax}	accumulation ratio for C_{max}
AUC	area under the plasma concentration-time curve
AUC_{inf}	area under the concentration-time curve from time zero extrapolated to infinity
AUC_{last}	area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration (t_{last})
AUC_{tau}	area under the plasma concentration-time curve from time zero to the end of the dosing interval
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 after oral administration
CL_{ss}/F	apparent total plasma clearance at steady state
C_{last}	observed plasma concentration at time of last quantifiable plasma concentration
C_{max}	maximum observed plasma concentration
CRU	Clinical Research Unit
CSR	Clinical Study Report
C_{trough}	trough observed plasma concentration
CV%	coefficient of variation
ECG	electrocardiogram
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MR_{AUC}	metabolite:parent ratio of AUC
MR_{Cmax}	metabolite:parent ratio of C_{max}
MW	molecular weight
NC	not calculated
NR	no result
PK	pharmacokinetic(s)
QD	once daily
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
SMA	spinal muscular atrophy
$t_{1/2}$	apparent plasma terminal elimination half-life

TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
t_{last}	time of last quantifiable plasma concentration
T_{max}	time of the maximum observed plasma concentration

4 INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 1 dated 23 April 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 AND ENDPOINTS

The objectives and corresponding endpoints are provided in **Table 1**.

Table 1:Objectives and Endpoints

Objectives	Endpoints
Primary	
To investigate the effect of multiple oral doses of risdiplam on the PK of a single oral dose of midazolam in healthy participants.	Midazolam concentrations and thereof derived PK parameters for midazolam (and its metabolite[s] as appropriate) alone and in combination with risdiplam.

Objectives	Endpoints
Secondary	
To assess the safety and tolerability of a single oral dose of midazolam alone and in combination with multiple oral doses of risdiplam in healthy participants.	Incidence and severity of adverse events (AEs); changes in vital signs, physical findings, electrocardiogram (ECG) parameters, and clinical laboratory test results during and after midazolam administration alone and in combination with risdiplam.
To assess the safety and tolerability of multiple oral doses of risdiplam administered once daily (QD) for 14 days.	Incidence and severity of AEs; changes in vital signs, physical findings, ECG parameters, and clinical laboratory test results during and after administration of multiple doses of risdiplam.
To assess the PK of risdiplam (and its metabolite[s] as appropriate) following multiple oral doses of risdiplam QD for 14 days.	Concentrations and thereof derived PK parameters for risdiplam and its metabolite(s) as appropriate.

6 STUDY DESIGN

This will be a Phase I, 2-part, open-label, non-randomized study to investigate the safety, tolerability, and PK of a multiple-dosing regimen of risdiplam (QD; Part 1) and the effect of risdiplam on the PK of midazolam (Part 2) following oral administration in healthy adult male and female participants.

In total a maximum of 40 participants may be enrolled in this study as follows:

- Part 1: 8 participants will be enrolled in order to obtain at least 6 evaluable participants.
- Part 2: 28 participants will be enrolled in order to obtain at least 26 evaluable participants.

The additional 4 participants are in case the dropout rate is higher than expected in order to achieve a sufficient number of evaluable participants. Participants enrolled in Part 1 of this study must not be enrolled in Part 2.

In Part 1, participants will receive a dose of 5 mg risdiplam QD for 14 consecutive days. The dose of 5 mg risdiplam has been shown to be safe and well tolerated for more than 1 year of treatment in patients with spinal muscular atrophy (SMA). The decision to proceed to Part 2 of the study will be made following review of all available safety and tolerability data, including AEs, ECGs, vital signs, laboratory safety test results (i.e., hematology, clinical chemistry, and urinalysis) collected up to (and including) 48 hours after last study drug administration and available plasma PK data up to (and including) 24 hours after last study drug administration from a minimum of 4 Part 1 participants. The risdiplam dose in Part 2 will be determined based on the PK and safety data obtained in Part 1, with the aim to achieve an average exposure (mean

concentration-time curve [AUC] over a dosing interval [AUC_{tau}] at steady state) of 2000 ng.h/mL in Part 2 (i.e., the therapeutic exposure observed in SMA patients).

