VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX15-440-101 Version 2.0 (Final Analysis)

A Phase 2, Randomized, Double blind, Controlled Study to Evaluate the Safety and Efficacy of VX 440 Combination Therapy in Subjects Aged 12 Years and Older With Cystic Fibrosis

Authors of SAP: [redacted]

Version: Version 1.0
Version Date of SAP: 12 June 2017

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, Massachusetts 02210-1862

1 TABLE OF CONTENTS

3 INTRODUCTION

This statistical analysis plan (SAP) for the final analysis is based on the approved clinical study protocol (CSP), Version 2.0, dated 16 SEP 2016, approved electronic case report form (eCRF), Version 1.0, dated 13 Jul 2016, and approved eCRF completion guidelines, Version 1.0, dated 18 Oct 2016. This SAP will also be used to perform two separate interim analyses (IAs), after all subjects participating in Part 1 have completed the safety follow-up, and correspondingly, after all subjects participating in Part 2 have completed the safety follow-up.

This is a Phase 2, randomized, double-blind, placebo- and TEZ/IVA-controlled, parallel group, multicenter study to evaluate the safety and efficacy of VX-440 combination therapy in subjects aged 12 years and older with cystic fibrosis.

This SAP (Methods) documents the planned statistical analyses of efficacy endpoints and safety endpoints.

Vertex Biometrics will perform the statistical analysis for each IA, and the final analysis. SAS® Version 9.2 or higher software (SAS Institute, Cary, North Carolina, USA) will be used to generate all statistical outputs (tables, figures, listings, and datasets).

The SAP (Methods) will be finalized and approved prior to the data cut for the first IA. 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. Any changes made to the SAP Methods after the clinical database lock has occurred will be documented in the clinical study report for this study.

4 STUDY OBJECTIVES

4.1 Primary Objective

- To evaluate the safety and tolerability of VX-440 in [redacted] triple combination with TEZ and IVA
- To evaluate the efficacy of VX-440 in [redacted] triple combination with TEZ and IVA

4.2 Secondary Objectives

- To evaluate the pharmacodynamic (PD) effect of VX-440 in [redacted] triple combination with TEZ and IVA on sweat chloride concentrations
- To evaluate the PK of VX-440 when administered in [redacted] triple combination with TEZ and IVA
- To evaluate the PK of TEZ, IVA, and their respective metabolites when administered with VX-440

5 STUDY ENDPOINTS

5.1 Efficacy Endpoint

5.1.1 Primary Efficacy Endpoint

- Absolute change in percent predicted forced expiratory volume in 1 second[1] ($ppFEV_1$) from baseline through Day 29 (Parts 1 and 2) [redacted]

5.1.2 Secondary Efficacy Endpoints

- Absolute change in sweat chloride concentrations from baseline through Day 29 (Parts 1 and 2) [redacted]
- Relative change in $ppFEV_1$ from baseline through Day 29 (Parts 1 and 2) [redacted]

[redacted]

- Absolute change in Cystic Fibrosis Questionnaire-Revised[2, 3, 4] (CFQ-R) respiratory domain score from baseline at Day 29 (Parts 1 and 2) [redacted]
- PK parameters of VX-440, TEZ, M1-TEZ, IVA, and M1-IVA

[redacted]

5.2 Safety Endpoints

The safety and tolerability is evaluated via the following endpoints:

- adverse events (AEs)
- clinical laboratory values
- standard 12-lead electrocardiograms (ECGs)
- vital signs
- pulse oximetry

6 STUDY DESIGN

6.1 Overall Design

This is a Phase 2, randomized, double-blind, placebo- and TEZ/IVA-controlled, parallel-group, multicenter study designed to evaluate the safety and efficacy of VX-440 in [redacted] triple combination with TEZ and IVA.

Approximately 198 subjects with CF will be enrolled across Parts 1 [redacted] Enrollment of Parts 1 [redacted] will be sequential, while enrollment of Part 2 will be in parallel with Part 1 Cohort 1B. [redacted]

Part 1 will consist of 2 cohorts: Cohort 1A and Cohort 1B. The start of dosing of Cohort 1A and Cohort 1B will be sequential. After all Cohort 1A subjects complete the Day 15 Visit, a blinded review of all available safety and PK data will be conducted by the Vertex study team and lead investigator(s). Dosing of Cohort 1B will begin after the blinded review, if supported by safety and PK data.

Part 2 will initiate after the Cohort 1A blinded review, if supported by safety and PK data. [redacted]

Key study elements of each part are summarized in Table 6-1. The treatment arms and randomization ratios for each part are summarized in Table 6-2. A schematic of the study design is shown in (Parts 1 and 2) [redacted]

Table 6-1 Key Study Elements by Part

	Part 1[a]	**Part 2**	[redacted]
Genotype	*F508del*/MF	*F508del*/*F508del*	
Age	≥18 years	≥18 years	
$ppFEV_1$ criteria	≥40 to ≤90	≥40 to ≤90	
Number of subjects	Approximately 42[a]	Approximately 24	
Stratification[c]	$ppFEV_1$[d] • ≥70 • <70	$ppFEV_1$ • ≥70 • <70	
Study design	Parallel	Parallel	
Comparator	Placebo	TEZ/IVA	
VX-440 treatment duration	4 weeks	4 weeks	

IVA: ivacaftor; MF: minimal function; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours; TC: triple combination; TEZ: tezacaftor

[a] Part 1 consists of Cohort 1A and Cohort 1B. Approximately 10 subjects will be in Cohort 1A and approximately 32 subjects will be in Cohort 1B.

[redacted]

[c] Additional stratification information is provided in Section 8.1.3 of protocol.

[d] Stratification will be conducted for Cohort 1B subjects only.

