Statistical Analysis Plan (SAP)

Protocol Title: An Open-Label Study Evaluating the Safety and Efficacy of Ropanicant in Participants with Moderate to Severe Major Depressive Disorder

Protocol Number: CTP2S1911A4B2

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Statistical Analysis Plan

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Protocol Title: An Open-Label Study Evaluating the Safety and Efficacy of Ropanicant in Participants with Moderate to Severe Major Depressive Disorder.

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Revision History

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2.0	21-May-2024	[redacted]	Section 4.6, Table 1, 12-Lead ECG section updated as per latest protocol version 2.0, dated 13May2024. Section 14, Changes from Analysis Planned in Protocol updated as per latest protocol version 2.0, dated 13May2024.
3.0	14-Aug-2024	[redacted]	Section 10.2.2, Instead of actual, scheduled sampling times will be presented for the individual graphs. Section 10.3.1, PK parameter derivation updated. Section 10.4, dose-normalized $AUC_{0\text{-}inf}$ added to the analysis as per protocol.

I confirm that I have reviewed this document and agree with the content.

Approvals

[redacted]

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1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
[redacted]	[redacted]
ICEs	Intercurrent events
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass index
CI	Confidence Interval
PK	pharmacokinetic(s).
PD	pharmacodynamic(s).
qd	once a day.
bid	twice a day
MDD	major depressive disorder.
ANOVA	analysis of variance.
AUC	area under the curve.
$AUC_{0\text{-}inf}$	area under the concentration-time curve from time zero extrapolated to infinity.
$AUC_{0\text{-}t}$	area under the concentration-time curve from time zero to the last measurable time t.
$AUC_{0\text{-}tau}$	area under the concentration-time curve from time zero to tau (tau = dosing interval).
$AUIC_{0\text{-}tau}$	area under the percent inhibition from baseline-time curve from time zero to tau (tau = dosing interval).
$t_{1/2}$	terminal elimination half-life
CRF	Case Report Form.
CV	Coefficient of Variation.
ECG	Electrocardiogram.
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
NA	Not Applicable

Abbreviation	Description
PT	Preferred Term
QC	Quality Control
QTc	Corrected QT Interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TFL	Table, Figure and Listing
WHO	World Health Organization

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies which will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

2.1. Responsibilities

[redacted] will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

2.2. Timings of Analyses

The primary analysis of safety and efficacy and/or pharmacokinetics is planned after all subjects complete the final study visit or terminate early from the study.

3. Study Objectives

3.1. Primary Objective

- To evaluate the safety and tolerability of ropanicant in participants with MDD.

3.2. Secondary Objective(s)

- To evaluate the efficacy of ropanicant in participants with MDD.
- To evaluate the PK of ropanicant in participants with MDD.

3.3. Exploratory Objective(s)

- To further evaluate the efficacy of ropanicant in participants with MDD.
- [redacted].

4. Study Details/Design

4.1. Brief Description

This is an open-label, parallel-group study to evaluate the safety and efficacy of ropanicant in participants with moderate to severe MDD. The study will be conducted at study center(s) located in the US.

Approximately 36 participants will be randomly assigned to receive ropanicant either [redacted] for 2 weeks, in a ratio of 1:1:1 (12 participants in each treatment group). Following a screening period of up to 4 weeks, the participants will be treated for 2 weeks. The screening period may be extended up to 5 weeks in case of washout of compounds with longer $t_{1/2}$.

Screening
At the screening visit, all participants will provide written informed consent to participate prior to any study-related assessments being performed. Participants will be assigned a unique ID number after the ICF is signed; this number will be used throughout the study to identify the participant. Demographic information and medical history including history of all medications used in the past year will be collected at the screening visit. A prior diagnosis of MDD must have been made according to DSM-5 performed by a qualified healthcare professional, which will be confirmed by MINI during the screening visit. At the screening visit, the participant will undergo preliminary screening procedures to determine eligibility, including completion of MADRS and CGI-S. The severity of each participant's MDD will be evaluated by using the MADRS score. The complete assessments to be performed are itemized in the SOA (Table 1).

Open-label treatment period
At the baseline visit (Day 1), the participant's eligibility will be assessed again according to the assessments described in the SOA (Table 1). If eligible, the participant will be randomly assigned to receive ropanicant either [redacted], for 2 weeks. After the blood samples (for laboratory assessments) have been collected at the baseline visit (Day 1), the first dose of study drug will be administered to the participant at the study site. [redacted]

The participant will return to the study site on Day 7 and Day 14 (EOT visit) and will undergo the assessments described in the SOA (Table 1).

Follow-up period/EOS visit (Day 21)
A follow-up visit (Day 21) will be conducted 3 weeks (± 3 days) after the baseline visit (Day 1). [redacted]

A participant is considered to have completed the study if he/she has completed the 2-week open-label treatment period, the EOT visit, and the follow-up visit.

Early Termination visit (ET)
In the event a participant discontinues study drug prematurely, every effort will be made to continue the participant in the study and have all planned assessments completed until the EOT visit. If a participant withdraws from the study prematurely for any reason, the participant will be encouraged where possible to return to the study site for an ET visit (Table 1).

4.2. Subject Selection

4.2.1. Inclusion Criteria

Refer protocol Section 5.1 Inclusion Criteria.

4.2.2. Exclusion Criteria

Refer protocol Section 5.2 Exclusion Criteria:

4.3. Determination of Sample Size

The study will randomize approximately 36 participants to either [redacted] ropanicant in a 1:1:1 ratio (12 participants in each treatment group). No prospective calculations of statistical power have been made and the sample size has been selected based on clinical reasoning to provide information on safety, tolerability, and reduction in depressive symptoms following either qd or bid dosing of ropanicant.

4.4. Treatment Assignment and Blinding

The study participants will be randomly assigned at the baseline visit (Day 1) to receive ropanicant either [redacted], in a ratio of 1:1:1 (12 participants in each treatment group). An IRT will be used to administer the randomization schedule. The randomization schedule will be stratified by gender. This is an open-label study.

