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VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan

(Methods)

Protocol Number: VX17-121-001 Version 3.0 (Final Analysis)

A Phase 1/2 Study of VX-121 in Healthy Subjects and in Subjects With Cystic Fibrosis

Author of SAP: [redacted]

Version: 2.0

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Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210, USA

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4 INTRODUCTION

The statistical analysis plan (SAP) describes the statistical methods to be used for the analyses of safety and efficacy data to support the preparation of regulatory submissions and the final analysis 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 addresses the objectives of the study and describes the planned safety and efficacy analyses and data presentations. [redacted]. Analyses and data presentations for Parts A, B and C will be generated by [redacted] using SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA). Analyses and data presentations for Part D will be performed by Vertex Pharmaceuticals Incorporated (Vertex) Biometrics Department using SAS® Version 9.4 or higher.

This SAP will be finalized and approved prior to the database lock. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP prior to the clinical database lock for the final analysis, and any changes made to the SAP after the clinical database lock will be documented and discussed in the clinical study report for this study.

The analysis and reporting of the pharmacokinetic (PK) objective of the study will be described in the Clinical Pharmacology Analysis Plan (CPAP) which will be developed separately by the Clinical Pharmacology Department at Vertex.

5 STUDY OBJECTIVES

5.1 Primary Objectives

Part A: To evaluate the safety and tolerability of single ascending doses of VX-121 in healthy subjects

Part B: To evaluate the safety and tolerability of multiple ascending doses of VX-121 for 10 days in healthy subjects

Part C: To evaluate the safety and tolerability of multiple ascending doses of VX-121 administered in triple combination (TC) with tezacaftor (TEZ)/ ivacaftor (IVA) for 14 days in healthy subjects

Part D: To evaluate the safety and tolerability of VX-121 in TC with TEZ/IVA in subjects with cystic fibrosis (CF)

5.2 Secondary Objectives

Part A

- To evaluate the PK of VX-121 after administration of single ascending doses of VX-121 in healthy subjects
- To evaluate the relative bioavailability (BA) of a tablet formulation of VX-121 relative to suspension in healthy subjects
- To evaluate the effect of milk on the PK of VX-121 after administration of suspension and tablet formulations

Part B

- To evaluate the PK of VX-121 after administration of multiple ascending doses of VX-121 for 10 days in healthy subjects

Part C

- To evaluate the PK of VX-121 after administration of multiple ascending doses of VX-121 in TC with TEZ/IVA for 14 days in healthy subjects
- To evaluate the PK of TEZ, IVA, and their respective metabolites when administered in TC with VX-121 for 14 days in healthy subjects

Part D

- To evaluate the PK of VX-121 when administered in TC with TEZ/IVA in subjects with CF
- To evaluate the PK of TEZ, IVA, and their respective metabolites when administered in TC with VX-121 in subjects with CF
- To evaluate the PD effect of VX-121 in TC with TEZ/IVA in subjects with CF
- To evaluate the efficacy of VX-121 in TC with TEZ/IVA in subjects with CF

6 STUDY ENDPOINTS

6.1 Primary Endpoints

Parts A, B, C, and D: Safety and tolerability will be based on the assessment of adverse events (AEs), laboratory test results, standard 12-lead electrocardiograms (ECGs), vital signs, and spirometry (Part D only)

6.2 Secondary Endpoints

- **Parts A, B, C, and D:** PK parameter estimates of VX-121 derived from plasma concentration-time data
- **Parts C and D:** PK parameter estimates for TEZ and metabolites (M1-TEZ and M2-TEZ) and IVA and metabolites (M1-IVA and M6-IVA) derived from plasma concentration-time data
- **Part D:** Sweat chloride levels as a biomarker of PD effects
- **Part D:** Spirometry as preliminary evidence of efficacy

7 STUDY DESIGN

7.1 Parts A, B, and C (Healthy Subjects)

This is a 4-part, randomized, double-blind, placebo-controlled, single- and multiple-dose, first-in-human and first-in-patient dose escalation study of VX-121 that includes an evaluation of relative BA and the effect of milk on VX-121 exposure.

A schematic of the study design for Parts A, B, and C is shown in Table 7-1. Up to 2 additional cohorts each in Parts A (Cohorts A7 and A8), B, and C may be enrolled based on data from previous cohorts; these cohorts will follow the corresponding schedule of assessments.

There is no prespecified ratio of males to females, but reasonable effort will be made to enroll females of non-childbearing potential in all dosing cohorts. Subjects will be allowed to participate in up to 2 cohorts (subjects may enroll in 2 cohorts in Part A or 1 cohort in Part A and 1 cohort in either Part B or Part C; see Section 9.1.1.1 of the protocol).

The decision to initiate successive cohorts and dose selection will be based on safety and tolerability data from preceding dose group(s) and available PK data from all subjects in the preceding cohort (minimum of 6 subjects to ensure 4 subjects receiving active drug). Refer to Section 9.7.1 of the protocol for dose escalation criteria and Section 9.8.1 of the protocol for stopping rules.

Subjects will receive VX-121 as a suspension, under fed conditions. The tablet formulation may be used instead of the suspension in any remaining cohorts of the study if supported by preliminary PK data from Cohort A9. The existing restrictions on dairy consumption (Section 9.4.1 of the protocol) may be removed pending the results from Cohorts A3 and/or A9.

