1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX21-548-103 (Final Analysis)

A Phase 2, Randomized, Double-blind, Active-controlled, Dose-ranging, Parallel-design Study of the Efficacy and Safety of VX-548 in Subjects With Painful Diabetic Peripheral Neuropathy

[redacted]

Version: 1.0
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4 INTRODUCTION

This statistical analysis plan (SAP) for the final analysis is based on the most recent approved clinical study protocol (CSP), the most recent approved electronic case report form (eCRF), and the most recent approved eCRF completion guidelines. This SAP documents the planned statistical analysis of efficacy and safety endpoints defined in the study protocol of VX21-548-103 and provides additional details and clarifications.

The Vertex Biometrics Department will perform the final statistical analysis of the efficacy and safety data; SAS® Version 9.4 Software (SAS Institute, Cary, North Carolina, USA) or higher will be used to generate all statistical outputs (tables, figures, listings and datasets).

The SAP (Methods) will be finalized and approved before the clinical data lock for the final analysis. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP prior to the clinical database lock. Any revisions made to the SAP after the clinical data lock will be documented in the clinical study report for this study.

Analyses addressing the pharmacokinetic (PK) objective of the study will be described in the Clinical Pharmacology Analysis Plan (CPAP) which will be developed separately by the Vertex Clinical Pharmacology department.

5 STUDY OBJECTIVES

5.1 Primary Objective

- To evaluate the efficacy of three VX-548 doses in treating subjects with painful diabetic peripheral neuropathy (DPN)
- To evaluate the safety and tolerability of VX-548

[redacted]

6 STUDY ENDPOINTS

6.1 Primary Endpoint

- Change from baseline in the weekly average of daily pain intensity on a numeric pain rating scale (NPRS) at Week 12

6.2 Secondary Endpoints

- Change from baseline in the weekly average of the Daily Sleep Interference Scale (DSIS) at Week 12
- Proportions of subjects with ≥30%, ≥50%, and ≥70% reductions from baseline in the weekly average of daily pain intensity on the NPRS at Week 12
- Proportion of subjects categorized as much improved or very much improved at Week 12 on the patient global impression of change (PGIC) assessment
- Safety and tolerability based on the incidence and type of adverse events (AEs) and changes from baseline in clinically significant laboratory test results, vital signs, and ECGs at each visit

[redacted]

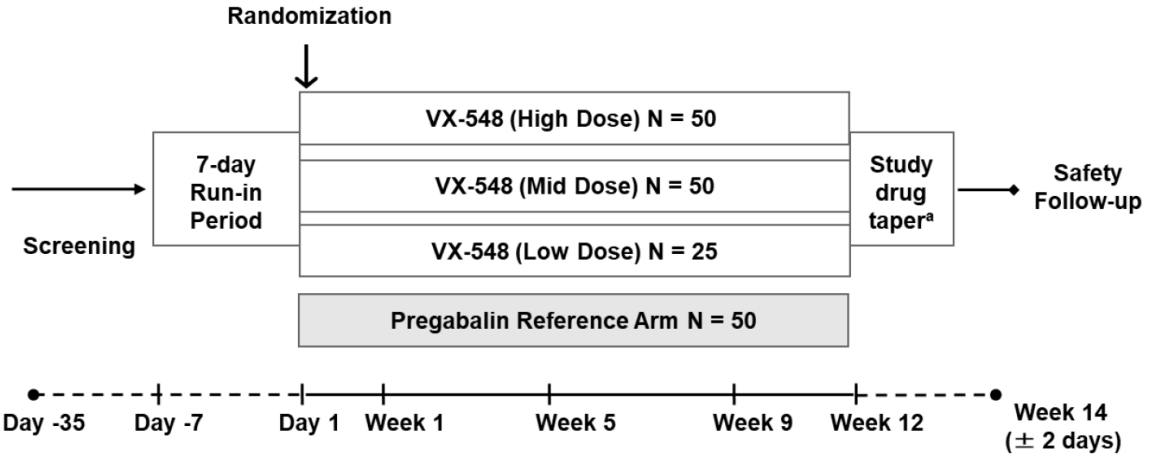
7 STUDY DESIGN

7.1 Overall Design

This is a Phase 2, randomized, double-blind, active-controlled, dose-ranging, 4-arm parallel-design study evaluating the efficacy and safety of three different doses of VX-548 in treating diabetic peripheral neuropathy.

Subjects who meet eligibility criteria during Screening Visits 1 and 2 will enter a 7-day Run-in Period to establish their baseline NPRS pain score. Subjects with a baseline average NPRS score of ≥4 points with limited variation (SD <25% of mean) will be eligible for the 12-week Treatment Period followed by a Safety Follow-up Visit (Figure 7-1).

Figure 7-1 VX21-548-103 Study Design



N: number of subjects
[a] At the end of the Treatment Period (Week 12), subjects will taper off capsule (pregabalin reference or matched placebo) study drug for 7 days.