4.5. Administration of Study Medication

Participants will be randomly assigned to receive open-label ropanicant (study drug) either [redacted], for 2 weeks.

On the day of the study visits, participants will be instructed not to take their study drug at home, as it will be administered at the study site. On days with no scheduled study visits, at about the same time every day, the participant will take 1 tablet/day in the morning (for qd dosing) or 2 tablets/day (~12 hours apart for bid dosing). Tablets are to be taken with a glass of water (with or without food).

4.6. Study Procedures and Flowchart

Study procedures and their timing are summarized in the SOA (Table 1)

Adherence to the study design requirements, including those specified in the SOA, is essential and required for study conduct. As protocol waivers or exemptions are not allowed with the exception of immediate safety concerns, these should be discussed with the medical monitor/sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study drug.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and collected before the ICF is signed may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the time frame defined in the SOA (Table 1).

In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution, and monitoring may be implemented by the sponsor or the investigator, per local regulatory agency/ethics requirements.

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Repeat or unscheduled samples may be collected for safety reasons or for technical issues with the samples.

Table 1: Schedule of Assessments

	Screening	Open-Label Treatment			Follow-Up	
Visit	**Visit 1 (Screening)**	**Visit 2 (Baseline)**	**Visit 3**	**Visit 4[a] (EOT)**	**Visit 5 (EOS)**	**ET[a]**
Days from Randomization	**Day -28 to -1[b]**	**Day 1[b]**	**Day 7**	**Day 14**	**Day 21**	
Clinic Visit Window (days)	**NA**	**NA**	**±1 day**	**±3 day**	**±3 day**	
Weeks from Randomization	**Week -4 to -1**	**Week 0**	**Week 1**	**Week 2**	**Week 3**	
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Demographics	X					
Medical history	X					
MINI	X					
MGH ATRQ	X					
Physical examination	X	X[C]		X		X
Height	X					
Body weight	X	X	X	X	X	X
BMI	X					
Laboratory assessments[d]	X	X	X	X	X	X
Urine drug screen[d]	X	X[C]	X	X		X
Pregnancy test[e]	X	X[C]	X	X	X	X
Vital signs	X	X[C]	X[f]	X[f]	X	X
12-Lead ECG	X[I]	X[C,I]	X[f]	X[f]		X
C-SSRS	X	X[C]	X	X	X	X
CGI-S	X	X[C]	X[f]	X[f]		X
MADRS	X	X[C]	X[f]	X[f]	X	X
PK sample[g]		X		X[h]		
[redacted]		X		X	X	
Study drug administration[j]		X	X	X		
Study drug dispensation		X	X			
Compliance check			X	X		X
AEs	X	X[C]	X	X	X	X
Concomitant medications	X[k]	X[C]	X	X	X	X

a) In the event a participant discontinues study drug prematurely, every effort will be made to continue the participant in the study and have all planned assessments completed until the EOT visit. If a participant withdraws from the study prematurely for any reason, the participant will be encouraged where possible to return to the study site for an ET visit.
b) Screening period may be extended up to 5 weeks in case of washout of compounds with longer t1/2.

Assessments included in inclusion/exclusion criteria at the screening visit and the baseline visit (Day 1) should be performed in order to exclude noneligible participants as quickly as possible and minimize inconvenience for them, therefore, assessments should be performed in the order as follows: MINI (at the screening visit only), MGH ATRQ (at the screening visit only), MADRS, CGI-S, C-SSRS, vital signs, ECG, pregnancy test (for WOCBP), and laboratory tests (The baseline visit [Day 1] laboratory samples should only be collected after randomization).

c) To be collected prior to randomization to ensure the participant is still eligible to participate in the study.

d) Clinical laboratory tests will be performed at a central laboratory. Protocol-required clinical laboratory assessments are included in protocol Table 8-1.

e) At the screening visit, a serum hCG pregnancy test will be done for WOCBP. At all other visits, a urine pregnancy test will be done.

f) Vital signs and ECGs on Day 7 and Day 14 will be performed 1 hour after administration of the study drug (Tmax of ropanicant). For participants on bid dosing of ropanicant: Vital signs and ECGs will be performed 1 hour after administration of the morning dose of study drug only. MADRS and CGI-S will be collected prior to dosing.

g) Full PK sampling will be performed at the site on Day 1 and Day 14 for the participants receiving bid dosing of ropanicant only. On Day 1 and Day 14, participants from bid dosing group will stay at the study center for 24 hours after the morning dose. PK samples will be collected prior to the administration of the study drug and at 0.5, 1, 2, 4, 6, and 12 hours after the first dose (morning dose) and at 0.5, 1, 2, 4, 6, and 12 hours after the second dose (evening dose) at the baseline visit (Day 1) and Day 14. The sample at 12 hours after the first dose will be collected prior to the administration of the second dose. The sample at 12 hours after the second dose on Day 1 will be collected prior to the administration of the first dose on Day 2.

h) On Day 14, the 1-hour postdose PK sample will be collected after the 1-hour postdose vital signs and ECG assessments.

i) [redacted]

j) Participants will receive ropanicant either [redacted], for 2 weeks. On the day of the study visits, participants will be instructed NOT to take their dose of study drug at home, as it will be administered at the study site.

k) Includes history of all medications used in the past year.

l) ECG will be performed in triplicates at screening and baseline visits and the average of the three readings will be reported and used for interpretation. A triplicate ECG reading is considered more reliable than single reading.

5. Endpoints

5.1. Primary Endpoints (Safety)

- Incidence of AEs.
- Incidence of SAEs.
- [redacted]
- Absolute values and change from baseline in laboratory assessments.
- Absolute values and change from baseline in vital signs.
- Absolute values and change from baseline in ECG assessments
- C-SSRS scores during the study.

5.2. Secondary Endpoints (Efficacy)

- Absolute values and change from baseline in MADRS total score at Day 14.
- Proportion of participants with CGI-S score <3 at Day 14.
- Proportion of participants with ≥2 points decrease from baseline on CGI-S scale at Day 14.