Table 6-2 Treatment Arms and Planned Doses by Part

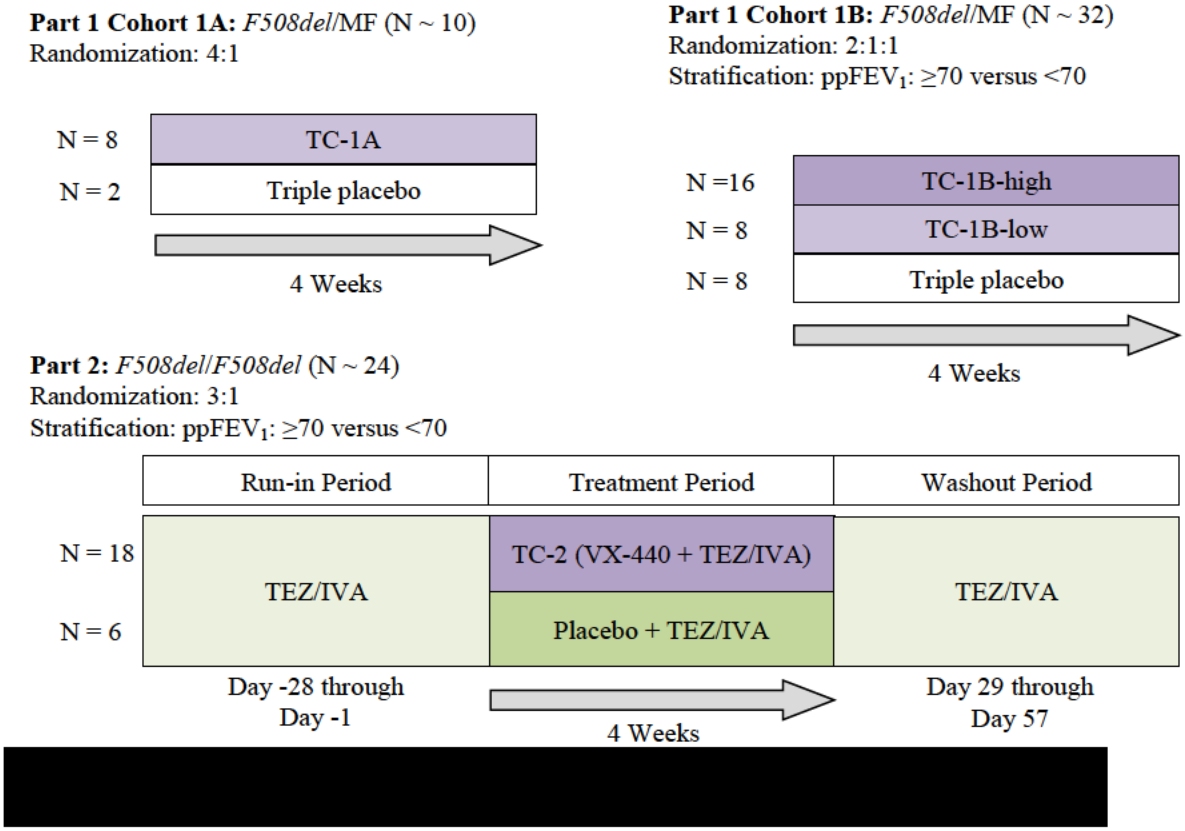
Part Randomization ratio	**Treatment Arm**	**VX-440 Dosage**	**TEZ Dosage**	**IVA Dosage**
Part 1 Cohort 1A	TC-1A	200 mg q12h	100 mg qd	150 mg q12h
4:1	Triple placebo	Placebo	Placebo	Placebo
Part 1 Cohort 1B	TC-1B-high	600 mg q12h[a]	50 mg q12h	300 mg q12h[a]
2:1:1	TC-1B-low	200 mg q12h	50 mg q12h	150 mg q12h
	Triple placebo	Placebo	Placebo	Placebo
Part 2[b]	TC-2	600 mg q12h[a]	50 mg q12h	300 mg q12h[a]
3:1	TEZ/IVA	Placebo	100 mg qd	150 mg q12h
[redacted]				

[a] In the "TC-1B-high" and "TC-2" treatment arms, the dosage of VX-440 will be determined based on safety and PK data from Cohort 1A. The planned dose is shown, but may be reduced to 400 mg q12h.

[b] In Part 2, all subjects will also receive TEZ 100 mg qd/IVA 150 mg q12h during the Run-in Period and the Washout Period.

[redacted]

Figure 6-1 Schematic of the Study Design for Parts 1 and 2



IVA: ivacaftor; MF: minimal function; N: number of subjects; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours; qd: daily; TEZ: tezacaftor; TC: triple combination

Notes: Schematic is not drawn to scale. TC includes VX-440, TEZ, and IVA. The dose of each component of the TC is shown by treatment arm in Table 6-2. In Part 2, the dose of TEZ/IVA during the Run-in Period and the Washout Period will be TEZ 100 mg qd/IVA 150 mg q12h. Additional stratification information is provided in Section 8.1.3 of protocol.

[redacted]

6.2 Sample Size and Power

6.2.1 Primary Objectives

The primary objectives of the study are the evaluation of safety, tolerability, and efficacy of VX-440 [redacted], and of VX-440 in TC with TEZ/IVA (all parts). The sample size calculations described below are deemed adequate to evaluate the objectives of the study, based on clinical and statistical considerations.

6.2.1.1 Safety and Tolerability

The primary safety endpoint is the incidence of AEs. Approximately 198 subjects will be enrolled in the study, with approximately 160 subjects receiving active VX-440 in [redacted] triple combination with IVA and/or TEZ. The sample size for each treatment group will provide sufficient data for a descriptive analysis of AEs. Table 6-3 provides the probability of observing an AE in at least 1 subject based on sample sizes ranging from 10 to 50 subjects per treatment group and AE incidences ranging from 5% to 15%. The probability calculations are based on a binomial model using the probability calculator in the PASS software package (Version 11.0).