Staggered Dosing in Cohorts A1 and C1

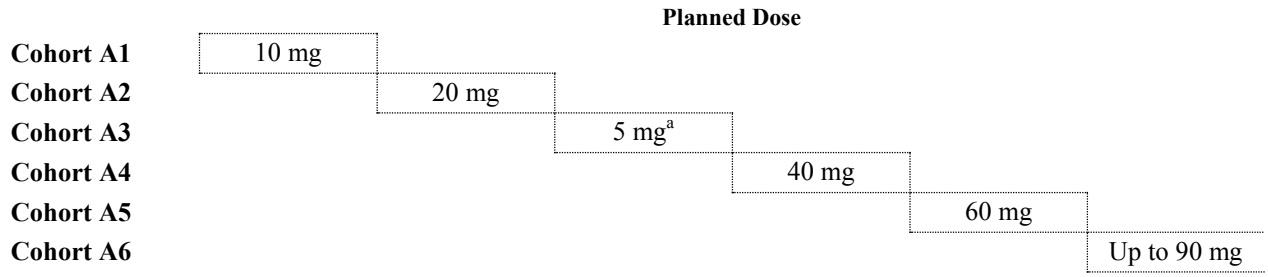
Dosing in the first cohort of Parts A and C (Cohorts A1 and C1) will initiate with staggered dosing in 2 subjects (1 active, 1 placebo) followed by a minimum 24-hour observation before dosing of the remaining subjects in the cohort (Section 9.1.1 of the protocol). Staggering at higher doses may be conducted if deemed necessary based on review of emerging safety data.

Cohort A9

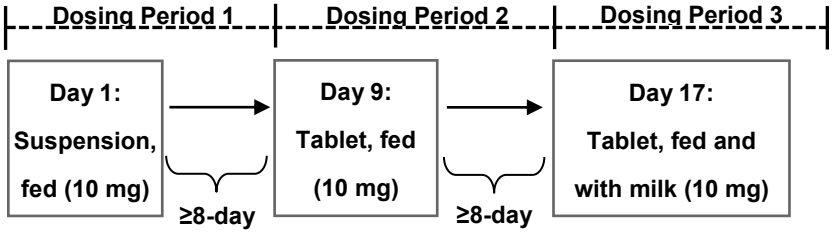
Cohort A9 will not be initiated until all documentation required to support administration of the VX-121 tablet has been submitted to and approved by the competent authority (IRB/IEC, as applicable).

Table 7-1 Study Design for Parts A, B, and C

Part A: Single-dose escalation of VX-121
Approximately 8 subjects per cohort, randomized 3:1 (VX-121:placebo) except for Cohort A9



Cohort A9 (Approximately 8 subjects, open-label VX-121, single sequence)[b]



Part B: Multiple-dose escalation of VX-121
Approximately 8 subjects per cohort, randomized 3:1 (VX-121:placebo)

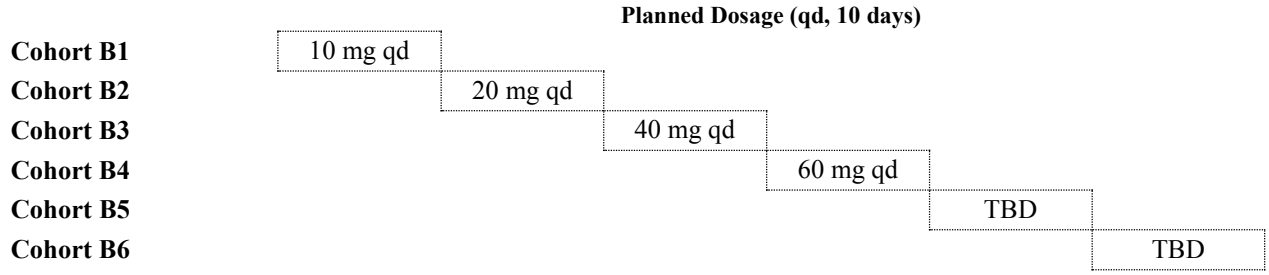


Table 7-1 Study Design for Parts A, B, and C

Part C: Multiple-dose escalation of VX-121 in TC with TEZ/IVA[c] Approximately 8 subjects per cohort, randomized 3:1 (VX-121/TEZ/IVA:triple placebo)		
	Planned Dosage (qd, 14 days)	
Cohort C1	10 mg qd	
Cohort C2		20 mg qd

Notes: In Part A, planned doses are shown; any cohort may be initiated at a lower or higher dose level than the planned dose based on emerging safety, tolerability, and PK data. No dose increment will be expected to yield greater than a 3-fold increase (Cohorts A1 through A3) or a 2-fold increase (all other Part A cohorts and Part B cohorts) in exposure from the preceding dose level. Dose escalation criteria and predefined stopping criteria are described in Section 9.7.1 and Section 9.8.1 of the protocol.

[a] In addition to randomized study drug administration depicted above, after a washout of at least 8 days all subjects will receive an additional 5 mg single dose of open-label VX-121 suspension with milk to evaluate the effect of milk on VX-121 exposure.

[b] Subjects will receive a single dose of VX-121 on 3 dosing occasions with at least an 8-day washout between dosing occasions. VX-121 doses include a single oral dose of suspension, a single oral dose of tablet to evaluate the relative BA of the tablet, and a single oral dose of tablet with milk to evaluate the effect of milk on VX-121 exposure (the planned dose is 10 mg for both formulations, but it will not exceed the highest dose that was safe and well tolerated in a previous Part A cohort).