5.3. Exploratory Endpoints

- Absolute values and change from baseline in MADRS total score at Days 7 and 21.
- Proportion of participants with reduction of ≥50% from baseline in MADRS total score at Day 14.
- Proportion of participants who achieved an MADRS total score ≤9 at Day 14.
- Proportion of participants with CGI-S score <3 at Day 7.
- Proportion of participants with ≥2 points decrease from baseline on CGI-S scale at Day 7.
- Absolute values and change from baseline in CGI-S score at Days 7 and 14.

5.4. Pharmacokinetic Endpoints

- PK parameters of ropanicant including, but not limited to, C_{max}, T_{max}, C_{trough}, C_{avg}, $AUC_{0\text{-}tau}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $t_{½}$, CL/F, Vz/F, R_{ac} for C_{max}, and R_{ac} for AUC.

5.5. Pharmacodynamic Endpoints

- [redacted]

6. Analysis Sets

6.1. Enrolled Set

The enrolled set will consist of all participants who sign the ICF.

6.2. Safety Set

The safety set will consist of all participants who receive any study drug. The safety set will be used for safety analyses. All analyses using the safety set will group participants according to treatment actually received.

6.3. mFAS

The mFAS will include all participants who are randomized and receive study drug and have a baseline and at least 1 post baseline efficacy assessment of MADRS. All analyses using the mFAS will group participants according to randomized treatment. This population will be used for efficacy analyses.

6.4. Pharmacokinetic Set

The PK set will consist of all participants who receive at least 1 dose of study drug and have at least 1 evaluable plasma concentration data. This population will be used for PK analyses.

6.5. [redacted]

[redacted]

6.6. Protocol Deviations

All subjects protocol deviations will be summarized with number and percentage by treatment group: Protocol deviations data will be summarized on all randomized subjects.

A listing will be produced containing the following information:

- Date
- Minor or Major deviation
- Category of deviation
- Description of deviation

The listing will be presented for the all randomized subjects.

7. General Aspects for Statistical Analysis

7.1. General Methods

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables and figures will be provided.

- Summary tables will be organized by treatment group. Descriptive statistics for continuous variables will include number of subjects (n), mean, standard deviation, median, minimum, and maximum, unless otherwise noted. Frequency and percentage will be calculated for categorical variables. Unless stated otherwise, all summary tables will present descriptive statistics and/or frequencies by treatment.

- All data listings will be sorted by treatment and subject number. Data listing will be provided for all randomized subjects with exception of few listings which will be provided for all enrolled subjects.

- Unscheduled assessments will not be included in summary tables unless specified otherwise but will be included in the subject listings.

7.2. Key Definitions

7.2.1. Baseline

In general, the last non-missing valid observation before first dose of study drug will serve as the baseline measurement.

7.2.2. Change from Baseline

Change or CFB = Post-baseline value – Value at baseline.

Relative change or %CFB = [(Post-baseline value – Value at baseline)/ Value at baseline] x100.

7.2.3. Study Completion

A participant is considered to have completed the study if he/she has completed the 2-week open-label treatment period, the EOT visit, and the follow-up visit.

7.2.4. Duration of AE

Duration of AE [days] = Date of stop of AE – Date of start of AE + 1.

7.2.5. Study Day 1

Study day 1 will be the first day of study drug administration.

First day of study drug administration is defined as first dispensation date.

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7.3. Missing Data

7.3.1. Missing Dates

No missing date will be imputed.

7.3.2. Missing values

Efficacy - Missing Values at Baseline: If a value is missing at baseline but there are non-missing post-baseline values, the missing baseline will be imputed as the first post-baseline non-missing assessment of the subject.

7.4. Visit Windows

All assessments will be included in the listings. No visit windows will be applied to assessments.

7.5. Pooling of Centers

Data from all centers/sites will be pooled together.

7.6. Subgroups

NA

8. Demographic, Other Baseline Characteristics and Medication

8.1. Subject Disposition and Withdrawals

Number and percentage of subjects enrolled, screen failed, re-screened, randomized, completed treatment and study or discontinued, together with the reasons for discontinuation will be summarized for all enrolled subjects. This will also include the number of subjects in each analysis set.

Subject dispositions will be listed for all randomized subjects.

8.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics (Height, Weight, BMI, MADRS and CGI-S) will be summarized using descriptive statistics. Demographic and baseline characteristics data will be listed for all randomized subjects.

Age at date of informed consent = (Date of informed consent - Date of birth + 1) / 365.25 and truncated to complete years.

Height (in cm) = height (in inches) * 2.54

Weight (in kg) = weight (in lbs) * 0.4536

BMI (kg/m2) = Weight(kg)/[Height(m)2]

8.3. Medical History

Medical history will be coded by System Organ Class (SOC) and Preferred Term (PT) using MedDRA version 26.1 (or) higher version.

Medical history will be summarized by treatment group and overall, and sorted by frequency (descending order based on overall totals) by SOC and PT.

All available medical history information will be listed on all randomized subjects.

8.4. Medication

All non-study medications will be classified using the dynamic version of the World Health Organization Drug Dictionary (WHODD) coding dictionary version Global B3 Sep 2023 or higher version. Coding includes the Anatomical Therapeutic Chemical (ATC) classification levels 1 and 2 and preferred term.

8.4.1. Prior Medication

A medication is regarded as ‘prior’ if the stop date of the event is prior to the first dose of study drug, irrespective of the start date.

Prior medications will be summarized by the ATC levels and preferred term. All non-study medications will be listed on all randomized subjects.

8.4.2. Concomitant Medication

A medication is regarded as ‘concomitant’ if it is not ‘prior’ and the start date or stop date is between the date of first dose of study drug (included) and the End of study date (included).

A medication is regarded as 'concomitant' if ticked as ongoing on the CRF.

Concomitant medications will be summarized by the ATC levels and preferred term. All non-study medications will be listed on all randomized subjects.

8.4.3. [redacted]

[redacted]

8.5. Extent of Exposure

Study Drug Exposure, study duration and cumulative dose will be summarized for each treatment group and overall, and will be listed on all randomized subjects.