Table 6-3 Probability of Observing an Adverse Event

	Number of Subjects per Treatment Group[b]				
AE Incidences[a]	**10**	**20**	**30**	**40**	**50**
5%	40%	64%	79%	87%	92%
10%	65%	88%	96%	98%	>99%
15%	80%	96%	>99%	>99%	>99%

AE: adverse event
[a] AE incidences are based on 4 weeks of treatment in Parts 1 and 2, [redacted]
[b] Applies to Parts 1 [redacted]

6.2.1.2 Efficacy

The primary efficacy endpoint is the absolute change from baseline in $ppFEV_1$ through Day 29 in Parts 1 and 2, [redacted] Table 6-4 provides the power to reject the null within-group hypothesis of no difference in the mean absolute change from baseline for $ppFEV_1$ through Day 29 or Week 12, as applicable, for any treatment group in Parts 1, 2, [redacted] with a sample size ranging from 8 to 44 subjects per treatment group. The power calculations are based on a 2-sided 1-sample *t*-test at alpha = 5% using the PASS software package (Version 11.0), assuming an absolute mean change of 3 to 7 percentage points and an SD of 8 percentage points in the absolute change from baseline for $ppFEV_1$. Sample sizes of 16 to 44 subjects per treatment group provide adequate power for mean changes of 5 to 7 percentage points as expected in Parts 1, 2, [redacted].

Table 6-4 Power for Within-group Difference for Mean Absolute Change From Baseline in $ppFEV_1$

Mean Absolute Change From Baseline in $ppFEV_1$	Number of Subjects per Treatment Group[a]							
	8	**16**	**20**	**22**	**24**	**40**	**42**	**44**
3%	15%	29%	36%	39%	42%	64%	66%	68%
4%	23%	46%	56%	61%	65%	87%	89%	90%
5%	33%	65%	76%	80%	83%	97%	98%	98%
6%	45%	80%	89%	92%	94%	>99%	>99%	>99%
7%	57%	90%	96%	97%	98%	>99%	>99%	>99%

$ppFEV_1$: forced expiratory volume in 1 second; SD: standard deviation
Note: An SD of 8 percentage points for the absolute change from baseline in $ppFEV_1$ was used for power calculations.
[a] Applies to Parts 1 [redacted]

6.2.2 Secondary Objectives

A secondary objective of the study is the evaluation of the PD effect of VX-440 in TC with TEZ/IVA (all parts) [redacted]

6.2.2.1 Pharmacodynamic Effect (Part 1)

The absolute change from baseline through Day 29 in sweat chloride is a secondary endpoint used to evaluate the PD objective of the study. In Part 1, a test for a decreasing dose-response trend between placebo and the TC dose groups will be performed using a multiple

comparisons procedure (MCP). The procedure consists of testing the null hypothesis of the lack of a decreasing dose-response trend versus a decreasing trend using the 1-sided maximum *t*-statistic that controls the type I error at alpha = 5%. The procedure requires a family of candidate dose-response models to be prespecified, the range of plausible and diverse dose-response profiles.

The candidate models that best describe the expected decreasing dose-response profile of the TC groups compared to placebo include a linear model, a maximum effect (E_{max}) model, and a sigmoid E_{max} model. The contrasts (i.e., linear combinations of the treatment group means through Day 29) selected to perform the MCP that captures the shape of these candidate models are described in Table 6-5 below.

Table 6-5 Contrast Coefficients for the Multiple Comparisons Procedure in Part 1, Cohort 1B

Candidate Model	Placebo	TC-1B-low	TC-1B-high
Linear	1.0	0.0	-1.0
E_{max}	1.0	-0.5	-0.5
Sigmoid E_{max}	0.5	0.5	-1.0

E_{max}: maximum effect; TC: triple combination

Table 6-6 provides the power to detect a dose-response trend with the MCP procedure for 3 different expected dose-response profiles with a total sample size of 32 subjects in Cohort 1B assigned to TC-1B-high, TC-1B-low, and placebo in the ratio 2:1:1, based on 5000 simulations for each profile using the MCPMod R software package [Version 1.0-8].

Table 6-6 Power to Detect a Dose-response Trend Based on Change From Baseline in Sweat Chloride in Part 1, Cohort 1B

	Mean Change From Baseline in Sweat Chloride			
Candidate Model	Placebo	TC-1B-low	TC-1B-high	Power
Linear	0	-15	-20	95%
Sigmoid E_{max}	0	0	-20	99%
E_{max}	0	-20	-20	96%

E_{max}: maximum effect; TC: triple combination
Note: A 1-sided maximum *t*-statistic with a sample size of 32 subjects in Cohort 1B assigned to TC-1B-high, TC-1B-low, and placebo at a ratio 2:1:1 was used for power calculations. An SD change from baseline in sweat chloride of 13 mmol/L was used for power calculations.

Table 6-7 provides the power to reject the null within-group hypothesis of no difference in the mean absolute change from baseline for sweat chloride through Day 29 (Parts 1 and 2) [redacted] for any treatment group with a sample size ranging from 8 to 44 subjects per treatment group. The power calculations are based on a 2-sided 1-sample *t*-test at alpha = 5% using the PASS software package (Version 11.0), assuming a mean change of -10 to -20 mol/L and an SD of 13 mmol/L in the absolute change from baseline for sweat chloride.

Table 6-7 Power for Within-group Difference for Mean Absolute Change From Baseline in Sweat Chloride

Mean Absolute Change From Baseline in Sweat Chloride (mmol/L)	Number of Subjects per Treatment Group[a]							
	8	16	20	22	24	40	42	44
-10	47%	82%	90%	93%	95%	>99%	>99%	>99%
-12	61%	93%	97%	98%	99%	>99%	>99%	>99%
-15	80%	99%	>99%	>99%	>99%	>99%	>99%	>99%
-18	92%	>99%	>99%	>99%	>99%	>99%	>99%	>99%
-20	96%	>99%	>99%	>99%	>99%	>99%	>99%	>99%

SD: standard deviation
Note: An SD of 13 mmol/L for the absolute change from baseline in sweat chloride was used for power calculations.
[a] Applies to Parts 1 [redacted]

6.3 Randomization

Treatment arms, randomization ratios, and stratification factors for each part are described in Table 6-1. An interactive web response system (IWRS) will be used to assign subjects to treatment. The randomization code list will be produced by Vertex Biostatistics or a qualified randomization vendor.