A total of approximately 175 subjects will be randomized 2:2:1:2 to 4 treatment arms: VX-548 (high, mid, or low dose) or pregabalin (reference arm) (Table 7-1). Randomization will be stratified by sex (female and male) and body mass index (≥30 and <30 kg/m^2). To maintain the blind, all subjects will receive the same number of tablets once daily (qd) in the morning and the same number of capsules 3 times per day in a double-dummy design. After the Treatment Period, subjects will taper off capsule (pregabalin reference or matched placebo) study drug for 7 days (4 days of dosing every 12 hours, then 3 days of dosing qd), and the Safety Follow-up Visit will occur an additional 7 (± 2) days later.

Table 7-1 VX21-548-103 Treatment Arms

Treatment	Active Dose	Number of Subjects (Planned)
VX-548 (high dose)	69 mg qd	50
VX-548 (mid dose)	46 mg qd	50
VX-548 (low dose)	23 mg qd	25
Pregabalin	100 mg tid	50

qd: once daily; tid: 3 times per day
Note: To maintain the blind, all subjects will receive the same number of tablets and the same number of capsules at the same respective frequency (i.e., qd for tablets and tid for capsules during the Treatment Period) in a double-dummy design.

Subjects will stop taking pain medications (including pregabalin, if applicable), except acetaminophen (500 mg), for at least 14 days before the first dose of study drug. Acetaminophen will be permitted as a pain rescue medication as needed (prn) throughout the study. Subjects will be permitted to take 500 mg every 4 to 6 hours prn, up to a maximum of 2500 mg in any 24-hour period. Subjects will record rescue medication use, and their current pain score on the NPRS immediately before each administration of rescue medication. Rescue medication usage will only be documented up to treatment discontinuation.

7.2 Sample Size and Power

The sample size is based on the primary analysis of the primary endpoint. With 37 evaluable subjects in the VX-548 high or mid dose group and 18 evaluable subjects in the VX-548 low dose group, there is more than 90% power in any VX-548 dose group to detect a mean change from baseline of 3 with a single group *t*-test at the 2-sided 0.05 significance level, assuming the SD is 2.3. With an evaluable sample size of 37, a 2-sided 95% CI for the mean change from baseline in the high or mid dose group will extend 0.77 on either side of the observed mean, assuming the CI is based on the *t*-statistic and the observed SD is 2.3. Under the same assumptions and an evaluable sample size of 18, a 2-sided 95% CI for the mean change from baseline in the low dose group will extend 1.14 on either side of the observed mean. To account for a 25% dropout rate, 50 subjects each will be enrolled in the VX-548 high dose, VX-548 mid dose, and the pregabalin groups; 25 subjects will be enrolled in the VX-548 low dose group. The total sample size is approximately 175 subjects.

The study is not powered for comparison between the VX-548 doses and the pregabalin reference arm.

7.3 Randomization

Refer to Section 9.2 of the CSP for details.

7.4 Blinding and Unblinding

Refer to Section 10.7 of the CSP for details.

8 ANALYSIS SETS

8.1 All Subjects Set

The **All Subjects Set** is defined as all subjects who have been randomized or have received at least 1 dose of study drug. This analysis set will be used in subject listings and disposition summary table, unless otherwise specified.

8.2 Full Analysis Set

The **Full Analysis Set (FAS)** is defined as all randomized subjects who have received at least 1 dose of study drug. The FAS is to be used to summarize subject demographics and baseline characteristics. It is also to be used in all efficacy analyses, in which subjects will be analyzed according to their randomized treatment group.

8.3 Safety Set

The **Safety Set** is defined as all subjects who have received at least 1 dose of study drug. The Safety Set is to be used for all safety analyses in which subjects will be analyzed according to the treatment they received.

9 STATISTICAL ANALYSIS

9.1 General Considerations

The Schedule of Assessments is provided in Section 3 of the CSP. The precision standards for reporting variables are provided in an internal Biometrics document that specifies the programming rules including the precision for derived variables.

All individual subject data for subjects who were randomized or received at least 1 dose of study drug will be presented in individual subject data listings.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), median, minimum value (min), and maximum value (max), unless otherwise specified.

Categorical variables will be summarized using counts and percentages.

Baseline value: The baseline for the weekly average of NPRS and DSIS will be defined as average of the non-missing scores from Day -7 to Day -1. For the weekly average of NPRS, baseline values will be calculated if there are at least 4 non-missing scores. For weekly average of DSIS, baseline values will be calculated if there are at least 3 non-missing scores. For ECGs, the baseline values will be defined as the most recent average of non-missing triplicate measurements collected before the first dose of the study drug. For all other variables, baseline values will be defined as the most recent non-missing measurement collected before the first dose of study drug, unless otherwise specified.

Change (absolute change) from baseline will be calculated as post-baseline value – baseline value.

Treatment-emergent (TE) Period will include the time period from the date of the first dose of study drug to either (1) the Safety Follow-up Visit, (2) the ETT Visit if it replaces the Safety Follow-up Visit, or (3) 14 days after the last dose for subjects who do not have a Safety Follow-up Visit or equivalent.

Unscheduled visits: Unscheduled visit measurements will be included in the analysis as follows:

- In scheduled visit windows per specified visit windowing rules
- In the derivation of baseline
- In the derivation of maximum and minimum values during the TE period, and maximum and minimum change from baseline values during the TE period for safety analyses
- In individual subject data listings as appropriate

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Appendix A.