8.6. Treatment Compliance

Compliance will be assessed by counting returned study drug during the study site visits and documented in the source documents and eCRF. Data for all reports of abuse, overuse, or lost/stolen/missing or unaccounted product should be provided.

[redacted]

9. Efficacy

No formal statistical hypothesis and significance testing will be performed for this study.

9.1. Efficacy Endpoint(s) Analysis

Analysis of change from baseline in MADRS total score at Day 14 will be analyzed using an Analysis of Covariance (ANCOVA) model (with SAS Proc Mixed procedure), that includes the randomized treatment, the stratification factor gender, and the baseline MADRS total score as fixed effects. The covariance parameters will be estimated by restricted maximum likelihood method, and the degrees of freedom will be calculated using the procedure of Kenward and Roger (1997). Least square mean for each single treatment and the difference [redacted] along with 95% confidence interval will be calculated using mFAS analysis set.

Additionally, the Absolute values of MADRS total score for each treatment arm will be analyzed separately using an Analysis of variance (ANOVA) model (with SAS Proc Mixed procedure), with the main effects as randomized treatment, visit, treatment by visit interaction, and stratification factor gender as fixed effects and subject as random effect. The model will be fit using restricted maximum likelihood method, and the Kenward and Roger adjustment for standard errors will be implemented. Least square mean within each single treatment for visits (Baseline, Day 7 and Day 14) and the difference (Day 7 vs Baseline and Day 14 vs Baseline) along with 95% confidence interval will be calculated using mFAS analysis set.

Summary table by visit by treatment with absolute values and change from baseline in MADRS total score will be provided using the mFAS analysis set.

The proportion of participants with CGI-S score <3 at Day 14 and proportion of participants with ≥2 points decrease from baseline on CGI-S scale at Day 14 will be analyzed using a logistic regression model (using SAS Proc Logistic procedure), that includes the randomized treatment, the stratification factor gender, and the measures recorded at baseline as fixed effects using the mFAS analysis set. The odds ratio [redacted] and its 95% confidence interval will be estimated and provided.

Frequency table with percentage by visit by treatment will be provided for binary assessment using mFAS analysis set.

If the assumptions underpinning the ANCOVA are found to be violated, either a log transform or an analysis based on ranked data will be performed as appropriate and least squares means, 95% confidence intervals, and p-values of the treatment comparisons for descriptive purposes along with basic arithmetic summary statistics (mean, median, SD, standard error of the mean, min, and max) will be provided.

[redacted]

Analysis of PK endpoints is detailed in Section 10 (Pharmacokinetcs).

Sample SAS codes on efficacy analysis are provided in Appendix 1.

9.2. Exploratory Endpoints Analyses

Analysis of change from baseline in MADRS total score at Days 7 and 21 and CGI-S score at Days 7 and 14 will be analyzed using an Analysis of Covariance (ANCOVA) model (with SAS Proc Mixed procedure), that includes the randomized treatment, the stratification factor gender, and the respective baseline score as fixed effects. The covariance parameters will be estimated by restricted maximum likelihood method, and the degrees of freedom will be calculated using the procedure of Kenward and Roger (1997). Least square mean for each single treatment and the difference [redacted] along with 95% confirdence interval will be calculated using mFAS analysis set.

Summary table by visit by treatment with absolute values and change from baseline in MADRS total score and CGI-S score will be provided using the mFAS analysis set.

The proportion of participants with reduction of ≥50% from baseline in MADRS total score at Day 14, proportion of participants who achieved an MADRS total score ≤9 at Day 14, The proportion of participants with CGI-S score <3 at Day 7, and proportion of participants with ≥2 points decrease from baseline on CGI-S scale at Day 7 will be analyzed using a logistic regression model (using SAS Proc Logistic procedure), that includes the randomized treatment, the stratification factor gender, and the measures recorded at baseline as fixed effects using the mFAS analysis set. The odds ratio [redacted] and its 95% confidence interval will be estimated and provided.

Frequency table with percentage by visit by treatment will be provided for binary assessment using mFAS analysis set.

If the assumptions underpinning the ANCOVA are found to be violated, either a log transform or an analysis based on ranked data will be performed as appropriate and least squares means, 95% confidence intervals, and p-values of the treatment comparisons for descriptive purposes along with basic arithmetic summary statistics (mean, median, SD, standard error of the mean, min, and max) will be provided.

[redacted]

Sample SAS codes on efficacy analysis are provided in Appendix 1.

10. Pharmacokinetics

The PK analyses will include listings, summary tables, and figures of plasma concentrations for ropanicant and derived PK parameters as described below. The non-compartmental analysis (NCA) will be performed using appropriate software, i.e., Phoenix™ WinNonlin® (Version 8.3 or higher, Certara Corporation) to report based on this SAP. All other analyses will be produced using SAS® (Version 9.4 or higher, SAS Institute Inc.).

Plasma concentration data and derived PK parameters for ropanicant will be listed and summarized by treatment and day for the PK set. Derived PK parameters for ropanicant will be listed and summarized by treatment, day and dose (morning, evening, or daily dose) for the PK set.

10.1. PK Sampling Schedule

Blood samples for PK analysis will be collected on Day 1 and Day 14 for the participants receiving bid dosing of ropanicant only. PK samples will be collected prior to the administration of the study drug and at 0.5, 1, 2, 4, 6, and 12 hours after the first dose (moring dose) and at 0.5, 1, 2, 4, 6, and 12 hours after the second dose (evening dose) at the baseline visit (Day 1) and Day 14. The sample at 12 hours after the first dose will be collected prior to the administration of the second dose. The sample at 12 hours after second dose on Day 1 will be collected prior to the administration of the first dose on Day 2.