6.4 Blinding and Unblinding

6.4.1 Blinding

All subjects, site personnel (including the investigator, the site monitor, and the study team), and the Vertex study team will be blinded to the treatment codes with the exception of the following:

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of the subject and her fetus in the event of a pregnancy
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy serious adverse event (SAE) processing and reporting regulations
- Unblinded statistician preparing the final (production) randomization list who is not part of the study team
- Vertex IWRS Manager
- Vertex Clinical Supply Chain
- IDMC
- Vendor preparing the unblinded analysis for the ongoing reviews of efficacy and safety data, and the IDMC
- Vendor analyzing PK samples

- Vertex Modeling and Simulation personnel or vendor conducting the population PK and PK/PD analyses
- Vertex medical monitor (or contract medical monitor) may, for matters relating to safety concerns, unblind individual subjects at any time

Vertex Drug Metabolism and Pharmacokinetics laboratory personnel will not be involved in the conduct of the study and will be unblinded to the bioanalysis results but will remain blinded to subject number and treatment assignment.

Spirometry and Sweat Chloride Data Blinding: During the conduct of the study, the Vertex study team will not have access to the spirometry results or sweat chloride concentration values after the morning dose on Day 1. Furthermore, sites, subjects, and their parents/caregivers/companions should not be informed of their study-related spirometry and sweat chloride results during the Treatment Period regardless of whether the subject has prematurely discontinued treatment.

A limited Vertex team will be unblinded and have access to safety, efficacy, and PD data for the purpose of conducting ongoing reviews of safety and efficacy data for planning and enabling clinical development, regulatory, and chemistry, manufacturing, and controls (CMC) decisions. Members of the limited unblinded Vertex team will not be part of the Vertex study team and will not be involved in or influence the conduct of the study.

The Vertex study team and lead investigator(s) will conduct a blinded review of all available safety and PK data after all Cohort 1A subjects complete the Day 15 Visit. The Vertex study team will not have access to unblinded data from ongoing reviews by the limited Vertex team.

After all subjects within Parts 1 and 2 have completed the Safety Follow-up Visit, results from each part will be unblinded for full review by the Vertex study team (Section 12.3.6.1 of protocol).

6.4.2 Unblinding

At the initiation of the study, each study site will be instructed on the method for breaking the blind. The unblinding method will be either a manual or electronic process.

Unblinding of the individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, investigators will use their best judgment as to whether to unblind without first attempting to contact the medical monitor to discuss and agree to the need for unblinding. If investigators deem it not necessary to unblind immediately, they will first attempt to contact the medical monitor to discuss and agree to the need for unblinding. If investigators have tried but are unable to reach the medical monitor, they will use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding without having successfully reached and discussed the situation with the medical monitor.

Contact information for the medical monitor (or appropriate backup) will be provided in a separate document.

In addition, the Vertex Medical Information Call Center ([redacted]) will answer calls 24 hours a day, 7 days a week, 365 days of the year, and will triage these calls to the study medical monitor or appropriate backup.

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor will be notified within 24 hours of the unblinding event. The reason and the date of the unblinding will be documented clearly in the subject's study file. Information about the treatment assignment obtained from the unblinding will be maintained in a secure location with controlled access and will not be shared with the sponsor (Vertex), contract research organization (CRO), or any site personnel (other than the physician treating the subject). In addition, the investigator will consider whether the clinical event that prompted unblinding will be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to Vertex GPS or designee, per Section 13.1.2 of the protocol.

Vertex GPS or designee will also unblind any SAE reports in compliance with regulatory reporting requirements. In addition, Vertex may, for matters relating to safety concerns, unblind individual subjects at any time.

7 ANALYSIS SETS

The following analysis sets are defined: All Subjects Set, Full Analysis Set and Safety Set.

7.1 All Subjects Set

The **All Subjects Set** will include all subjects who were randomized or received at least 1 dose of study drug. This analysis set will be used for all individual subject data listings and disposition summary tables, unless otherwise specified.

7.2 Full Analysis Set

The **Full Analysis Set** (FAS) will be defined as 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 to summarize subject demographics and baseline characteristics, and for all PD and efficacy analyses, unless specified otherwise. Subjects will be analyzed according to the treatment they were randomized to.

7.3 Safety Set

7.3.1 Parts 1[redacted]

The **Safety Set** will include all subjects who received at least 1 dose of study drug. The Safety Set will be used for all safety analyses, unless otherwise specified. Subjects will be analyzed according to the treatment they received.

For Part 1, if a subject received at least 1 dose of the higher TC treatment group in the increasing priority order: Triple placebo, TC-1A, TC-1B-low, TC-1B-high, the subject will be analyzed in the higher treatment group.

[redacted]

7.3.2 Part 2

The **Safety Set for the Run-in Period** will include all subjects who received at least 1 dose of study drug TEZ/IVA in the Run-in Period. This Safety Set will be used for individual subject data listings for the Run-in Period, unless specified otherwise.

The **Safety Set for the Treatment Period** will include all subjects who received at least 1 dose of study drug in the Treatment Period. This Safety Set will be used for all safety analyses for the Treatment Period, unless specified otherwise.

If a subject received at least 1 dose of the higher TC treatment group in the increasing priority order: placebo + TEZ/IVA, TC-2 (VX-440 + TEZ/IVA), the subject will be analyzed in the higher treatment group.

Note: The safety analysis will focus on the Safety Set for the Treatment Period only, unless otherwise specified.

8 STATISTICAL ANALYSIS

8.1 General Considerations

The analysis will be performed for each part, and presented by treatment group and overall, for the Treatment Period, unless specified otherwise. The treatment groups are defined as follows:

- Part 1: F508del/MF genotype group
    - TC-1B-high, TC-1B-low, TC-1A, and placebo, with the TEZ component in the TC-1B-low and TC-1B-high groups administered as 50 mg q12h, and that in the TC-1A group administered as 100 mg qd. More specifically, Part 1 includes cohorts 1A and 1B; Cohort 1A includes TC-1A while Cohort 1B includes TC-1B-low and TC-1B-high. The placebo group is randomized in both cohorts.
- Part 2: F508del/F508del genotype group
    - TC-2, and TEZ/IVA, with the TEZ component in the TC group administered as 50 mg q12h

[redacted]

The Schedule of Assessments is provided in Appendix A. 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.

All individual subject data for those randomized or dosed with any amount of study drug will be presented in data listings.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, standard error (SE), median, minimum value (min), and maximum value (max). SE may not be reported for safety summary tables.