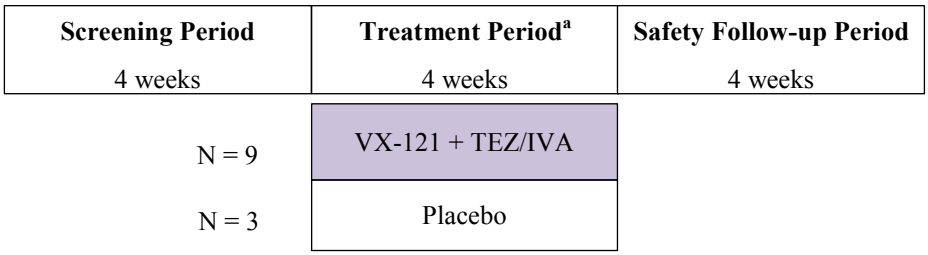
[c] The dosage of TEZ/IVA will be TEZ 100 mg qd/IVA 150 mg q12h, which will be administered as TEZ 100-mg/IVA 150-mg FDC in the morning and IVA 150 mg in the evening.

7.2 Part D (Subjects With CF)

A schematic of the study design for Part D is shown in Figure 7-1, which has a randomized, double-blind, placebo-controlled, parallel-group design. After completing the Screening Period, approximately 12 subjects will be randomized 3:1 to TC:placebo.

Screening in Part D will be initiated after the completion of Parts A, B, and C (cohorts needed for Part D dose selection only) through the Safety Follow-up Visit. The decision to proceed to Part D will be based on an evaluation of safety, tolerability, and PK data from completed cohorts in Parts A, B, and C. These data will be submitted to the IEC for approval before proceeding to screening for Part D. Refer to Section 9.3.2 of the protocol for additional details.

Figure 7-1 Schematic of Study Design for Part D



[a] The planned VX-121 dose for Part D is 10 mg qd. This dose is predicted to provide an approximate AUC_{0-24h} of 10 µg·h/mL, which is within the predicted efficacious exposure range based on in vitro data. Based on emerging safety, tolerability, and PK data from Parts A, B, and C, the planned dose for Part D may be lowered to 5 mg qd. The total daily dose of VX-121 in Part D will be at least 1 dose level below the highest total daily dose tested in Part C. The dosage of TEZ/IVA in the TC will be TEZ 100 mg qd/IVA 150 mg q12h, which will be administered as TEZ 100 mg/IVA 150 mg FDC in the morning and IVA 150 mg in the evening.

7.3 Sample Size and Power

No formal sample size calculations have been performed. The number of subjects participating in each cohort of Parts A, B, and C is typical for first in human studies in healthy subjects and is considered sufficient to achieve the objectives of the study. Approximately 12 subjects in Part D is considered sufficient to meet the objectives of the study for this early assessment in subjects with CF.

7.4 Randomization

A randomization list for each part will be produced by Vertex Biostatistics or a qualified randomization vendor. The Vertex study biostatistician will review and approve the dummy randomization list. The final randomization list will be reviewed and approved by a designated unblinded biostatistician who is not a member of the study execution team (SET).

Parts A, B, and C

Subjects will be assigned a unique subject number (unique to subject and cohort). Only subjects who have completed screening assessments and are eligible for participation in the study will be randomized to receive active study drug or placebo during the Treatment Period. A list identifying subjects by their subject number will be maintained in the study file at the CRU.

Part D

Subjects will be assigned a unique subject number. Only subjects who have completed screening assessments and are eligible for participation in the study (and qualify to enter the Treatment Period) will be randomized to receive active study drug or placebo during the Treatment Period.

An interactive web response system (IWRS) will be used to assign subjects to treatment.

7.5 Replacement

Subjects who withdraw or are withdrawn before the first dose of study drug on the Day 1 Visit may be replaced.

Subjects who withdraw or are withdrawn for nonsafety reasons during the study drug treatment period(s) may be replaced at Vertex's discretion.

7.6 Blinding and Unblinding

Refer to the Section 10.7 of the protocol for details.

8 ANALYSIS SETS

8.1 All Subjects Set

For subjects other than those from Cohort A9, the **All Subjects Set** will include all subjects who were randomized or received at least 1 dose of study drug.

For subjects from Cohort A9, the All Subjects Set will include all subjects who were assigned a subject identification number or received at least 1 dose of study drug.

The All Subjects Set will be used for individual subject data listings, and the disposition summary table, unless specified otherwise.

8.2 Full Analysis Set (Part D Only)

The **Full Analysis Set** (FAS) will include all randomized subjects who carry the intended *CFTR* allele mutation and have received at least 1 dose of study drug in the Treatment Period. The FAS will be used for all PD and efficacy analyses in which subjects will be analyzed according to their randomized treatment group, unless otherwise specified.

8.3 Safety Set

The **Safety Set** will include all subjects who received at least 1 dose of study drug. All safety, demographics, baseline characteristics, study drug exposure, and concomitant medications will be summarized for the Safety Set.

9 STATISTICAL ANALYSIS

9.1 General Considerations

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

Continuous data 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).

Categorical data will be summarized using frequency counts and percentages. Percentages will be presented to 1 decimal place, unless otherwise specified.

Treatment-emergent (TE) Period

For subjects participating in Part A (excluding Cohorts A3 and A9), Parts B and C, the **TE Period** will be from the first dose date of study drug to (1) the Safety Follow-up Visit for subjects who have a Safety Follow-up Visit, or (2) 7 days after the last dose of study drug for subjects who do not have a Safety Follow-up Visit.