Incomplete/missing data: Details on how to handle missing data are described in subsequent sections when applicable.

Outliers: No formal statistical analyses will be performed to detect and/or remedy the presence of statistical outliers.

Multiplicity: There is no multiplicity adjustment for this Phase 2 study.

9.2 Background Characteristics

9.2.1 Subject Disposition

The disposition summary will be provided by treatment group and overall.

The number of subjects in the following categories will be summarized:

- All Subjects Set
- Randomized
- Full Analysis Set (FAS)
- Safety Set
- Randomized but not dosed

The number and percentage (based on the FAS) of subjects in each of the following disposition categories will be summarized:

- Completed treatment

- Prematurely discontinued treatment and the reason for discontinuation from treatment
- Completed study
- Prematurely discontinued the study and the reason for discontinuation from study
- Complete taper
- Did not complete taper

A disposition listing and a randomization listing of subjects will be provided.

9.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized based on the FAS by treatment group and overall.

Demographic data will include the following:

- Age at screening (in years)
- Age at screening category (≥18 to <65, ≥65)
- Sex (male, female)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not collected per local regulations)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, not collected per local regulations, Other and Multiracial [if 2 or more races reported from a subject])

Baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- BMI category (≥ 30 and < 30 kg/m^2)
- Baseline HbA1c (%)
- Baseline HbA1c category (<7 and ≥ 7%)
- Baseline weekly average of NPRS
- Baseline weekly average of NPRS category (<8, ≥8)
- Baseline weekly average of DSIS
- Baseline NPSI total score
- Baseline SF-36 physical component summary score
- Baseline SF-36 mental component summary score
- Baseline SF-MPQ-2 total score

- Baseline BDI-2 total score

The scoring of NPSI, SF-36, SF-MPQ-2 and BDI-2 are included in Appendix B.

In addition to demographic data and baseline characteristics, data listings will also be provided for:

- Informed consent
- Inclusion/exclusion criteria violation for subjects with any such violations

9.2.3 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized descriptively based on the FAS by MedDRA system organ class (SOC) and preferred term (PT). This summary will be provided by treatment group and overall. The corresponding data listing will also be provided.

9.2.4 Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary and categorized as the following for the purposes of analysis:

Prior medication: Medication that started before the first dose of study drug, regardless of when dosing of the medication ended

Concomitant medication: Medication continued or newly received after the date and time of the first dose of study drug through the end of the TE Period

A given medication may be classified as a prior medication, a concomitant medication, or both a prior and a concomitant medication.

If a medication start date/time is on or after the first dose of study drug, then the medication will be classified as a concomitant medication regardless of whether the medication end date/time is missing. If a medication end date/time is before the first dose of study drug, then the medication will be classified as a prior medication regardless of whether the medication start date/time is missing.

Note that a medication that started before the first dose of study drug and continued after the first dose will be classified as a prior medication and separately as a concomitant medication. If a medication has a missing or partially missing start or end date/time and it cannot be determined whether it was taken before the first dose of study drug or concomitantly, it will be classified as a prior and a concomitant medication.

Details for imputing missing or partial start/end date and time of medication are described in Appendix C.

Prior and concomitant medications will be summarized based on the FAS by Preferred Name and listed. This summary will be provided by treatment group and overall. Prior pain medications will be included in the summary of prior medications and will also be summarized and listed separately. Concomitant analgesic medications other than rescue medication will be included in the summary of concomitant medications and will also be summarized and listed separately. Rescue medication, as collected in the e-diary, will not be

included in the summary of concomitant medications and will be summarized separately. Prior and concomitant non-pharmacological treatments or procedures will be listed.

9.2.5 Study Drug Exposure and Study Drug Compliance

Study drug exposure and study drug compliance will be summarized based on data collected in eCRF.

Duration of study drug exposure (in days) will be calculated as (last date of dosing in the treatment period – first date of dosing +1). Duration of study drug exposure in weeks will be summarized by treatment group (based on FAS) using descriptive summary statistics and by frequency count and percentages for the following categories: ≤1 week, >1 and ≤ 2 weeks, >2 and ≤ 3 weeks, …, >11 weeks and ≤ 12 weeks and >12 weeks.

Study drug compliance rate will be calculated as 100× [1- (total number of days of study drug interruption between the last dose date in the treatment period and first dose date)/ (duration of study drug exposure in days)]. Study drug compliance rate will be summarized descriptively (based on FAS) by treatment group and overall and into the categories of <80%, and ≥80%.

9.2.6 Important Protocol Deviations

An important protocol deviation (IPD) is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. IPD rules will be developed and finalized before database lock. IPDs will be identified by the PD review team according to the protocol deviation plan.

IPDs will be summarized descriptively based on FAS by treatment group and overall, as well as presented in an individual data listing.

9.3 Efficacy Analysis

All efficacy analyses described in this section will be based on the FAS. Subjects will be analyzed according to their randomized treatment assignment.