A Dose Escalation Meeting will be conducted prior to the start of Part 2, in order to evaluate the Part 1 data and to select the risdiplam dose to be administered in Part 2 of this study.

In Part 2, all study participants will receive a single oral dose of 2 mg midazolam on Day 1. On Day 3, the 14-day QD treatment period with risdiplam will begin (targeting a mean AUC_{tau} at steady state of 2000 ng.h/mL; the precise dose will be based on the results of Part 1), with single dose administration of 2 mg midazolam again on Day 15 (1 hour after the thirteenth dose of risdiplam).

7 TREATMENT

Part 1

The following is the treatment naming convention that will be used in all TFLs:

Treatment
5 mg risdiplam QD

Part 2

The following is the treatment naming convention and ordering that will be used in all TFLs for PK and AE data.

Treatment	**Order in TFLs**
2 mg midazolam	1
8 mg risdiplam QD	2
2 mg midazolam and 8 mg risdiplam QD	3

The following is the treatment sequence naming convention that will be used in all other TFLs.

Treatment Sequence
Day 1: 2 mg midazolam; Days 3 to 14: 8 mg risdiplam QD; Day 15: 2 mg midazolam and 8 mg risdiplam QD; Day 16: 8 mg risdiplam QD

8 SAMPLE SIZE JUSTIFICATION

In total a maximum of 40 participants may be enrolled in this study as follows:

- Part 1: 8 participants will be enrolled in order to obtain 6 evaluable participants. The Part 1 sample size was determined by practical considerations and not based on statistical power calculations.

- Part 2: 28 participants will be enrolled in order to obtain at least 26 evaluable participants. The Part 2 sample size is based on estimates for the within-subject coefficient of variation of 26% and 35% for AUC extrapolated to infinity (AUC_{inf}) and C_{max} of midazolam, respectively, from a previous clinical study[3]. A sample size of 26 evaluable participants ensures that the two-sided 90% confidence interval for the geometric population mean of the individual exposure ratios of Day 16 to Day 1 will lie within the 0.75 to 1.33 limits of the geometric population mean with at least 80% probability (power).

The additional 4 participants are in case the dropout rate in is higher than expected.

9 DEFINITION OF ANALYSIS POPULATIONS

Safety Population: all participants who received at least 1 dose of the study treatment (risdiplam or midazolam), whether prematurely withdrawn from the study or not, will be included in the safety analysis.

PK Population: all participants who have received at least 1 dose of study treatment (risdiplam or midazolam), and who have data from at least 1 postdose PK sample will be included in the PK analysis population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

All Subjects Population: any participants 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.

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). Data will be summarized separately by part.

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 [AUC] 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.

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 ECGs) and unscheduled (clinical laboratory parameters) readings (see Section 10.1.2 for definitions of repeat and unscheduled readings).

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.

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. 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, Baseline Characteristics and Subject Disposition

The demographic variables age, sex, race, ethnicity, body weight, height, and body mass index (BMI) will be listed and summarized by part (under Safety population).

Subject disposition will be listed and summarized by part (under Safety population).

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Analysis

Part 1

The following PK parameters will be determined where possible from the plasma concentrations of risdiplam and respective metabolites on Days 1 and 14, as appropriate, using non-compartmental methods performed using Phoenix WinNonlin (Version 8.1 or higher):