For subjects participating in Cohort A3 in Part A, 2 TE periods will be analyzed:

- **TE Period 1 (suspension [fed])** will begin from the administration of study drug on Day 1 (1) until the administration of VX-121 in fed state and with milk, or (2) the Safety Follow-up Visit for subjects who do not have the dose of VX-121 in fed state and with milk, and have a Safety Follow-up Visit, or (3) 7 days after the last dose of study drug for subjects who do not have the dose of VX-121 in fed state and with milk, and do not have a Safety Follow-up Visit.
    - **TE Period 2 (suspension [fed and with milk])** will begin from the administration of study drug on Day 9 through the Safety Follow-up Visit or 7 days after the last dose of study drug, whichever comes first.

For subjects participating in Cohort A9 in Part A, 3 TE periods will be analyzed:

- **TE Period 1 (suspension [fed])** will begin from the administration of study drug on Day 1 (1) until the administration of of VX-121 tablet in the fed state, or (2) the Safety Follow-up Visit for subjects who do not have the dose of VX-121 tablet in the fed state and have a Safety Follow-up Visit, or (3) 7 days after the last dose of study drug for subjects who do not have the dose of VX-121 tablet in the fed state and do not have a Safety Follow-up Visit.

- **TE Period 2 (tablet [fed])** will begin from administration of VX-121 tablet in the fed state (1) until the administration of VX-121 tablet in the fed state and with milk, or (2) the Safety Follow-up Visit for subjects who do not have the dose of VX-121 tablet in the fed state and with milk and have a Safety Follow-up Visit, or (3) 7 days after the last dose of study drug for subjects who do not have the dose of VX-121 tablet in the fed state and with milk, and do not have a Safety Follow-up Visit.
- **TE Period 3 (tablet [fed and with milk])** will begin from the administration of VX-121 tablet in fed state and with milk through the Safety Follow-up Visit or 7 days after the last dose of study drug for subjects who do not have a Safety Follow-up Visit..

For subjects participating in Part D, the **TE Period** will be from first dose date of study drug to Safety Follow-up Visit for subjects who have a safety follow-up visit; or 28 days after the last dose date of study drug for subjects who do not have a safety follow-up visit.

Treatment Groups

The Treatment Groups in Part A (excluding Cohorts A3 and A9), B, C and D will be defined as the corresponding VX-121 dose groups.

The 2 Treatment Groups in Cohort A3 will correspond to suspension [fed] and suspension [fed and with milk] respectively.

The 3 Treatment Groups in Cohort A9 will correspond to suspension [fed], tablet [fed] and tablet [fed and with milk] respectively.

Baseline value

The baseline value will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug. If a pre-dose measurement is missing and no drug-free unscheduled assessments are performed before the first dose of the study, the baseline will be missing. For ECG, the baseline value will be defined as the most recent non-missing measurement (or the average of triplicate measurements, if the most recent non-missing measurements are obtained in triplicate), before the first dose of study drug of the Treatment Period.

Absolute change from baseline will be calculated as post-baseline value – baseline value.

Relative change from baseline will be calculated as (post-baseline value – baseline value)/baseline value.

Visit Window: For Parts A, B and C, the majority of assessments are predicted to be on schedule. Visit windows will not add significant value to the analysis and will not be applied. For Part D, the analysis visit windows for protocol-defined visits are provided in Appendix A.

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

1) In scheduled visit windows per specified visit windowing rules
2) In the derivation of baseline and last on-treatment measurements
3) In the derivation of maximum and minimum values during TE period, and maximum and minimum change from baseline values during TE period for safety analyses
4) In individual subject data listings as appropriate.

Incomplete/missing data (e.g., dates, post-baseline values) will not be imputed, unless otherwise specified; i.e., all missing values and missing post-baseline values will remain as missing in all statistical analyses and listings, unless otherwise specified.

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

All subject level data, including those derived, will be presented in the individual subject data listings; listings will be based on the All Subjects Set.

Unless otherwise specified, the analyses will be presented by treatment group/treatment sequence. Separate summary tables will be produced for each part. The number of cohorts and the dose levels of each cohort are subject to change to reflect the actual cohorts enrolled and dose levels.

The treatment group and treatment sequence for all cohorts in each part will be labeled as follows.

- Part A (Cohorts A1, A2 and A4 through A6, or A7, A8 when applicable): Placebo, VX-121 10 mg, VX-121 20 mg, VX-121 40 mg, VX-121 60 mg, VX-121 90 mg and VX-121 Total.

- Part A (Cohort A3): Placebo and VX-121 5 mg within the sequence of Placebo -> VX-121 (fed with milk) ; VX-121 5 mg and VX-121 5 mg [fed with milk] within the sequence of VX-121 5 mg -> VX-121 5 mg (fed with milk) , and VX-121 Total.

- Part A (Cohort A9): VX-121 10 mg suspension [fed], VX-121 10 mg tablet [fed], and VX-121 10 mg tablet [fed with milk]

- Part B: Placebo, VX-121 10 mg qd, VX-121 20 mg qd, VX-121 40 mg qd, VX-121 60 mg qd, and VX-121 Total

- Part C: Triple Placebo, VX-121 10 mg qd + TEZ 100 mg qd/IVA 150 mg q12h, and VX-121 20 mg qd+ TEZ 100 mg qd/IVA 150 mg q12h, and VX-121 Total when there are more than one TC doses.

- Part D: Triple Placebo, and VX-121 TBD mg + TEZ 100 mg qd/IVA 150 mg q12h.

9.2 Background Characteristics

9.2.1 Subject Disposition

Disposition summary will be based on the All Subjects Set.