10.2. Plasma PK Endpoint and Analysis

Secondary PK parameters, including maximum observed concentration (C_{max}), time to reach the observed maximum concentration (T_{max}), concentration at the end of the dosing interval (C_{trough}), average concentration over a dosing interval at steady-state (C_{avg}), area under the concentration-time curve over the dosing interval ($AUC_{0\text{-}tau}$), area under the concentration-time curve from time zero to the last measure concentration ($AUC_{0\text{-}t}$), area under the concentration-time curve from time zero extrapolated to infinity ($AUC_{0\text{-}inf}$), terminal elimination half-life ($t_{1/2}$), apparent clearance (CL/F), apparent volume of distribution (V_z/F), accumulation ratio for C_{max}, accumulation ratio for AUC, will be calculated for each dose on Day 1 and Day 14, as applicable.

10.2.1. Handling of Missing Data or Data Below the Lower Limit of Quantification

Missing concentration data for participants who were administered the scheduled study treatment will be considered as random non-informative missing and will not be imputed. Missing values will be examined on a case-by-case basis to confirm this.

The data will be handled as follows for the graphical presentation of individual plasma concentrations and for the derivation of the PK parameters (using actual sampling times):

- The time of collection of the pre-dose sample will be set to zero (time 0);
- Actual post-dose sampling times are expressed relative to the time of dosing (if the actual time of sampling is missing, the planned time will be used);
- Pre-dose plasma concentrations below the limit of quantification (BLQ) before dosing on Day 1 will be treated as zero;
- Concentration values BLQ prior to the first quantifiable concentration will be treated as zero.
- Post-dose BLQ values after the first quantifiable time point will be set to zero for calculation of

plasma concentration summary statistics unless they are between two quantifiable values when they will be set to missing;

- For calculation of PK parameters and individual profile plots, BLQ values after C_{max} will be set to missing for each profile;

- Samples taken far from the intended sampling time point may be excluded from by-time point summary statistics; this will be determined by the pharmacokineticist with input from the sponsor. Actual time for each sample collected will be used in the calculation of PK parameters. Therefore, samples will not be excluded from the PK parameter calculation based on time collection differences;

- No further imputation will be applied to any missing values.

10.2.2. Handling of the Difference between the Scheduled and the Actual Sampling Times

The actual clock time for dosing and the actual clock time for each collection time for the PK samples will be recorded. For all sampling times, the actual sampling times will be calculated as the difference between the sample collection actual clock time and the actual clock time of the start of dosing. The actual post-dose sampling times expressed in hours and rounded off to 3 decimal places will be used to calculate the PK parameters; pre-dose sampling times occurring prior to dosing will be reported as zero (0.000), regardless of the time difference.

Scheduled sampling times will be presented in concentration tables, mean graphs and for the individual graphs. A by-subject listing of the actual times for PK collections will be provided for PK samples.

10.2.3. Listing and Presentation of Individual PK Data

Plasma concentrations of ropanicant will be listed and descriptively summarized by treatment and day. Individual and mean plasma concentration versus time curves will be presented for both linear and log-linear scales. Descriptive statistics (arithmetic mean, standard deviation, coefficient of variation, and geometric mean and geometric coefficient of variation, minimum, maximum, and median, plus percentage of concentration values below the lower limit of quantification) for plasma concentrations will be presented.

10.3. Pharmacokinetic Parameters

10.3.1. PK Parameter Derivation

Plasma concentrations of ropanicant will be used to calculate PK parameters by standard non-compartmental methods. The PK parameters will be calculated if a participant has 3 or more plasma concentrations of ropanicant above the LLOQ for the morning, evening doses, or combined on Day 1 or Day 14.

The PK Parameters will be obtained by a [redacted] PK scientist with following specifications:

1. Dosing type: Extravascular

2. Calculation of AUC: Linear up log down

3. Calculation of Kel: best fit approach

The following PK parameters will be calculated for the morning, evening doses, and combined on Day 1 and Day 14, unless specified otherwise:

Parameter	Definition	Method of Determination
AUC_{0-tau}	Area under the concentration-time curve for one dosing interval calculated from time zero to 12 hours. A nominal time of 12 hours is considered the dosing interval.	Linear up log down Calculated for the evening dose on Day 1 and both doses on Day 14.
AUC_{0-12}	Area under the concentration-time curve for the first dosing interval calculated from time zero to 12 hours. A nominal time of 12 hours is considered the dosing interval.	Linear up log down Calculated for the morning dose on Day 1.
AUC_{0-24}	Area under the concentration-time curve for the daily dosing interval calculated from time zero to 24 hours. A nominal time of 24 hours is considered the daily dosing interval.	Linear up log down Calculated for the entire day on Day 1 and Day 14.
AUC_{0-t}	Area under concentration-time curve calculated from time zero to the last non-zero concentration	Linear up log down Calculated for the morning dose, evening dose, and entire day on Day 1 and Day 14
C_{max}	Maximum observed concentration	Observed directly from data Calculated for the morning dose, evening dose, and entire day on Day 1 and Day 14
C_{trough}	Observed concentration at the end of the dosing interval	Observed directly from data, the 12 hour time point after each dose.
C_{avg}	Average concentration over a dosing interval at steady-state	Calculated as $AUC0-_{tau}$/tau. tau = 12 hours Calculated for the evening dose on Day 1 and both doses on Day 14.
T_{max}	Time to reach C_{max}	Observed directly from data Calculated for the morning dose, evening dose, and entire day on Day 1 and Day 14. If the C_{max} is not unique, then the first maximum is used.