Parameter	Definition
AUC_{tau}	area under the plasma concentration-time curve from time zero to the end of the dosing interval (Days 1 and 14 for risdiplam and metabolites, as applicable, only)
C_{max}	maximum observed plasma concentration
C_{trough}	trough observed plasma concentration (risdiplam and metabolites, as applicable, only)
T_{max}	time of the maximum observed plasma concentration
$t_{1/2}$	apparent plasma terminal elimination half-life (where possible)
λ_z	apparent terminal elimination rate constant
CL_{ss}/F	apparent total plasma clearance at steady state calculated as Dose/AUC_{tau} (Day 14, risdiplam only)
AR_{AUC}	accumulation ratio for AUC calculated as Day 14 AUC_{tau}/Day 1 AUC_{tau} (risdiplam only)
AR_{Cmax}	accumulation ratio for C_{max} calculated as the Day 14 C_{max}/ Day 1 C_{max} (risdiplam only)
MR_{AUC}	metabolite:parent ratio of AUC (as applicable)
MR_{Cmax}	metabolite:parent ratio of C_{max} (as applicable)

Part 2

The following PK parameters will be determined where possible from the plasma concentrations of risdiplam (Days 3 and 16) or midazolam (Days 1 and 15) and respective metabolites, as appropriate, 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 time of last quantifiable concentration (t_{last}), calculated using the linear

	trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (midazolam and metabolites, as applicable, only)
AUC_{tau}	area under the plasma concentration-time curve from time zero to the end of the dosing interval (Days 3 and 16 for risdiplam and metabolites, as applicable, only)
AUC_{inf}	area under the concentration-time curve from time zero extrapolated to infinity (Day 1 for midazolam and metabolites, where possible)
C_{max}	maximum observed plasma concentration
C_{trough}	trough observed plasma concentration (risdiplam and metabolites, as applicable, only)
T_{max}	time of the maximum observed plasma concentration
t_{last}	time of last quantifiable plasma concentration (midazolam and metabolites, as applicable, only)
$t_{1/2}$	apparent plasma terminal elimination half-life (where possible)
λ_z	apparent terminal elimination rate constant
CL/F	apparent total plasma clearance after oral administration calculated as Dose/AUC_{inf} (Days 1 and 15, midazolam only)
CL_{ss}/F	apparent total plasma clearance at steady state on Day 16 (risdiplam only)
AR_{AUC}	accumulation ratio for AUC calculated as Day 16 AUC_{tau}/Day 3 AUC_{tau} (risdiplam only); Day 3 corresponds to the first dose of risdiplam in Part 2
AR_{Cmax}	accumulation ratio for C_{max} calculated as the Day 16 C_{max}/Day 3 C_{max} (risdiplam only); Day 3 corresponds to the first dose of risdiplam in Part 2
MR_{AUC}	metabolite:parent ratio of AUC (as applicable)
MR_{Cmax}	metabolite:parent ratio of C_{max} (as applicable)

Additional PK parameters may be determined where appropriate. If AUC_{inf} cannot be properly estimated, AUC_{last} (area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration) will be reported in addition to the associated parameters t_{last} and C_{last}. In addition, an alternate partial AUC from time zero to a common postdose time may be calculated.

The PK 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_{last} (if applicable), C_{max}, C_{trough}, 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 MRC_{max}) will be calculated as follows:

$$MR_{AUC} = \frac{AUC_{0-\infty}\ \text{metabolite}}{AUC_{0-\infty}\ \text{parent drug}}$$

$$MR_{C\,max} = \frac{C_{max}\ \text{metabolite}}{C_{max}\ \text{parent drug}}$$

MR_{AUC} and MRC_{max}) will be corrected for molecular weight (MW), with the MWs as follows:

risdiplam: 401.46 g/mol
metabolite M1: 417.5 g/mol

AUC_{last} or other common partial area may be used to determine metabolite ratios (MR_{AUC}) if AUC_{inf} cannot be calculated.

10.3.1.1 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 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 for the first dose, these values may be set to zero by default.

10.3.1.2 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.

- Lambda z (λ_z) derived parameters ($t_{1/2}$, AUC_{inf}, CL/F, andCLss/F) will only be calculated if the R^2 adjusted value of the regression line is ≥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 AUC_{inf}, $t_{1/2}$, and CL/F values will not be reported.