The number and percentage of subjects in the following disposition categories will be summarized by treatment group/treatment sequence and overall for each part:

- Randomized
- Safety Set
- Full Analysis Set

The number and percentage (based on Safety Set) of subjects in each of the following disposition categories will be summarized by treatment group/treatment sequence and overall, when applicable:

- Completed study drug treatment
- Prematurely discontinued treatment and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation

9.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics summary will be based on the Safety Set.

Demographics and baseline characteristics (age, sex, race, ethnicity, weight, height, body mass index (BMI) and etc.) will be summarized overall and by treatment group for Parts A (Cohorts A1, A2 and A4 through A6, or A7, A8 when applicable), B, C, and D and by treatment sequence for Cohorts A3 and A9.

No statistical tests will be done to evaluate baseline imbalances between groups.

9.2.3 Medical History

Medical history will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA). For the Safety Set, medical history will be summarized descriptively by system

organ class and preferred term and by treatment group/treatment sequence and overall for each part. 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 (WHO-DD) September 2017, Format B2 or higher. Medications used in the study will be categorized as prior and/or concomitant medications as follows:

1. **Prior medication**: Medication that started before the first dose of study drug, regardless of when dosing of the medication ended
2. **Concomitant medication**: Medication received at or after the first dose of study drug, medication that was received before initial dosing and continued after initial dosing of study drug, or medication with missing stop date

If a medication start date is on or after the date of initial dosing of the study drug, then the medication will be summarized as concomitant medication regardless of whether the medication end date is missing or not. If a medication end date is before the date of initial dosing of the study drug, then the medication will be summarized as prior medication regardless of whether the medication start date is missing or not. Note that medication that started before initial dosing of the study drug and continued after initial dosing will be summarized as prior medication and separately as concomitant medication.

Missing or partial dates will be imputed for medication. Algorithm for missing or partial start date is:

Missing day: first day of the month is imputed;
Missing month: January is imputed;
Missing year: not imputed.

Algorithm for missing or partial end date is:

Missing day: last day of the month is imputed;
Missing month: December is imputed (31 December if day is also missing);
Missing year: not imputed.

Missing data algorithms will be reviewed to ensure the algorithms work. For example, end date will not be before the start date after the imputation.

For Cohorts A3 and A9, concomitant medications will be assigned to each TE period based on the start date of the medication and the study drug administration dates (concomitant medications taken during the TE period will be assigned to the TE period, and so forth).

Note that a concomitant medication may be assigned to multiple TE periods.

Prior medications will not be summarized, but will only be listed based on All Subjects Set. Concomitant medications will be summarized using preferred name by treatment group/treatment sequence and overall for each part. Concomitant Medications summary will be based on the Safety Set.

Prior and concomitant non-drug therapy will also be listed based on All Subjects Set.

9.2.5 Study Drug Exposure and Compliance

Study drug exposure in Parts B, C and D (i.e., duration of treatment) will be summarized by treatment group and overall for the Safety Set.

Study drug exposure (in days) will be defined as (last date of dosing – first date of dosing) + 1.

The study drug administration will be presented in an individual subject listing.

Compliance analysis will be provided for Part D only based on the FAS, and will be presented by treatment group and overall. Study drug compliance will be calculated as: 100 × [1 - (total number of days of study drug interruption) / (duration of study drug exposure in days)]. A study drug interruption on a given day is defined as an interruption of any study drugs on that day. Study drug compliance will be summarized descriptively by the number of subjects (n), mean, SD, median, min, and max. It will also be summarized in categories: <80% and ≥80% using frequency tables.

In addition, percentage of tablets taken will be calculated using the following formula: 100 x [(total number of tablets dispensed for the Treatment Period) – (total number of tablets returned] / (total number of tablets planned to be taken per day x duration of study drug exposure in days). Summary similar to the study drug compliance will be produced based on the FAS for Part D only.

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 PD plan.

IPDs will be provided in an individual subject data listing.

9.3 Efficacy Analysis

9.3.1 Spirometry (Part D Only)

The spirometry parameters: FEV_1 (L), forced vital capacity (FVC) (L), FEV_1/FVC (ratio), and forced expiratory flow, midexpiratory phase ($FEF_{25\%-75\%}$) (L/s) and their corresponding percent predicted values (percentage point) and change from baseline will be summarized by treatment group using descriptive statistics for the FAS. Percent predicted FEV_1 is the ratio of FEV_1 (L) and predicted FEV_1 (L), expressed as a percentage. See Appendix B for more details.

In addition, a mixed-effects model for repeated measures (MMRM) with change from baseline at Day 15 and Week 4 predose for percent predicted forced expiratory volume in 1 second ($ppFEV_1$) as the dependent variable will be performed for the FAS. The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the *F* test for fixed effects will be estimated using the Kenward-Roger approximation. A compound symmetry covariance structure will be used to model the within-subject errors. Conditional on the fixed effects, missing data due to treatment or study discontinuation will be assumed to be missing at random.

The adjusted means and 2-sided 95% CIs of the treatment effect through Day 29 (averaged over Day 15 and 29), with corresponding *P* values for all within-group comparisons, will be estimated using MMRM.

In addition, the adjusted mean and 95% CI of the within-treatment difference at each post-baseline visit through Day 29 for each treatment group will be provided along with the *p*-value.

9.4 Safety Analysis

Safety is the primary objective of this study. The overall safety profile of VX-121 will be assessed in terms of the following primary (safety) endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values as specified in the CSP.
- ECG outcomes
- Vital signs (including pulse oximetry [Part D only])
- Spirometry (Part D only)

All safety analyses will be performed by treatment group/treatment sequence for each part as applicable based on the Safety Set. All safety data will be presented in the individual subject data

listings based on the All Subjects Set. No statistical hypothesis testing will be performed for safety analysis.