λ_z or K_{el}	Apparent first-order terminal elimination rate constant.	Estimated by linear regression of the terminal elimination phase of the log-linear drug concentration-time curve.[1]
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time of zero extrapolated to infinity	$AUC_{0\text{-}t} + C_{last}/\lambda_z$, where C_{last} is the last measurable concentration (For Day 1 morning dose only)
Residual Area	Residual area	Calculated as 100*(1- $AUC_{0\text{-}t}$ / $AUC_{0\text{-}inf}$) [2] (For Day 1 morning dose only)
CL/F	Apparent clearance	Day 1 morning dose: Estimated as Dose/$AUC_{0\text{-}inf}$ Day 1 evening dose and Day 14 morning and evening doses: Estimated as Dose/$AUC_{0\text{-}tau}$
V_z/F	Apparent volume of distribution	Day 1 morning dose: Estimated as Dose/(K_{el}*$AUC_{0\text{-}inf}$) Day 1 evening dose and Day 14 morning and evening doses: Estimated as Dose/(K_{el}*$AUC_{0\text{-}tau}$)
$t_{1/2}$	terminal elimination half-life	ln(2)/K_{el}

[1] Note for K_{el}: Best fit method will be used to calculate the K_{el} from at least 3 post C_{max} concentration data points excluding the C_{max}. R_{sq} adjusted, the goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of K_{el} should be ≥ 0.8. The timepoint where ln-linear K_{el} calculation begins ($K_{el\ Lower}$) and the actual sampling time of the last measurable concentration used to estimate the K_{el} ($K_{el\ Upper}$), as well as the R_{sq} adjusted for the ln-linear regression for the calculation of the elimination rate constant will be reported.

If the K_{el} cannot be measured (e.g.: fewer than 3 non-zero concentrations in the terminal elimination phase), then elimination related PK parameters (K_{el}, $K_{el\ Lower}$, $K_{el\ Upper}$, $AUC_{0\text{-}inf}$, R_{sq} adjusted, Residual area, $t_{1/2}$, CL/F, V_z/F, and $AUC_{0\text{-}tau}$ (if it is extrapolated) will not be reported for PK profiles. If R_{sq} adjusted < 0.8, then K_{el}, and its related PK parameters (K_{el}, $K_{el\ Lower}$, $K_{el\ Upper}$, $AUC_{0\text{-}inf}$, R_{sq} adjusted, Residual area, $t_{1/2}$, CL/F, V_z/F, and $AUC_{0\text{-}tau}$ (if it is extrapolated) will be excluded in summary and inferential statistics and flagged in individual listings.

[2] If Residual Area is >20%, then $AUC_{0\text{-}inf}$, CL/F (Day 1 morning), and V_z/F (Day 1 morning) will be excluded in summary statistics and flagged in individual listings.

10.3.2. PK Parameters Summarization

PK parameters will be summarized by treatment, day and dose (morning, evening and daily dose) using the following descriptive statistics:

Variable	Summarized with:
$AUC_{0\text{-}tau}$, $AUC_{0\text{-}12}$, $AUC_{0\text{-}24}$,	n, arithmetic mean, SD, CV%, minimum, median, maximum,

Variable	Summarized with:
$AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, C_{trough} and C_{avg}	geometric mean and geometric CV%
$t_{1/2}$, CL/F, and V_z/F	n, arithmetic mean, SD, CV%, minimum, median, maximum, geometric mean and geometric CV%
T_{max} (actual time)	n, minimum, median, and maximum

PK Reporting Precision:

Statistics	**Degree of Precision**
Minimum, Maximum	3 significant digits or as needed based on actual measured values
Mean (arithmetic and geometric), Median	4 significant digits or as needed based on actual measured values
Standard deviation	5 significant digits or as needed based on actual measured values
CV% and Geometric CV%	1 decimal point or as needed based on actual measured values

For PK concentration and parameter listings, the final reportable results or data will be presented by rounding off to 2 decimal digits, except for the following situations (this applies to individual data):

- K_{el} data, and Rsq adjusted: rounded off to four decimal digits. CL/F may also be rounded off to four decimal digits depending on the majority of the value.
- PK parameters related to time such as T_{max}, $K_{el\ Lower}$, and $K_{el\ Upper}$ must be reported with the same precision as the actual sampling time: rounded off to 3 decimal digits.

Concentration versus time data: reported as they appear in corresponding dataset.

10.4. Planned Statistical Models for PK Parameters and Concentrations

The log transformed PK parameters (dose-normalized C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}tau}$) will be analyzed using ANOVA model (with SAS Proc Mixed procedure) with the main effects as randomized treatment, visit, treatment by visit interaction, and stratification factor gender as fixed effects and subject as random effect. The model will be fit using restricted maximum likelihood method, and the Kenward and Roger adjustment for standard errors will be implemented. Least square mean for each single treatment and the difference along with 95% confirdence interval will be calculated using PK analysis set.

The log transformed PK parameters $AUC_{0\text{-}inf}$ will be analyzed using ANOVA model (with SAS Proc Mixed procedure) with the main effects as randomized treatment, and the stratification factor gender. The model will be fit using restricted maximum likelihood method, and the Kenward and Roger adjustment for standard errors will be implemented. Least square mean for each single treatment and the difference along with 95% confirdence interval will be calculated using PK analysis set.

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The rank transformed PK parameters (T_{max}) will be analyzed using ANOVA model (with SAS Proc Mixed procedure) with the main effects as randomized treatment, visit, treatment by visit interaction, and stratification factor gender as fixed effects and subject as random effect. The model will be fit using restricted maximum likelihood method, and the Kenward and Roger adjustment for standard errors will be implemented. Least square mean for each single treatment and the difference along with 95% confirdence interval will be calculated using PK analysis set.

An analysis of the accumulation ratio of AUC (AUC_{0-12} on Day 1 morning dose and AUC_{0-tau} on Day 14 morning dose) and C_{max} (on Day 1 and Day 14 morning dose) will be undertaken.

For each PK parameter, statistical comparisons will be performed across the visits (Day 1 and 14). The estimated ratio (Day 14/Day 1) of model-adjusted geometric means will be used to perform this comparison.

In order to estimate the geometric mean ratio, a linear mixed effects model will be fit to the data. The response variable will be the natural-log transformed PK parameter (C_{max} and AUC_{0-tau}), and the model will include treatment (dose level), visit, treatment-by-visit interaction and stratification factor gender as fixed effects and subject as random effect. The model will be fit using restricted maximum likelihood method, and the Kenward and Roger adjustment for standard errors will be implemented. The model has the form:

ln(PK Parameter) = μ + Treatment + Visit + Treatment*Visit + gender + Subject + ϵ,

where μ represents the overall mean, Treatment is a fixed effect with three levels, Visit is a fixed effect with two levels, Treatment*Visit is the interaction term, Gender is a fixed effect with two levels, subject is a random effect with a constant variance component, and ϵ represents the associated model error with constant variance.