Categorical variables will be summarized using counts and percentages. Percentages will be presented to 1 decimal place.

Baseline value, unless otherwise specified, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug on Day 1 of the Treatment Period. For ECG, baseline will be defined as the most recent non-missing measurement (the average of triplicate measurements, if the most recent non-missing measurement is obtained in triplicate), before the first dose of study drug on Day 1 of the Treatment Period.

Absolute change from baseline will be calculated as postbaseline value – baseline value.

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

Treatment-emergent (TE) period for Parts 1 [redacted] will include the time from the first dose of study drug in the Treatment Period to the Safety Follow-up (SFU) Visit, or 28 Days after the last dose of study drug for subjects who do not complete the SFU Visit.

For Part 2, the TE period will be defined separately for the Run-In Period, and the Treatment Period:

- The TE period for the Run-in Period will include the time from the first dose of study drug in the Run-in Period to: (1) the last day prior to the first dose of study drug in the Treatment Period for subjects who complete the Run-in Period and continue to the Treatment Period, or (2) the SFU Visit for subjects who do not continue to the Treatment Period and have an SFU Visit, or (3) 28 days after the last dose of study drug in the Run-in Period for subjects who do not have an SFU Visit (e.g., subjects who do not meet the criteria to enter the Treatment Period and re-enter Study 661-110).
- The TE period for the Treatment Period will include the first dose of study drug in the Treatment Period to: (1) the SFU Visit, or (2) 28 days after the last dose of study drug for subjects who do not have an SFU Visit (e.g. subjects whose Early Treatment Termination (ETT) Visit occurs 3 weeks or later following the last dose of study drug and the ETT visit replaces the SFU visit, or who leave the Treatment Period early and re-enter Study 661-110).

Note: only data collected up to the end of study for a subject will be included in analysis.

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

- In scheduled visit windows per specified visit windowing rules
- In the derivation of baseline and last on-treatment measurements
- In the derivation of maximum and minimum on-treatment values, and maximum and minimum change from baseline values 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 B.

Incomplete/missing data will not be imputed, unless specified otherwise.

Outliers: No formal statistical analyses will be performed to detect or remedy the presence of statistical outliers, unless specified otherwise.

Multiplicity: There will be no multiplicity adjustment for performing multiple hypothesis tests, unless specified otherwise.

8.2 Background Characteristics

8.2.1 Subject Disposition

For the Treatment Period in Part 1, Part 2, [redacted], subject disposition will be summarized as described below.

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

- All Subjects Set (randomized or dosed in the Treatment Period)
- Randomized
- Full Analysis Set (FAS)
- Safety Set (for Part 2, this is the Safety Set for the Treatment Period)

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

- Completed study drug treatment
- Prematurely discontinued treatment and the reason for discontinuation (i.e., discontinued all study drugs)
- Completed study (i.e., completed Safety Follow-up Visit or completed all study drugs and re-entered Study 661-110 without Safety Follow-up per protocol)
- Prematurely discontinued the study and the reason for discontinuation

For the Run-in Period in Part 2, a separate disposition table will be provided with the following categories:

- All Subjects Set (enrolled or dosed in the Run-in Period)
- Completed treatment in the Run-in Period (i.e., completed randomization)
- Prematurely discontinued treatment during the Run-in Period and the reason for treatment discontinuation (i.e., discontinued all study drugs in the Run-in Period)
- Prematurely discontinued the study during the Run-in Period and the reason for study discontinuation

A listing will be provided by part, for subjects who discontinued treatment (including the Run-in Period in Part 2) or who discontinued study with reasons for discontinuation. A randomization listing of subjects will also be provided, by part.

8.2.2 Demographics and Baseline Characteristics

Demographics, medical history and baseline characteristics will be summarized based on the FAS, and presented by treatment group and overall, for each part and cohort, as applicable.

Demographic data will include the following:

- Age at baseline (in years)
- Sex (female and male)
- 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, and Other)

Baseline characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

[redacted]

Stratification categories will include the following:

- $ppFEV_1$ at stratification (< 70 and ≥ 70)

[redacted]

For subjects who are naïve to TEZ/IVA treatment in Part 2, $ppFEV_1$ at Day -14 will be used for stratification; otherwise, $ppFEV_1$ at screening will be used for stratification.

Disease characteristics will include the following:

- $ppFEV_1$ at baseline (<40, ≥ 40 to <70, ≥70 to ≤90, >90)
- $ppFEV_1$ at baseline (continuous)
- Sweat Chloride at baseline (continuous)
- FEV_1 (L) at baseline (continuous)
- CFQ-R Respiratory Symptoms domain at baseline (continuous)
- Prior use of dornase alfa before first dose of study drug (Yes, No)
- Prior use of inhaled antibiotic before first dose of study drug (Yes, No)
- Prior use of any bronchodilator before first dose of study drug (Yes, No)
- Prior use of any inhaled bronchodilator before first dose of study drug (Yes, No)
- Prior use of any inhaled hypertonic saline before first dose of study drug (Yes, No)
- Prior use of any inhaled corticosteroids before first dose of study drug (Yes, No)

- Colonization with *Pseudomonas aeruginosa* at baseline (Positive, Negative)

A summary of medical history will be provided by MedDRA system organ class (SOC) and preferred term (PT) for the FAS. In addition, the number of subjects reported to have had positive cultures for respiratory pathogens in 2 years prior to screening will be summarized for the FAS. Further, the CFTR genotype for each subject will be provided in an individual subject data listing.

8.2.3 Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHODDE) and categorized as follows:

For Parts 1 [redacted]

Prior medication: any medication that started before the first dose date of study drug, regardless of when the medication ended.

Concomitant medication: medication continued or newly received on or after the first dose date of study drug through the end of the TE period.

Post-treatment medication: medication continued or newly received after the TE period.

For Part 2:

Prior medication: any medication that started before the first dose date of study drug in the Run-in Period, regardless of when the medication ended.

Concomitant medication during the Run-in Period: medication continued or newly received on or after the first dose date of study drug during the Run-in Period through the end of the TE period for the Run-in Period.