9.3.1 Analysis of Primary Endpoint

9.3.1.1 Definition of Primary Estimand

The primary endpoint is the change from baseline in the weekly average of daily pain intensity on an NPRS at Week 12. The primary estimand is defined as the following:

- Treatment: VX-548 + rescue medication (if used)
- Population: Study population defined by the study inclusion and exclusion criteria
- Variable: change from baseline in the weekly average of daily pain intensity on an NPRS at Week 12

- Handling of intercurrent events:
  - The hypothetical strategy will be used to handle treatment discontinuation, which means that the observed NPRS scores up to treatment discontinuation will be used.
  - The treatment policy strategy will be used to handle rescue medication use, which means that the observed NPRS scores on the days when subjects take rescue medication will be used.
- Population level summary: Variable mean

9.3.1.2 Primary Analysis

The primary analysis of the primary estimand will be a within-group comparison in any VX-548 dose group.

The weekly average of daily pain intensity on an NPRS (hereafter referred to as "weekly average of NPRS") will be calculated as the average of the non-missing NPRS scores at the baseline and in each week during the treatment period as defined in Appendix A. The baseline score will be calculated if there are at least 4 non-missing NPRS scores during Days -7 to -1. The Week 1 to Week 12 scores will be calculated if there are at least 3 non-missing NPRS scores in each week. The NPRS scores collected up to treatment discontinuation will be used in the calculation of the weekly average of NPRS.

The primary efficacy analysis will be based on a mixed-effects model for repeated measures

(MMRM), with change from baseline in weekly average of NPRS at each week as the dependent variable; and fixed effects of treatment group, week (categorical), treatment group-by-week interaction, baseline weekly average of NPRS, baseline weekly average of NPRS-by-week interaction. The model will be estimated using restricted maximum likelihood. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors (SE). An unstructured co(variance) structure will be used to model the within-subject errors. If there is a convergence issue, then a compound symmetric covariance matrix will be used to model the within-subject errors. The least squares (LS) mean change from baseline at Week 12 for each treatment group will be presented with the corresponding SE, 95% CI and P-value.

9.3.2 Analysis of Secondary Efficacy Variables

Change from baseline in the weekly average of the DSIS at Week 12: The change from baseline in the weekly average of DSIS at Week 12 will be analyzed similarly to the primary analysis as specified in Section 9.3.1.2. The model will include the change from baseline in weekly average of DSIS scores as the dependent variable; and fixed effects of treatment group, time (categorical), treatment group-by-time interaction, baseline weekly average of DSIS, baseline weekly average of DSIS-by-time interaction. The LS mean change from baseline at Week 12 for each treatment group will be presented with the corresponding SE and95% CI. In addition, the LS mean change from baseline at each week will also be presented together with the corresponding SE and 95% CI by treatment group. The LS mean

change from baseline and SE at each week will also be presented in figure by treatment group.

The weekly average of DSIS will be calculated by averaging the non-missing DSIS scores at the baseline and in each week during the treatment period as defined in Appendix A. They will be calculated if there are at least 3 non-missing DSIS scores for each week, including the baseline. The DSIS scores collected up to treatment discontinuation will be used in the calculation of the weekly average of DSIS.

Proportion of subjects with ≥ 30%, ≥ 50%, and ≥ 70% reduction from baseline in the weekly average of daily pain intensity on the NPRS at Week 12:

The percentage reduction in the weekly average of NPRS at Week 12 will be calculated as 100% × (weekly average at baseline − weekly average at Week 12) / weekly average at baseline. The weekly average at baseline and at Week 12 are the scores used for the primary analysis.

Subjects with ≥30% reduction from baseline at Week 12 will be defined as "responders". Subjects with <30% reduction from baseline at Week 12 or subjects who discontinued treatment early will be defined as "non-responders". Subjects who complete treatment but have missing weekly average at Week 12 will have the data imputed based on the last available weekly average and their response status will be determined based on the imputed score. The proportion of subjects with ≥30% reduction from baseline in the weekly average of NPRS at Week 12 will be summarized descriptively by treatment group.

The proportion of subjects with ≥50% and ≥70% reduction from baseline will be defined and summarized similarly.

Proportion of subjects categorized as much improved or very much improved at Week 12 on the PGIC assessment: The proportion of subjects categorized as much improved or very much improved at Week 12 on the PGIC assessment will be summarized descriptively by treatment group. Subjects who complete treatment but have missing data at Week 12 will have the data imputed from the last available measurement. Subjects who discontinue treatment will be considered as "non-responders".

[redacted]

9.3.4 Multiplicity Adjustment

There is no multiplicity adjustment for this Phase 2 study.

9.4 Safety Analysis

The overall safety profile of VX-548 will be assessed in terms of the following safety and tolerability endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (hematology, serum chemistry, coagulation, and urinalysis)
- ECG outcomes
- Vital signs

- Physical examination test values
- C-SSRS

All safety analyses will be performed based on the Safety Set based on actual treatment. In the unexpected scenario that a subject receives more than one treatment in the study, the following algorithm will be used to define actual treatment: for any dosed subjects, the actual treatment is defined as the VX-548 highest dose level among all received VX-548 treatment if the subject received any VX-548 treatment, regardless of the randomized treatment assignment; the actual treatment is defined as pregabalin if the subject did not receive any VX-548 treatment but did receive any pregabalin.