Table 9-1 shows the safety summaries (e.g., raw value, change from baseline, incidence, and clinical abnormalities and etc) that will be summarized for TEAEs, clinical lab values, 12-lead ECGs, vital signs, spirometry and physical examination. Details are provided in the corresponding subsections.

The incidence of TEAEs will be summarized. TEAE summaries will include the following: all TEAEs (regardless of severity or relationship to study drug), serious adverse events (SAEs), TEAE severity, TEAE relationship, and discontinuations of study drug treatment due to TEAEs.

For the non-AE safety evaluations (clinical laboratory, ECGs and vital signs), raw values, and changes from baseline will be summarized as indicated in **Table 9-1**. For example, an "X" under the raw value column (third column) means that the "Raw value" for the safety evaluation will be summarized in tables; an "X" under the "Change from Baseline" column (fourth column) means that change will be summarized in tables.

Throughout this section, "change" refers to absolute change from baseline.

Table 9-1 Summaries Planned for Safety Data

Safety Assessment	Incidence	Raw Value	Change from Baseline	Clinical Abnormalities	Threshold Analysis
TEAEs	X			NA	
Hematology/and chemistry		X	X	Listing only	X (Part D only)
Coagulation		X (Part D only)	X (Part D only)		
Urinalysis		Listing only			
12-lead ECG		X	X		X (Part D only)
Vital signs		X	X		X (Part D only)
Spirometry (Part D)		X	X	NA	
Physical Examination		Listing only		NA	

ECG: electrocardiogram; TEAEs: treatment-emergent adverse events; NA: Not applicable; X: safety assessment will be summarized in tables

9.4.1 Adverse Events

AEs will be coded according to MedDRA (Version 20.1 or above). The number and percentage of subjects experiencing an AE will be summarized by the MedDRA System Organ Class (SOC) and Preferred Term (PT). AEs will be classified as pretreatment or treatment-emergent.

Pretreatment AEs are defined as AEs that were reported or worsened (either in severity or seriousness) after signing the ICF up to the start of study drug dosing.

Treatment-emergent adverse events (TEAEs) for all cohorts except Cohorts A3 and A9 are defined as any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug during the Treatment Period through the end of the TE Period for the Treatment Period.

For Cohort A3 and A9, TEAEs will be assigned to each treatment group based on the start date of the AE and the start of study drug administration dates within the corresponding TE Period.

For AEs with completely missing or partially missing start dates, if there is no clear evidence that the AEs started before or after study treatment, the AEs will be classified as TEAEs corresponding to the Treatment Period. Unless otherwise specified, TEAE refers to TEAE during the Treatment Period.

Details for imputing missing or partial start dates of adverse events are described in Appendix C, which is applicable to Part D only.

AE summary tables will be presented for TEAEs only and will include the following: (1) Overview of TEAEs (2) all TEAE; (3) related (defined as possibly related, related, or missing) TEAEs; (4) serious TEAEs; (5) TEAEs by severity; (6) TEAEs by relationship; and (7) TEAEs leading to treatment discontinuation.

Summaries will be presented using frequency counts and percentages by treatment group/treatment sequence for each part (i.e., number and percentage of subjects with an event); for the summary table of TEAE Overview, an additional column of overall will be provided. When summarizing the number and percentages of subjects, subjects with multiple occurrences of the same adverse event 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.

In addition, a listing containing individual subject AEs leading to death, SAEs, dose interruption, and discontinuation will be listed separately. All AEs through the Safety Follow-up Visit will be listed in an individual subject data listing, including pretreatment AEs.

9.4.2 Clinical Laboratory Assessments

All statistical analyses of laboratory values will be performed using SI units. Continuous hematology, clinical chemistry and coagulation (Part D only) results including baseline and change from baseline values will be summarized at each scheduled time point by treatment group/treatment sequence for each part using descriptive statistics.

For Part D, the number and percentage of subjects meeting at least 1 threshold analysis criterion event, during the TE period for Treatment Period, will be summarized by treatment group. The threshold analysis criteria are provided in Appendix D.

Clinically significant abnormal laboratory findings will be reported as AEs.

9.4.3 Electrocardiogram

A summary of raw values and change from baseline values will be provided for each scheduled time point by treatment group/treatment sequence for each part during the TE Period for the following 12-lead ECG measurements using descriptive statistics: RR interval, PR interval, QT interval, QTcF interval, QRS duration, and Heart Rate (beats per minute).

For Part D, the number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE period for the Treatment Period will be summarized by treatment group. The threshold analysis criteria are provided in Appendix D.

In addition, the number and percentage of subjects by maximum value of QT/QTc intervals during the TE period, categorized as ≤450 msec, >450 msec and ≤480 msec, >480 msec and ≤500 msec, and >500 msec, as well as maximum change from baseline value of QT/QTc intervals during the TE period, categorized as ≤0 msec, >0 msec and ≤30 msec, >30 msec and ≤60 msec, and >60 msec will be tabulated based on scheduled and unscheduled 12-lead ECG measurements by treatment group/treatment sequence for each part.

Clinically significant abnormal findings will be reported as AEs.

9.4.4 Vital Signs

A summary of raw values and change from baseline values will be provided for each scheduled time point by treatment group/treatment sequence for each part using descriptive statistics for the following vital signs measurements: BMI (kg/m^2), weight (kg), height (cm), systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), and respiratory rate (breaths per minute).