Concomitant medication during the Treatment Period: medication continued or newly received on or after the first dose date of study drug during the Treatment Period through the end of the TE period for the Treatment Period.

Post-treatment medication: medication continued or newly received after the TE period.

A given medication may be classified as follows: prior, concomitant, post-treatment, both prior and concomitant, both concomitant and post-treatment, or prior, concomitant, and post-treatment. In Part 2, concomitant may be concomitant during the Run-in Period, or concomitant during the Treatment Period, or both.

If a medication has a completely missing or partially missing start/stop date and it cannot be determined whether it was taken before the first dose date of study drug, concomitantly, or after the TE period, it will be classified as prior, concomitant, and post-treatment.

Prior medications and concomitant medications will be summarized descriptively using frequency tables by preferred name.

Summaries of medications will be based on the FAS, and presented by treatment group and overall for each part.

Post-treatment medications will be listed by subject.

Details for imputing missing or partial start and/or stop dates of medication are described in Appendix C.

8.2.4 Study Drug Exposure

Study drug exposure (in days) will be calculated as: last dose date of study drug – first dose date of study drug + 1 day, regardless of study drug interruption, and will be summarized descriptively. Study drug exposure will be summarized for the overall study drug period, which includes the Run-in Period, Treatment Period and Washout Period for Part 2, and the Treatment Period for Parts 1 [redacted] Further, study drug exposure for the combined Treatment Period and Washout Period in Part 2 will also be summarized descriptively.

Study drug exposure (in weeks) will be summarized descriptively by the number of subjects (n), mean, SD, SE, median, min, and max. It will also be summarized in categories: ≤2 weeks, >2- ≤4 weeks, and >4 weeks (for Parts 1 and 2); and ≤2 weeks, >2- ≤4 weeks, >4 - ≤8 weeks, >8 - ≤12 weeks, and >12 weeks (for Part 4), using counts and percentages. Additionally, the total study drug exposure, defined as the sum total of the study drug exposure across all subjects (in patient-weeks), will be provided.

Exposure summaries will be based on the Safety Set, and presented by treatment group and overall, for each part. For Part 2, exposure summaries will be based on the Safety Set for the Treatment Period.

8.2.5 Study Drug Compliance

Percentage of tablets taken will be calculated as: 100 × [(total number of tablets dispensed) – (total number of tablets returned)]/(total number of tablets planned to be taken per day × duration of study drug exposure in days). The maximum percentage of tablets taken will be 100%.

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 will be determined by an interruption of all drugs on that day.

Percentage of tablets taken and study drug compliance will be summarized descriptively by the number of subjects (n), mean, SD, SE, median, min, and max. It will also be summarized in categories: <80% and ≥80% using frequency tables.

For all parts, study drug compliance will be summarized for the Treatment Period only. Similarly, for all parts, percentage of tablets taken will be summarized for the Treatment Period only.

Percentage of tablets taken and study drug compliance summaries will be based on the FAS, and presented by treatment group and overall, for each part.

8.2.6 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.

The protocol deviations that should be considered as potential IPDs include, but are not limited to:

- Subject was enrolled in the study despite the violation of inclusion/exclusion criteria
- Subject was less than 80% compliant with study drug based on number of tablets taken
- Subject received prohibited concomitant medications
- Subject received the wrong treatment or incorrect doses
- Subject remained in the study despite meeting withdrawal criteria

Occurrence of any of these events should be considered as potential IPDs, but a blinded team should categorize them as IPDs only if they have the potential to significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

IPDs will be provided in an individual subject data listing for each part. Additionally, IPDs (from the clinical database or from the site deviation log) will be summarized descriptively based on the FAS and presented by treatment group [redacted] Details of the IPD rules are provided in Appendix D.

8.3 Efficacy Analysis

All efficacy analyses described in this section will be based on the FAS, unless otherwise specified. TC groups with TEZ 100 mg qd (Cohort 1A) and 50 mg q12h (Cohort 1B) for the same dose of VX-440 will be pooled for the primary model-based analysis of all efficacy and pharmacodynamic (PD) variables in Part 1. [redacted]

Treatment groups TC-1A and TC-1B-low in Part 1 will be presented both pooled and separately, for descriptive analysis.

The placebo group will include subjects from all cohorts within a part, for all analyses. The analysis will include all available measurements through the last scheduled on-treatment visit including measurements after treatment discontinuation, per the visit windowing rules described in Appendix B. The post-dose measurements on the same day will not be used for any model-based analyses, but only reported in descriptive analyses.

8.3.1 Primary Efficacy Variable

The primary efficacy variable is the absolute change from baseline for pre-dose percent predicted FEV_1 (in percentage units) through Day 29 in Parts 1 and 2, [redacted]

The percent predicted FEV_1 is the ratio of FEV_1 (L) to the predicted FEV_1 (L), expressed as a percentage. The predicted FEV_1 will be calculated using the Quanjer GLI-2012 Regression Equations and Lookup Tables, adjusting for age, height, sex and geographic region. Details are provided in Appendix E.

8.3.1.1 Primary Analysis of the Primary Efficacy Variable

8.3.1.1.1 Parts 1 and 2

The null hypothesis to be tested is that the mean absolute within-group change from baseline in percent predicted FEV_1 ($ppFEV_1$) through Day 29 is zero for VX-440 in triple combination (TC) with TEZ/IVA, for each part, separately. A 2-sided *p*-value of 0.05 or less will be interpreted as sufficient evidence to reject the null hypothesis.

The primary analysis will be performed using a mixed-effects model for repeated measures (MMRM) with change from baseline in $ppFEV_1$ as the dependent variable for each part, separately. This MMRM analysis will include all treatment groups within a part. For Part 1, the analysis will include 3 treatment groups: placebo, pooled TC-1A and TC-1B-low, and TC-1B-high. For Part 2, the analysis will include 2 treatment groups: placebo + TEZ/IVA, and TC-2 (VX-440 + TEZ/IVA). The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects, with the continuous baseline ppFEV1 as a covariate, and will include all data from each treatment group and visit in the analysis. 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. An unstructured covariance structure will be used to model the within-subject errors. If the model estimation does not converge, a reduced compound symmetry covariance structure will be used instead. Conditional on the observed data and covariates, missing $ppFEV_1$ data due to treatment or study discontinuation will be assumed to be missing at random; consequently, no imputation of missing data will be performed.