From this model, the difference in means will be estimated for Day 14 vs. Day 1 per dose level, accompanied by a corresponding (two-sided) 90% CI. The point estimate and confidence endpoints will be exponentiated using base e in order to obtain a point and interval estimate for the ratio of geometric means (presented to three decimal places). These transformed CI will indicate the degree of accumulation across Day 14 vs. Day 1 at each dose level, and for each PK parameter.

10.5. Interim Analyses

Not applicable

10.6. Deviation from Analyses Planned in Protocol

Not applicable

11. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12. Safety

The analysis set used for safety analyses will be the Safety Set (SS). Safety will be assessed based on adverse event (AE), clinical laboratory data, ECG parameters, vital signs, and C-SSRS scores.

12.1. Adverse Events / Adverse Drug Reactions

All reported AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). AE data will be presented in incidence tables. AEs will also be summarized by severity, seriousness, and relationship to treatment, AEs leading to treatment discontinuation, AEs leading to death and [redacted]

The incidence of TEAEs (events with onset dates on or after the start of the study drug) will be included in incidence tables. Events with missing onset dates will be included as treatment-emergent unless an incomplete date clearly indicates that the event started prior to the first study drug administration.

All AEs will be listed by subject, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

Adverse events (AEs) will be coded using MedDRA 26.1 or higher version.

Events that occur after a subject provides informed consent but before the time of the first dose of study drug will be considered non treatment-emergent AEs. Treatment-emergent AEs are defined as events that are newly occurring or worsening from the time of the first dose of study drug.

Missing dates will not be imputed. However, the following table will be utilized to categorize TEAEs.

AE Start Date	AE End Date	Rule on AE End Date	Rule on AE Start Date	TEAE
Not missing			AE Start Date < Treatment Start Date	N
			AE Start Date ≥ Treatment Start Date	Y
Partly missing	Not missing	AE End Date < Treatment Start Date		N
		AE End Date ≥ Treatment Start Date	non missing part of AE Start Date < Treatment Start Date	N
			non missing part of AE Start Date ≥ Treatment Start Date	Y
	Partly missing	non missing part of AE End Date < Treatment Start Date		N
		non missing part of AE End Date ≥ Treatment Start Date	non missing part of AE Start Date < Treatment Start Date	N
			non missing part of AE Start Date ≥ Treatment Start Date	Y
	Totally Missing or Ongoing		non missing part of AE Start Date < Treatment Start Date	N
			non missing part of AE Start Date ≥ Treatment Start Date	Y
Totally Missing	Not missing	AE End Date < Treatment Start Date		N
		AE End Date ≥ Treatment Start Date		Y
	Partly missing	non missing part of AE End Date < Treatment Start Date		N
		non missing part of AE End Date ≥ Treatment Start Date		Y
	Totally Missing or Ongoing			Y

An overall summary of AEs will show the number and percentage of subjects (and the corresponding number of AEs) by treatment group.

- any AEs
- any TEAE
- any TEAE by severity
- any treatment related TEAE
- any serious TEAE
- any serious treatment related TEAE
- any TEAE leading to treatment discontinuation
- [redacted]
- any TEAE leading to death

Summary tables by system organ class and preferred term will be provided for treatment group and overall for

- TEAEs
- TEAEs by maximum severity
- Treatment-related TEAEs
- Serious TEAEs
- Serious treatment related TEAE
- TEAE leading to treatment discontinuation
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted].

Separate listings will be provided in the tables section for

- any SAE
- any fatal AE
- any AE leading to treatment discontinuation

All TEAEs for each subject, including multiple occurrences of the same event, will be presented for all randomized subjects. In a separate listing all non-TEAEs of randomized subjects will be provided.

12.2. Laboratory Evaluations

Descriptive statistics will be performed for those laboratory parameters on a continuous scale for actual values and change from baseline at each visit, by treatment. Quantitative laboratory results with a preceding '<' or '>', the sign will be ignored and the numeral alone will be considered as the result for summarizing purposes. The listings will, however, display the result as captured in the database.

Categorical results will be summarized using frequency tabulations. Additionally, shift table of post-baseline to baseline of the values below normal range, within normal range and above normal range will be provided. Abnormal values for each analyte will be determined using reference ranges provided by the central laboratory. All laboratory results will be listed including unscheduled visits.

Urinalysis results evaluation (Normal, Abnormal Not Clinically Significant and Abnormal Clinically Significant) will be summarized at each protocol scheduled time point by treatment group using frequency tabulations. All abnormal laboratory values will be flagged in the listings.

The following table summarizes all laboratory parameters which will be assessed in the study.

Assessments	**Parameters**
Hematology	Hemoglobin Hematocrit RBC count Platelet count WBC count with differential as absolute and percentages.
Chemistry	AP AST ALT Creatine phosphokinase Chloride GGT Creatinine Calcium Direct bilirubin Glucose Potassium Sodium HDL LDL TBL Total cholesterol Total protein Triglycerides
Urinalysis	pH of freshly voided specimen Specific gravity Protein Glucose Ketones Bilirubin Nitrites WBC RBC Microscopic examination of the sediment
Pregnancy test	Serum hCG pregnancy test (at the screening visit only) Urine pregnancy test (at all other visits)
Other (at the screening visit only)	HIV Hepatitis B serum antigen FSH (investigator's discretion) Hepatitis C virus
Urine illicit drug screen	Phencyclidine Barbiturates Benzodiazepines Opiates Methadone Cocaine THC Methamphetamines/amphetamines

A listing with pregnancy test results will be summarized for all randomized female subjects.

12.3. Vital Signs

Vital signs (body temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate) will be evaluated at the visits indicated in the Schedule of Assessments. All vital signs will be measured in a semi-supine position after 5 minutes' rest.

Vital signs and body weight will be summarised at each protocol scheduled time point by treatment group. Actual values and changes from baseline will be presented. Vital signs and body weight will be listed for all randomized subjects.