10.3.1.3 Calculation of Area Under the Concentration-time Curve

- 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.

- If AUC_{inf} cannot be determined for all subjects in Part 2, an alternative AUC_{last}, C_{last} and t_{last} will be used in the assessment of the effect of multiple oral doses of risdiplam on the PK of a single oral dose of midazolam.

10.3.1.4 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 the CSR.

- 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 values >5% of C_{max} may be excluded from the summary statistics and statistical analysis at the discretion of the Pharmacokineticist.

10.3.2 Presentation of Pharmacokinetic Data

10.3.2.1 Presentation Pharmacokinetic Plasma Drug 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 plasma concentration data series to be summarized.
  - 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 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.

10.3.2.2 Presentation 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 3 concentrations, and/or 3 concentrations if the last is C_{max}.

The PK parameters and concentrations will be listed and summarized by part, analyte, profile day, and treatment.

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) by part, analyte, profile day, and treatment. 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.

10.3.3 Pharmacokinetic Statistical Methodology

The primary analysis is the evaluation of the PK of midazolam in combination with risdiplam (and metabolite M1, as appropriate) (‘Test’ group), compared to midazolam alone (‘Reference’ group).

No formal statistical analyses are planned for Part 1.

In Part 2, the effect of multiple oral doses of risdiplam on the PK of a single oral dose of midazolam (and its metabolite[s] as appropriate) will be explored using an analysis of variance[4] applied to the log-transformed PK parameters C_{max} and AUC_{inf} (or, if AUC_{inf} cannot be properly estimated, AUC_{last} or an alternate partial AUC from time zero to a common post-dose time, AUC_{last}). The model will include treatment as a fixed effect and subject as a random effect. From the model estimates, the geometric mean ratios (midazolam in combination with risdiplam versus midazolam alone) will be derived together with corresponding two-sided 90% confidence intervals.

10.4 Safety and Tolerability Assessments

10.4.1 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.

For Part 2 a TEAE occurring:

- during or after Day 1 dosing and prior to predose Day 3 will be assigned to ‘2 mg midazolam’ treatment
- during or after Day 3 dosing and prior to predose Day 15 will be assigned to ‘8 mg risdiplam QD’ treatment
- during or after Day 15 dosing will be assigned to ‘2 mg midazolam and 8 mg risdiplam QD’ treatment

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, treatment, intensity, 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, treatment, MedDRA system organ class, and preferred term. The frequency TEAE tables will be presented for all causalities and for TEAEs considered possibly related and 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.

10.4.2 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 and timepoint.

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

10.4.3 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 ^{o}C

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

10.4.4 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.

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, parameter and timepoint. Figures of mean ECG profiles will be presented.

10.4.5 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 medications will be listed.

Concomitant medications will be listed and summarized by part. The frequency (the number of treatments, the number of subjects receiving a concomitant medication, and the percentage of subjects receiving a concomitant medication) of concomitant medications will be summarized by part, treatment, medication, and preferred term.

10.4.6 Other Assessments

Medical history data will be listed.

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

10.4.7 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11 INTERIM ANALYSES

No formal interim analysis is planned. Data from Part 1 will be evaluated before the start of Part 2, and the dose selection for Part 2 will be based on Part 1 data.

The decision to proceed to Part 2 will be made following review of all safety and tolerability information collected up to 48 hours after last study drug administration (including AEs, ECGs, vital signs, and clinical laboratory test results), and of all PK data collected up to (and including) 24 hours after last study drug administration in Part 1 from a minimum of 4 participants.

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. [redacted], et al. The bioavailability and pharmacodynamics of midazolam (RO 21-3981 and its 1'-hydroxymethyl midazolam metabolite (RO 21-6347) following single dose intravenous, intramuscular, oral solution, and oral tablet administration to normal subjects. Research Report N-36884, October 9, 1982.

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