For Part D, the number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE period for the Treatment Period will be summarized by treatment group. The threshold analysis criteria are provided in Appendix D.

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

Clinically significant abnormal findings in vital signs will be reported as AEs.

9.4.5 Pulse Oximetry (Part D)

For the treatment-emergent pulse oximetry measurements, a summary of observed values and change from baseline values will be provided at each visit by treatment group, for the percent of oxygen saturation.

9.4.6 Physical Examination

Physical examination (PE) results will be presented in individual subject data listings only. Clinically relevant changes identified after screening will be reported as AEs.

9.6 Pharmacodynamic Analysis (Part D Only)

The sweat chloride value for a given visit will be calculated as the mean of the non-missing sweat chloride measurements obtained on the left and right arms at that visit. If one of the two arm measurements at a time point is missing, the other will be used as the mean. A volume ≥15 µL is required for an accurate determination of sweat chloride. Any results reported as having volume <15 µL will be considered missing. Any sweat chloride values reported as <10 mmol/L or >160 mmol/L will be considered missing.

The analysis of sweat chloride data will be based on the FAS. A summary of raw values and change from baseline values will be provided at each scheduled visit by treatment group and overall using descriptive statistics.

The same MMRM model as for $ppFEV_1$ will be used to analyze the change from baseline for sweat chloride. Adjusted means and 2-sided 95% CIs of the treatment effect through Day 29 (averaged over Day 15 and 29), with 2-sided *P* values for all within-group comparisons, will be estimated using MMRM.

In addition, a listing containing individual subject data at scheduled and unscheduled visits will be provided.

10 INTERIM AND IDMC ANALYSES

10.1 Interim Analysis

An IA of the continuous ECG data may be performed after all subjects in Part B have completed the Safety Follow-up Visit. These results will be reviewed by a small unblinded Vertex team.

10.2 IDMC Analysis

Not applicable

11 REFERENCES

Not applicable.

12 APPENDICES

Appendix A: Analysis Visit Windows (Part D Only)

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

Assessment	Visit[1]	Target Study Day	Analysis Visit Window[2,3,4] (in study days)
Safety Assessment			
Serum Chemistry Hematology Coagulation Vital Signs (including Weight and BMI)	Baseline Day 8 Day 15 Day 29 Safety Follow-up	1 8 15 29 Not applicable	≤1 Pre-dose (1[5], 12] (12, 22] (22, 43] Use nominal visit
Standard 12-lead ECG	Baseline Day 1 Postdose Day 8 Day 15 Predose and Postdose Day 29 Safety Follow-up	1 Not applicable 8 Not applicable 29 Not applicable	≤1 Pre-dose Use nominal visit (1, 12] Use nominal visit (22, 43] Use nominal visit
Efficacy Assessment and Pharmacodynamic Assessment			
Spirometry Sweat Chloride	Baseline Day 8 Day 15 Day 29 Safety Follow-up	1 8 15 29 Not applicable	≤1 Pre-dose (1, 12] (12, 22] (22, 43] >43

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

Assessment	Visit[1]	Target Study Day	Analysis Visit Window[2,3,4] (in study days)

Notes:
Visit name for analysis purpose is 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 a visit window, use the following rules:
   i. The measurement closest to the target day will be used; or
   ii. If there are multiple measurements with the same distance from the target day, the latest measurement will be used.

3 For lab, ECG and vital sign measurement collected on the date of first dose of study drug in Treatment Period, if it cannot be determined whether the measurement is before or after the first dose:
a. Scheduled measurement will be treated as pre-dose observation.
b. Unscheduled measurement will be treated as post-dose observation.

4 For safety assessment, Safety Follow-up analysis visit will be based on nominal Safety Follow-up visit. If a subject doesn't have a nominal Safety Follow-up visit but has an ETT visit with study day >43, then the ETT visit will be mapped into Safety Follow-up analysis visit.

Derived Variables:

1. Age (in years) at first dose date and nominal visit (for demographics, listing and the calculation of [percent] predicted spirometry variables):

   Obtain the age at informed consent (in days) in "yy, mm" format (e.g., 24 years, 6 months) from the Vital Signs (VS) page at the Screening Visit, and add 0.5 month to convert to days.

   Obtain the informed consent date.

   Then age (in years) at first dose or nominal visit = [(first dose date or nominal visit date – informed consent date) in days + age at informed consent (in days)]/365.25.

2. Missing first dose date or last dose date

   If the first dose date is missing, use Day 1 visit date to impute.

   If the last dose date is missing or partial date is reported, the last dose date will be imputed based on, in descending order priority, the Early Treatment Termination (ETT) visit date, last visit date before the Safety Follow-up or the last study drug administration date from EX SDTM domain, as appropriate.

3. Sweat Chloride:

   Non-missing sweat chloride concentrations from the left arm and right arm with assessment end date/time for a given arm up to 30 minutes after first dose time in treatment period will be considered for baseline.

4. Electrocardiogram:

   Baseline is defined as the most recent pretreatment measurement before the first dose of study drug in the Treatment Period (or the average of triplicate measurements, if the most recent non-missing measurement is obtained in triplicate). If multiple ECG measurements are obtained on the same calendar day during the TE period,

   - For summary purpose, the calculated average ECG will be used as the ECG value on that day (except for Day 1 and Day 15 for ECG in Part D);
   - For threshold analysis purpose, all reported ECG values will be used.

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

Assessment	Visit[1]	Target Study Day	Analysis Visit Window[2,3,4] (in study days)
5. Day 1 post dose could be included in the Analysis Visit Window.			