The adjusted means and 95% confidence intervals (CI) of the average treatment effect through Day 29 (Day 15 and Day 29 only) for each triple combination, with a 2-sided *p*-value will be estimated within MMRM using PROC MIXED in SAS, for all within-treatment and between-treatment comparisons, for each part, separately. Contrasts based on the fixed effects in the model, defined at the baseline covariate mean for the combined treatment groups using unique subjects in the FAS who have at least one post-baseline measurement through Day 29, will be used to estimate the average treatment effect across post-baseline visits through Day 29.

Further, the adjusted mean and 95% CI of the treatment difference between each triple combination and placebo at each post-baseline visit through Day 29 will be provided along with the corresponding *p*-value, for each part. 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, for each part.

The adjusted mean (with 95% CI) obtained from the MMRM analysis at each post-baseline visit through Day 29 will be plotted by treatment group, for each part. In addition, a waterfall plot showing the subject-level absolute change in $ppFEV_1$ at Day 29 will be presented, by treatment group. The plots will be based on the pooled treatment groups for Part 1.

In addition, for each part, descriptive analyses of the change from baseline will be performed for all treatment groups by post-baseline visit through the safety follow-up visit. Treatment groups in Part 1 will be presented both with TC-1A and TC-1B-low pooled, and separately for descriptive analysis.

[redacted]

[redacted]

8.3.2 Analysis of Secondary Efficacy Variables

The secondary efficacy variables include:

- Relative change in ppFEV$_1$ from baseline through Day 29 (Parts 1 and 2) [redacted]

- Absolute change in the CFQ-R respiratory domain score from baseline at Day 29 (Parts 1 and 2) [redacted]

[redacted]

The primary analysis of the secondary efficacy variables will pool treatment groups TC-1A and TC-1B-low in Part 1.

8.3.2.1 Relative change in $ppFEV_1$ from baseline through Day 29 (Parts 1 and 2) [redacted]

Parts 1 and 2

The relative change in $ppFEV_1$ from baseline through Day 29 is defined in Section 8.1. Analysis of this variable will be based on an MMRM model, similar to the primary analysis of the primary efficacy variable in Parts 1 and 2. The tabular presentation of results will also be similar.

[redacted]

8.3.2.2 Absolute change in the CFQ-R respiratory domain score from baseline at Day 29 (Parts 1 and 2) [redacted]

[redacted]

Parts 1 and 2

The absolute change in the CFQ-R respiratory domain score from baseline at Day 29 will use the 'Adolescents and Adults' Version for ages 14 and above at baseline, and will be based on the *CFQ-R scaled scores*, as described in Appendix F. Analysis of this variable will be based on an MMRM model, similar to the analysis of the primary efficacy variable in Parts 1 and 2. Sex, the continuous baseline $ppFEV_1$, and the continuous baseline CFQ-R respiratory domain score will be used as covariates in Parts 1 and 2. The presentation of results will also be similar.

[redacted]

8.3.2.9 Multiplicity adjustment

There will be no multiplicity adjustment to control the overall type 1 error rate for secondary efficacy variables.

[redacted]

[redacted]

8.3.5 Pharmacodynamic Analysis

The sweat chloride measurement 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 the pharmacodynamic (PD) effect of [redacted] VX-440 in TC with TEZ/IVA (all parts) on sweat chloride concentrations will be described in this section. The TC groups with TEZ 100 mg qd (Cohort 1A) and 50 mg q12h (Cohort 1B) for the same dose of VX-440 will be pooled for the primary model-based analysis of sweat chloride in Part 1. [redacted]

Treatment groups TC-1A and TC-1B-low in Part 1 will be presented both pooled and separately, for the descriptive analysis of sweat chloride.

8.3.5.1 Primary Analysis of the Dose Response trend of absolute change in sweat chloride from baseline through Day 29 (Part 1)

The null hypothesis to be tested is that the dose response of the mean absolute change from baseline through Day 29 for sweat chloride is not decreasing between placebo and the TC dose groups of Part 1, with TC-1A and TC-1B-low pooled. The test will be performed using the MCP procedure with the pre-specified contrasts provided in Section 6.2.2.1, within a linear MMRM framework using PROC GLIMMIX in SAS. The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects, with continuous baseline sweat chloride as a covariate, and will include all data from all treatment groups and visits through Day 29 for analysis. The dose response test will be based on the 1-sided maximum *t*-statistic of the individual *t*-statistics for the multiple pre-specified contrasts at alpha = 5%, based on the treatment group means through Day 29 (Day 15 and Day 29 only), using an unstructured covariance structure for the within-subject errors. If the model estimation does not converge, a reduced compound symmetry covariance structure will be used instead.

The tabular presentation of results for the average treatment effect across visits, and the treatment effect by visit will be similar to the primary analysis of the primary efficacy variable for Parts 1 and 2. The corresponding *p*-value for the decreasing dose response trend will be provided.

In addition, descriptive analyses of the change from baseline will be performed for all treatment groups by post-baseline visit, with TC-1A and TC-1B-low presented both pooled and separately, for descriptive analysis.

[redacted]

8.3.5.3 Absolute Change in Sweat Chloride from Baseline through Day 29 (Parts 1 and 2) [redacted]

8.3.5.3.1 Parts 1 and 2

The analysis of the absolute change in sweat chloride from baseline through Day 29 will be based on an MMRM model similar to the analysis of the primary efficacy variable in Part 1, with the continuous baseline sweat chloride as a covariate. The presentation of results will also be similar.

The adjusted mean (with 95% CI) obtained from the MMRM analysis at each post-baseline visit through Day 29 in the Treatment Period will be plotted by treatment group, for each part.

A waterfall plot showing the subject-level absolute change in sweat chloride at Day 29 will be presented, by treatment group. The plots will be based on the pooled treatment groups for Part 1.

In addition, for each part, descriptive analyses of the change from baseline will be performed for all treatment groups by post-baseline visit. Treatment groups TC-1A and TC-1B-low in Part 1 will be presented both pooled and separately, for descriptive analysis.