12.4. ECG

ECG results will be summarised at each protocol scheduled time point by treatment group. Actual values and changes from baseline will be presented. Additionally, a shift table of the overall ECG evaluation at the post-baseline visits compared to baseline will be provided. At screening and baseline visits, average of triplicate values will be considered for evaluation.

ECG results will be listed for all randomized subjects.

12.5. Physical Examination

Physical examination data (Normal/ Abnormal - Not Clinically Significant and Abnormal - Clinically Significant) at each visit will be listed by body system for all randomized subjects.

12.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

For this study, the following versions of the scale are used: the “baseline/screening” version (to assess suicidality history for study eligibility) and the “Since last visit” version (for all subsequent visits).

The C-SSRS data, i.e. suicidal ideation severity, suicidal ideation intensity, suicidal behavior, non-suicidal self-injuries behavior and lethality, will be summarized by treatment arm and visit for the Safety Population. Additionally, a frequency table of subjects answering Yes to questions of C-SSRS form by any question will be provided by treatment arm for the Safety Analysis Set. A listing of all randomized subjects will be provided.

13. Interim Analyses

No interim analysis will be performed.

14. Changes from Analysis Planned in Protocol

NA.

15. Reference List

NA

16. Programming Considerations

All statistical computations and construction of tables, listings and figures will be performed using SAS® for Windows Version 9.4 or higher (SAS® Institute Inc., Cary, NC, USA). Pharmacokinetic calculations will be performed using Phoenix™ WinNonlin® (Version 8.3 or higher, Certara Corporation) and/or SAS® (Version 9.4 or higher, SAS® Institute Inc.).

The format of the table shells will be followed as closely as possible; however, in the course of programming and familiarization with the database, some changes may become necessary. All changes will be documented. Major changes will be documented through a formal amendment to this document.

SDTM datasets will be created from the clinical database and external data, following the Study Data Tabulation Model Implementation Guide Version 3.2 or latest version. Analysis will be based on ADaM datasets created from the SDTM datasets.

The below programming considerations will be followed unless already specified in the above text.

16.1. General Considerations

- One SAS program can create several outputs, or a separate SAS program will be created for each output
- One output file can contain several outputs or each output will be stored in a separate file
- Output files will be delivered in Word format
- Numbering of TFLs will follow ICH E3 guidance

16.2. Table, Figure, and Listing Format

16.2.1. General

- All TFLs will be produced in landscape format, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities
- Legends will be used for all figures with more than one variable, group, or item displayed
- TFLs will be in black and white (no color), unless otherwise specified. Colors may be used in figures.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below)
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate

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16.2.2. Headers

- All output will have the following header at the top left of each page:

  Suven Life Sciences Ltd;
  Protocol No.: CTP2S1911A4B2, [redacted]
  Draft/Final Run

- All output will have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number will appear sequentially as page n of N, where N is the total number of pages in the table)

- The date the output was generated will appear along with the program name as a footer on each page.

16.2.3. Display Titles

- Each TFL will be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering will be followed. A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title will be centered. The analysis set will be identified on the line immediately following the title and will be enclosed in parenthesis. The title and table designation will be single spaced. A solid line spanning the margins will separate the display titles from the Column headers. There will be one blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(Analysis Set)

16.2.4. Column Headers

- Column headings will be displayed immediately below the solid line described above in initial upper-case characters.

- For numeric variables, include ‘unit’ in column or row heading when appropriate.

- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of subjects in the analysis set.

16.2.5. Body of the Data Display

16.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values will be left-justified;

- Whole numbers (e.g., counts) will be right-justified; and

- Numbers containing fractional portions will be decimal aligned.

16.2.5.2. *Table Conventions*

- Units will be included where available
- For categorical parameters,all categories will be presented in the table, even if n=0 for all treatment groups in a given category. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- An Unknown or Missing category will be added to each parameter for which information is not available for 1 or more subjects
- Unless otherwise specified, the estimated mean and median for a set of values will be printed out to 1 more significant digit than the original values, and standard deviations will be printed out to 2 more significant digits than the original values. The minimum and maximum will report the same significant digits as the original values. For example, systolic blood pressure will be presented as follows:

N	XX
Mean (SD)	XX.X (XX.XX)
Median	XX.X
Min, Max	XX, XX

- P-values will be output in the format: ‘0.xxx’, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999
- Percentage values will be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed and percentages equating to 100% will be presented as 100%, without decimal places
- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data will be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) will be displayed in decreasing order. If incidence for more than 1 term is identical, they will then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated will be reported as ‘-’

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- The percentage of subjects will normally be calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Details will be described in footnotes or programming notes, as necessary

- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, a footnote or programming note will be added describing whether the subject is included in the summary statistics for all relevant categories or just 1 category as well as the selection criteria

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by '(cont)' at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page

16.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time

- Missing data will be represented on subject listings as either a hyphen ('-') with a corresponding footnote ('- = unknown or not evaluated'), or as 'NA', with the footnote 'NA = not applicable', whichever is appropriate

- Dates will be printed in SAS DATE9.format ('DD_MMM_YYYY': 01JUL2000). Missing portions of dates will be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject will be output as 'NA', unless otherwise specified

- All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study

- Units will be included where available

16.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis

16.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display

- Footnotes will always begin with 'Note:' if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote will start on a new line, where possible

- Subject specific footnotes are avoided, where possible

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- Footnotes will be used sparingly and add value to the TFL. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page

- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, the date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z')

- Sources and/or cross-references in footnotes will use the keyword prefix (in singular form) for each reference and will be separated by a comma when mutiple cross-references are displayed
  Example
  Listing source: Listing 16.2.4.1.1, Listing 16.2.4.1.2, Listing 16.2.4.2.1

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17. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in [redacted]

[redacted]Conducting the Transfer of Biostatistical Deliverables SOP [redacted] and the SAS Programming and Vaidation Plan describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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21. Shells

Mock shells for tables, listings and figures will be created in a separate document as an attachment to the SAP which may be updated, revised and finalized separately from the SAP.