Only descriptive analyses of safety will be performed, and no statistical hypothesis testing will be performed.

9.4.1 Adverse Events

AEs will be coded according to MedDRA. For analysis purposes, AEs will be classified as pretreatment AEs and TEAEs as follows:

Pretreatment AEs: AEs that occurred before the first dose of study drug

Treatment-emergent AEs: AEs that worsened or started after the first dose of study drug through the end of the TE Period

For AEs with completely missing or partial start dates/times, if there is no clear evidence that the AEs started before or after the first dose of study drug, the AEs will be classified as TEAEs.

Imputation rules for missing or partial AE start dates/times are defined as Appendix D.

AE summary tables will be presented for TEAEs by treatment group, and will include the following:

- All TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Related TEAEs
- Serious TEAEs
- Related serious TEAEs
- TEAEs leading to death

Summaries will be presented by MedDRA SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once, and only the maximum severity level will

be presented in the severity summaries, and the strongest relationship level in the relationship summaries.

All AEs, including pretreatment AEs and TEAEs, will be presented in an individual subject data listing. In addition, listings containing individual subject AE data for TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption, SAEs and all deaths will be provided separately.

9.4.2 Clinical Laboratory Assessments

All statistical analyses of laboratory values will be performed using SI units. For treatment-emergent laboratory measurements, the observed values and change from baseline values of the continuous hematology, chemistry, and coagulation results will be summarized at each visit.

The number and percentage of subjects with selected test values meeting threshold analysis criteria during the TE period will be summarized. The threshold analysis shift from baseline criteria will also be summarized for selected chemistry measurements. The threshold analysis criteria are provided in Appendix E.

Results of urinalysis and the urine/serum pregnancy test will be in individual subject data listings only.

In addition, listings of individual subject hematology, chemistry, and coagulation values outside the normal reference ranges will be provided. These listings will include data from both scheduled and unscheduled visits.

9.4.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided at each visit and time point, as applicable, for the following ECG measurements: heart rate (HR; beats per minute [bpm]), PR interval (msec), RR interval (msec), QRS duration (msec), QT interval (msec), and QT corrected for HR intervals (QTcF [msec]).

The number and percentage of subjects meeting threshold analysis criteria during the TE period will be summarized. The threshold analysis criteria are provided in Appendix E. A listing containing individual subject measurements meeting the threshold value criteria at any time point will be provided. This listing will include data from both scheduled and unscheduled visits.

In addition, the number and percentage of subjects by maximum treatment-emergent value of QT/QTcF intervals, categorized as ≤450 msec, >450 msec and ≤480 msec, >480 msec and ≤500 msec, and >500 msec, as well as maximum treatment-emergent change from baseline value of QT/QTcF intervals, categorized as ≤0 msec, and >0 and ≤30 msec, >30 and ≤60 msec, and >60 msec, will be provided.

Since ECGs are performed in triplicate, the mean of the ECG measurements will be used as the ECG value for summaries of observed values and change from baseline values, and all reported ECG measurements will be used to conduct threshold analyses and to assess maximum treatment-emergent values.

9.4.4 Vital Signs

For the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized at each visit. The following vital signs parameters will be summarized: systolic and diastolic blood pressure (mm Hg), pulse rate (beats per minute), body temperature (°C), and respiratory rate (breaths per minute).

The number and percentage of subjects meeting threshold analysis criteria during the TE Period will be summarized. The threshold analysis criteria are provided in Appendix E.

In addition, a listing containing individual subject vital signs values will be provided. This listing will include data from both scheduled and unscheduled visits.

9.4.5 Physical Examination

Physical examination (PE) results will be presented in an individual subject data listing only.

9.4.6 Columbia-Suicide Severity Rating Scale

The proportion of subjects with at least one event during the TE Period of suicidal ideation, suicidal behavior, suicidal ideation or behavior, or self-injurious behavior without suicidal intent, as recorded on the Columbia-Suicide Severity Rating Scale (C-SSRS), will be summarized. C-SSRS results for subjects with responses of "Yes" at any visit will also be presented in an individual subject data listing.

10 SUMMARY OF INTERIM AND IDMC ANALYSES

Not applicable.

11 LIST OF APPENDICES

Appendix A Analysis Visit Windows for Safety and Efficacy Assessments

Table 12-1 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit/Time point[1]	Target Study Day /Time point per the protocol	Analysis Visit Window (in study days/time points) [2, 3, 4]
Safety Assessment			
Hematology Serum Chemistry	Baseline Week 3 Week 9 Week 12	Day 1 Day 22 Day 64 Day 85	[Screening Visit 1, Pre-dose Day 1] [Day 1 post-dose, 43] [44,74] [75,99]
Coagulation	Baseline Week 12	N/A Day 85	[Screening Visit 1, Pre-dose Day 1] [Day 1 post-dose,99]
Standard 12-Lead ECG	Baseline Day 1 Day 1 2 hrs post-dose Day 1 4 hrs post-dose Week 1 Week 5 Week 5 Pre-dose Week 5 2 hrs post-dose Week 5 4 hrs post-dose Week 12	Day 1 Day 1 Day 1 Day 8 Day 36 Day 36 Day 36 Day 36 Day 85	[Screening Visit 2, Pre-dose Day 1] Nominal Nominal Nominal [Day 2, 21] Nominal Nominal Nominal Nominal [61,99]
Vital Signs	Baseline Week 1 Week 3 Week 5 Week 7 Week 9 Week 12	Day 1 Day 8 Day 22 Day 36 Day 50 Day 64 Day 85	[Screening Visit 1, Pre-dose Day 1] [Post-dose Day 1,14] [15,29] [30,43] [44,57] [58,74] [75,99]
Efficacy Assessment			