Appendix B: Details of GLI Equations for Calculating ppFEV$_1$

Percent predicted values will be calculated for parameters of FEV_1, FVC, FEV_1/FVC, and $FEF_{25\%-75\%}$ using the Quanjer GLI-2012 Regression Equations and Lookup Tables.

The regression equations and lookup tables required to implement the Quanjer GLI-2012 predicted values are available in:

Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Quanjer GLI-2012 Regression Equation and Lookup Tables (Version 7 April 2013). Global Lung Function Initiative. [online] Available at: http://www.ers-education.org/home/browse-all-content.aspx?idParent=138978 [Accessed Mar 26, 2018].

The instructions and tools on how to implement the Quanjer GLI-2012 equations are:

Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Implementing GLI-2012 regression equations (Version 19 July 2015). Global Lung Function Initiative. [online] Available at: http://www.ers-education.org/home/browse-all-content.aspx?idParent=138979 [Accessed Mar 26, 2018].

Sanja Stanojevic. GLI-2012 - SAS Macro (Version 2, 7 April 2013). Global Lung Function Initiative. [online] Available at: http://www.ers-education.org/home/browse-all-content.aspx?idParent=138988 [Accessed Mar 26, 2018].

Data handling rule for spirometry is as follows:

- Input age with at least 2 decimal place
- Use age at each corresponding visit and height at screening.
- For race, map CRF black or AA to black, all other races in CRF (except white) are mapped to 'other'; multiple checks for race in CRF are also mapped to 'other'; white is a reference race in the equations and assumes 0 values for all race coefficients in the GLI equations.

Appendix C: Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start date are defined below. If the imputed AE start date is before the study informed consent date, the AE start date will be imputed using the study informed consent date.

- **If only Day of AE start date is missing:**
    - If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then
        - if AE start year and month are equal to the month and year of first dose date of the Treatment Period, then impute the AE start day as the day of first dose date of the Treatment Period;
        - else impute the AE start day as 1.
    - else impute the AE start day as 1.

  Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

- **If Day and Month of AE start date are missing:**
    - If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then
        - if AE start year is equal to the year of first dose date of the Treatment Period, then impute the AE start month and day as the month and day of first dose date of the Treatment Period;
        - else impute the AE start month as January and day as 1.
    - else impute the AE start month as January and day as 1.

  Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

- **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 site and
    - If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then impute the AE start date as the first dose date of the Treatment Period;
    - else impute the AE start date as the informed consent date.

Imputation rules for partial AE end date are defined below:

- Impute the AE end date as min (the last day of the month, end of study participation) if day is missing, or min (Dec, end of study participation) if month is missing.

Appendix D: Criteria for Threshold Analysis

Table 12-2 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Clinical Chemistry (LFT)		
ALT	>ULN - ≤3xULN >3x - ≤ 5xULN >5x - ≤ 8xULN >8x - ≤ 20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
AST	>ULN - ≤3xULN >3x - ≤ 5xULN >5x - ≤ 8xULN >8x - ≤ 20.0xULN >20.0xULN	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> 20 xULN	FDA DILI Guidance
Alkaline Phosphatase	>ULN - ≤ 1.5xULN >1.5 – ≤ 2.5 xULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	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 12-2 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
GGT	>ULN - ≤ 2.5xULN >2.5 – ≤ 5.0xULN >5.0 – ≤ 20.0xULN >20.0xULN	CTCAE grade 1-4
Clinical Chemistry (NON-LFT)		
Albumin	<LLN - ≥ 30 g/L <30 – ≥ 20 g/L <20 g/L	CTCAE grade 1-3
Amylase	>1x - ≤ 1.5xULN >1.5x - ≤ 2xULN >2x - ≤ 5xULN >5xULN	Criteria based upon CTCAE
Creatinine	>ULN - ≤ 1.5xULN >1.5 - ≤ 3.0xULN >3.0 - ≤ 6.0xULN >6.0xULN	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 - ≤ 2.5 x ULN >2.5 - ≤ 5 x ULN >5 - ≤ 10x ULN >10 x ULN	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 - ≥ 75.0 x 10e9 /L <75.0 – ≥ 50.0 x 10e9 /L <50.0 – ≥ 25.0 x 10e9 /L <25.0 x 10e9 /L	CTCAE grade 1-4
	Platelet increased >ULN	No CTCAE available

Table 12-2 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Reticulocytes/Erythrocytes (%)	<LLN >ULN	No CTCAE
Coagulation		
Activated partial thromboplastin time (PTT)	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.5 x ULN >2.5 x ULN	CTCAE grade 1-3
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.5 x ULN >2.5 x ULN	CTCAE grade 1-3

Table 12-3 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	

Table 12-3 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
QTc		To be applied to any kind of QT correction formula.
Borderline	>450 ms (Male) and <500ms; >470 ms and	
Prolonged*	<500ms (Female)	
Additional	≥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	

Note: Based on CPMP 1997 guideline.

Table 12-4 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
Pulse Rate	Same as above in ECG category	
SBP increased		809/770 analyses
	>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	

Table 12-4 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
SBP decrease		Per HV grade 1, 3, plus shift change
	<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	
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	

Table 12-4 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
Weight	Weight gain ≥5 % increase from baseline ≥10 % increase from baseline ≥ 20% increase from baseline	CTCAE grade 1-3
	Weight loss ≥5 % decrease from baseline ≥10 % decrease from baseline ≥ 20% decrease from baseline	CTCAE grade 1-3