Table 12-1 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit/Time point[1]	Target Study Day /Time point per the protocol	Analysis Visit Window (in study days/time points) [2, 3, 4]
NPRS via daily e-diary DSIS via daily e-diary	Baseline	N/A	[-7, -1]
	Week 1	N/A	[1, 7]
	Week 2	N/A	[8, 14]
	Week 3	N/A	[15,21]
	Week 4	N/A	[22,28]
	Week 5	N/A	[29,35]
	Week 6	N/A	[36,42]
	Week 7	N/A	[43,49]
	Week 8	N/A	[50,56]
	Week 9	N/A	[57,63]
	Week 10	N/A	[64,70]
	Week 11	N/A	[71,77]
	Week 12	N/A	[78,84]
Rescue medication via daily e-diary	Week 1	N/A	[1*, 7]
	Week 2	N/A	[8, 14]
	Week 3	N/A	[15,21]
	Week 4	N/A	[22,28]
	Week 5	N/A	[29,35]
	Week 6	N/A	[36,42]
	Week 7	N/A	[43,49]
	Week 8	N/A	[50,56]
	Week 9	N/A	[57,63]
	Week 10	N/A	[64,70]
	Week 11	N/A	[71,77]
	Week 12	N/A	[78,84]
PGIC	Week 1	Day 8	[Post-dose Day 1, 15]
	Week 5	Day 36	[29,43]
	Week 12	Day 85	[78,92]
	Safety Follow-up	N/A	Nominal

[redacted]

Notes: * only include Day 1 post-dose measurements.
[1] Visit/time point names for analysis purposes are used to report data in tables and figures.

[2]The analysis visit windows will be applied using the following rules for both scheduled and unscheduled visits:

a. If no numerical measurement is available within a visit window, the measurement will be considered missing for the visit.

b. If there is more than 1 numerical measurement available within the same visit window, use the following rules:

i. The measurement closest to the target day/time point will be used; or

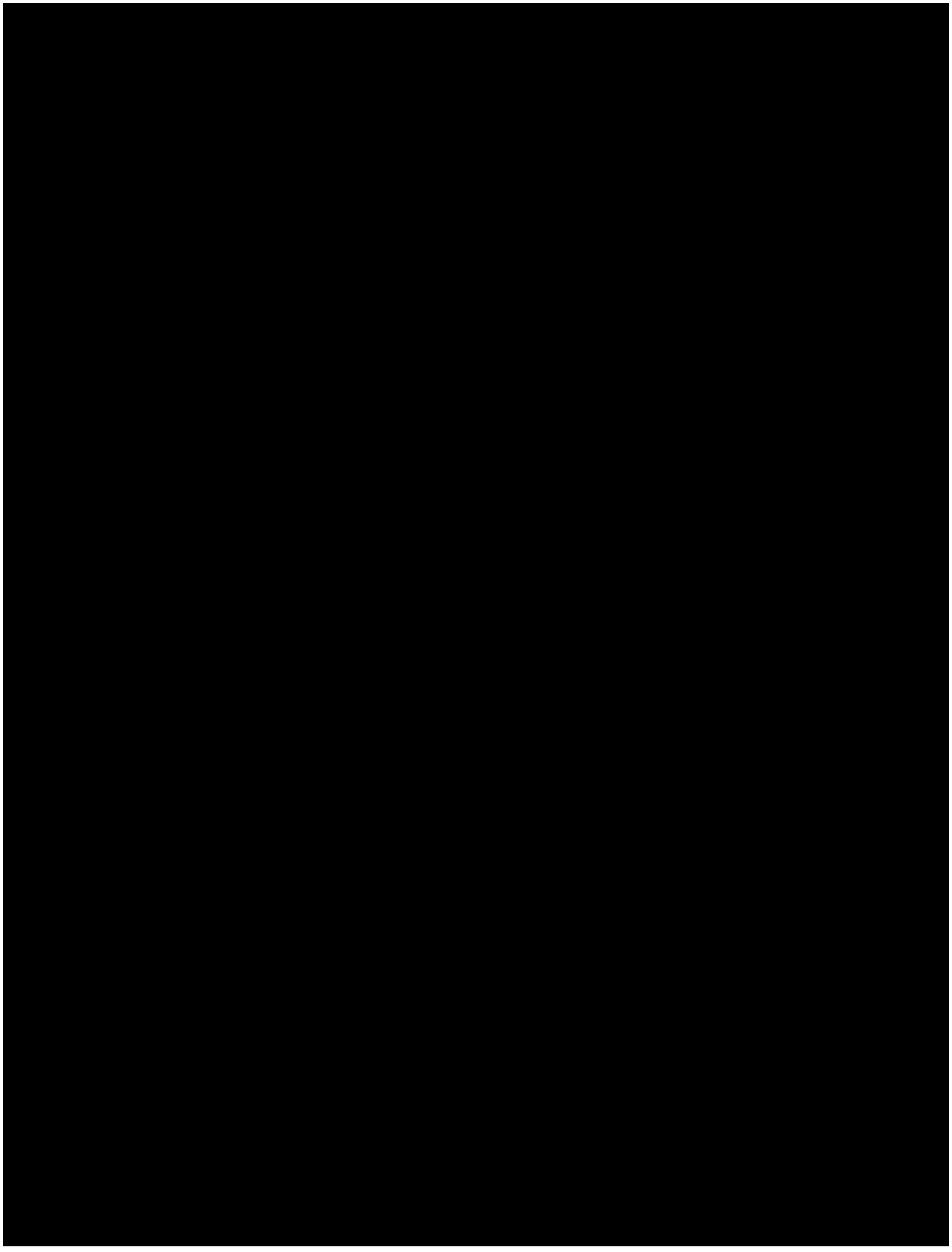
ii. If there are multiple measurements within the same distance from the target day/time point, the latest measurement will be used.

[3]For measurements collected on the date of the first dose of study drug, if it cannot be determined whether the measurement is before or after the first dose:

a. If a scheduled measurement is pre-dose in the CSP, it will be treated as a pre-dose observation. If a scheduled measurement is post-dose in the CSP, it will be treated as a post-dose observation.

b. Unscheduled measurements will be treated as post-dose observations.

[4]When defining baseline for efficacy and safety, refer to the generic baseline definition in Section 9.1.



[redacted]

[redacted]

Appendix C Imputation Rules for Missing Prior/Concomitant Medication Dates

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
    a. If day is missing, use the first day of the month.
    b. If day and month are both missing, use the first day of the year.
    c. If day, month and year are all missing, use a date before the first dose date.
2. Missing or partial medication stop date and time:
    a. If day is missing, use the last day of the month.
    b. If day and month are both missing, use the last day of the year.
    c. If day, month and year are all missing, assign 'continuing' status to stop date.

Table 12-2 Prior and/or Concomitant Categorization of a Medication

Medication Start Date	Medication Stop Date	
	< First Dose Date/Time of Study Drug	**≥ First Dose Date/Time and ≤ End Date of TE Period**
< First dose date/time of study drug	P	PC
≥ First dose date/time and ≤ end date of TE period	-	C

C: Concomitant; P: Prior

Appendix D Imputation Rules for Missing AE Dates and Times

Imputation rules for missing or partial AE start dates and times are defined below:

If Hour and/or Minute of AE start time are missing, do not impute:

- If the AE start date is before the first dose date, the AE will be classified as a pretreatment AE.
- If the AE start date is on or after the first dose date, the AE will be classified as a TEAE.

If only Day of AE start date is missing:

- If the AE start year and month are the same as that for the first dose date, then:
  - If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of the first dose date
  - Otherwise, impute the AE start day as 1.
- Otherwise, impute the AE start day as 1.

Compare the imputed AE start date with the TE period to determine whether the AE is a pretreatment AE or TEAE.

If Day and Month of AE start date are missing:

- If AE start year is the same as the year of the first dose date, then:
  - If the full (or partial) AE end date is NOT before the first dose date or the AE end date is missing, then impute the AE start month and day as the month and day of the first dose date;
  - Otherwise, impute the AE start month as January and the day as 1.
- Otherwise, impute the AE start month as January and the day as 1.

Compare the imputed AE start date with TE period to determine whether the AE is a pretreatment AE or TEAE.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing, then query the site with no imputation. Compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date, then the AE should be considered as a pretreatment AE. Otherwise, the AE will be considered as a TEAE.

If Hour and/or Minute of first dose time are missing:

- If the AE start date is before the first dose date, the AE will be classified as a pretreatment AE.
- If the AE start date is on or after the first dose date, the AE will be classified as a TEAE.

A missing or partially missing AE end date will not be imputed.

Appendix E Threshold Value Criteria

Table 11-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Clinical Chemistry		
ALT	>ULN - ≤3xULN >3x - ≤5xULN >5x - ≤8xULN >8x - ≤20xULN >20xULN	FDA DILI Guidance Jul 2009.
AST	>ULN - ≤3xULN >3x - ≤5xULN >5x - ≤8xULN >8x - ≤20xULN >20xULN	FDA DILI Guidance Jul 2009.
ALT or AST	(ALT>ULN - ≤ 3xULN) or (AST>ULN - ≤3xULN) (ALT>3x - ≤5xULN) or (AST>3x - ≤5xULN) (ALT>5x - ≤8xULN) or (AST>5x - ≤8xULN) (ALT>8x - ≤20xULN) or (AST>8x - ≤20xULN) ALT>20xULN or AST>20xULN	FDA DILI Guidance Jul 2009.
Alkaline Phosphatase	>ULN - ≤1.5xULN >1.5 - ≤2.5xULN >2.5 - ≤5xULN >5 - ≤20xULN >20xULN	FDA DILI Guidance Jul 2009.
Total Bilirubin	>ULN - ≤1.5xULN >1.5 - ≤2xULN >2 - ≤3xULN >3 - ≤10xULN >10xULN	FDA DILI Guidance Jul 2009.
Direct Bilirubin	>ULN - ≤1.5xULN >1.5 - ≤2xULN >2 - ≤3xULN >3 - ≤10xULN >10xULN	FDA DILI Guidance Jul 2009.
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	FDA DILI Guidance Jul 2009.

Table 11-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
GGT	>ULN - ≤2.5xULN >2.5 - ≤5xULN >5 - ≤20xULN >20xULN	CTCAE grade 1-4
Albumin	<LLN - ≥30 g/L <30 - ≥20 g/L <20 g/L	CTCAE grade 1-3
Creatinine	>ULN - ≤1.5xULN >1.5 - ≤3xULN >3 - ≤6xULN >6xULN	CTCAE grades 1-4
Lipase	>ULN - ≤1.5xULN >1.5x - ≤2xULN >2x - ≤5xULN >5xULN	Criteria based upon CTCAE
Total protein	<LLN >ULN	No CTCAE
Creatine kinase	>ULN - ≤2.5xULN >2.5 - ≤5xULN >5 - ≤10xULN >10xULN	CTCAE grades 1-4
Hematology		
Hemoglobin	Hgb decreased (anemia) <LLN - ≥100 g/L <100 - ≥80 g/L <80 g/L	CTCAE grade 1-3
	Hgb increased >ULN - ≤20 g/L above ULN >20 g/L above ULN - ≤40 g/L above ULN >40 g/L above ULN	CTCAE grade 1-3
Platelets	Platelet decreased <LLN - ≥75 x 10e9 /L <75 - ≥50 x 10e9 /L <50 - ≥25 x 10e9 /L <25 x 10e9 /L	CTCAE grade 1-4
	Platelet increased >ULN	No CTCAE available
Coagulation		
Activated partial thromboplastin time (PTT)	>ULN - ≤1.5xULN >1.5 - ≤2.5xULN >2.5xULN	CTCAE grade 1-3

Table 11-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - ≤1.5xULN >1.5 - ≤2.5xULN >2.5 x ULN	CTCAE grade 1-3

Table 11-4 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
HR	Bradycardia <50 bpm <45 bpm Decrease from baseline ≥10 bpm Decrease from baseline ≥20 bpm <50 bpm and decrease from baseline ≥10 bpm <50 bpm and decrease from baseline ≥20 bpm	Per HV grade 2, 3, plus shift change
	Tachycardia >100 bpm >115 bpm >130 bpm Increase from baseline ≥10 bpm Increase from baseline ≥20 bpm >100 bpm and increase from baseline ≥10 bpm >100 bpm and increase from baseline ≥20 bpm	Per HV grade 1, 2, 3, plus shift change
PR	≥240 ms ≥300 ms ≥200 ms and increase from baseline ≥40 ms ≥200 ms and increase from baseline ≥100 ms	
QRS	>110 ms >160 ms Increase from baseline ≥20 ms Increase from baseline ≥40 ms	
QTc	>450 to <500ms (Male) or >470 to <500ms (Female) ≥500 ms Increase from baseline Increase from baseline >10 ms Increase from baseline >20 ms Increase from baseline >40 ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula.

Table 11-5 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
Pulse Rate	Same as above in ECG category	
SBP increased	>140 mmHg >160 mmHg >10 mmHg increase from baseline >20 mmHg increase from baseline >140 mmHg & >10 mmHg increase from baseline >140 mmHg & >20 mmHg increase from baseline >160 mmHg & >10 mmHg increase from baseline >160 mmHg & >20 mmHg increase from baseline	
SBP decrease	<90 mmHg <80 mmHg >10 mmHg decrease from baseline >20 mmHg decrease from baseline <90 mmHg and >10 mmHg decrease from baseline <90 mmHg and >20 mmHg decrease from baseline <80 mmHg and >10 mmHg decrease from baseline <80 mmHg and >20 mmHg decrease from baseline	Per HV grade 1, 3, plus shift change
DBP increased	>90 mmHg >100 mmHg >5 mmHg increase from baseline >10 mmHg increase from baseline >90 mmHg and >5 mmHg increase from baseline >90 mmHg and >10 mmHg increase from baseline >100 mmHg and >5 mmHg increase from baseline >100 mmHg and >10 mmHg increase from baseline	
DBP decreased	<60 mmHg <45 mmHg >5 mmHg decrease from baseline >10 mmHg decrease from baseline <60 mmHg and >5 mmHg decrease from baseline <60 mmHg and >10 mmHg decrease from baseline <45 mmHg and >5 mmHg decrease from baseline <45 mmHg and >10 mmHg decrease from baseline	
Oxygen saturation decreased	<88% <95% and decrease from baseline >5% of absolute oxygen saturation	

12 REFERENCES

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