[redacted]

[redacted]

8.4 Safety Analysis

For Parts 1 [redacted] all safety analyses will be based on data from the TE Period for all subjects in the Safety Set. For Part 2, all safety analyses will be based on the TE Period for the Treatment Period for all subjects in the corresponding Safety Set for the Treatment Period.

The overall safety profile of study drug will be assessed in terms of the following safety and tolerability endpoints:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (i.e., hematology, serum chemistry, coagulation, and urinalysis)
- ECGs
- Vital signs
- Pulse oximetry

All safety data will be summarized by treatment group and overall, for each part.

All safety data will be presented in individual subject data listings.

8.4.1 Adverse Events

For analysis purposes, AEs will be classified as pretreatment AEs, TEAEs, or post-treatment AEs, defined as follows:

For Parts 1 [redacted]

Pretreatment AE: any AE that started before the first dose date of study drug

TEAE: any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug through the end of the TE period

Post-treatment AE: any AE that worsened (either in severity or seriousness) or that was newly developed beyond the TE period

For Part 2:

Pretreatment AE: any AE that started before the first dose date of study drug

TEAE during the Run-in Period: any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug through the end of the TE period for the Run-in Period

TEAE during the Treatment Period: any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug through the end of the TE period for the Treatment Period

Post-treatment AE: any AE that worsened (either in severity or seriousness) or that was newly developed beyond the 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.

Details for imputing missing or partial start dates of adverse events are described in Appendix H.

AE summary tables will be presented for TEAEs only, for the TE period, or accordingly, the TE Period for Treatment Period in Part 2, by treatment group and overall, for each part and cohort, as applicable, for the following:

- Number of TEAEs (total number of TEAEs only)
- Subjects with any TEAEs
- Subjects with TEAEs by Strongest Relationship
- Subjects with TEAEs by Maximum Severity
- Subjects with TEAEs Leading to Study Drug Discontinuation (Discontinuation of all study drug)
- Subjects with TEAEs Leading to Study Drug Interruption (Interruption of all study drug)
- Subjects with Serious TEAEs
- Subjects with TEAE Leading to Death

Summaries will be presented by MedDRA system organ class (SOC) and preferred term (PT) using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentages of subjects, subjects with multiple occurrences of the same adverse event or a continuing 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.

All AEs, including pre-treatment AEs, TEAEs for all applicable periods (Run-in, Treatment, Washout), and post-treatment AEs, will be presented in an individual subject data listing based on the All Subjects Set. Further, subjects who enrolled from Study 661-110 will be identified from the subject ID in the listing.

8.4.2 Clinical Laboratory

For the treatment-emergent laboratory assessments, the observed values and change from baseline values of the continuous hematology, chemistry, and coagulation results will be summarized in SI units at each scheduled visit, by treatment group and part.

The number and percentage of subjects meeting at least 1 threshold analysis criterion event during the TE period, or accordingly, the TE period for the Treatment Period in Part 2, will be summarized by treatment group and overall for each part. The threshold analysis criterion shift from baseline will also be summarized for selected laboratory parameters. The threshold analysis criteria are provided in Appendix I.

For LFT laboratory test (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin), a scatter plot of the maximum treatment-emergent value versus the baseline value corresponding to xULN will be presented. Further, a scatter plot of the maximum treatment-emergent value of ALT and AST, separately, versus the maximum treatment-emergent value of total bilirubin corresponding to xULN will also be presented by treatment group, for each part. The plots will be based on the pooled treatment groups for Part 1. [redacted]

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

In addition, a listing containing individual subject hematology, chemistry, and coagulation values outside the normal reference ranges will be provided. This listing will include data from both scheduled and unscheduled visits.

8.4.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided at each scheduled visit and time point, by treatment group, for each part, for the following ECG interval measurements (in ms): RR, PR, QT, and QT corrected for HR (QTcF), QRS duration, and HR (beats per minute).

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE period, or accordingly, the TE period for the Treatment Period in Part 2, will be summarized by treatment group and overall, for each part. The threshold analysis criteria are provided in Appendix I.

8.4.4 Vital Signs

For the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized by treatment group, at each scheduled visit, for each part

and cohort, as applicable. The following vital signs parameters will be summarized: systolic and diastolic blood pressure (mm Hg), body temperature (°C), HR (beats per minute), and respiratory rate (breaths per minute).

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE period, or TE period for the Treatment Period in Part 2, will be summarized by treatment group and overall, for each part. The threshold analysis criteria are provided in Appendix I.

8.4.5 Pulse Oximetry

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

The number and percentage of subjects with shift changes from baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the TE Period, or accordingly, the TE period for the Treatment Period in Part 2, will be summarized by treatment group and overall, for each part.

8.4.6 Physical Examination

PE findings will be presented as an individual subject data listing only.

[redacted]

9 INTERIM AND IDMC ANALYSES

9.1 Interim Analysis

The first interim analysis will be performed after all subjects in Part 1 have completed the Safety Follow-up Visit. All Data from Part 1 will be unblinded after the data from Part 1 are cleaned for analysis and a data cut is performed. The Vertex Study Team will be unblinded to the interim analysis results from Part 1.

The second interim analysis will be performed after all subjects in Part 2 have completed the Safety Follow-up Visit. The Vertex Study Team will be unblinded to the interim analysis results from Part 2, following a process similar to Part 1.

9.2 IDMC Analysis

An independent data monitoring committee (IDMC) was formed before study initiation. The IDMC's objectives and operational details were defined in a separate document (IDMC Charter) which was finalized before the first subject was screened in the study. The IDMC's planned safety reviews of study data are outlined in the IDMC Charter and IDMC Statistical Analysis Plan. Further, planned ongoing reviews of key study data by the limited Vertex team are also described in the IDMC Statistical Analysis Plan.

10 REFERENCES

[1]Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall G, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.

[2]Quittner AL, Modi A, Cruz I. Systematic review of health-related quality of life measure for children with respiratory conditions. Pediatr Respir Rev. 2008;9:220-32.

[3]Goss C, Quittner AL. Patient-reported outcomes in cystic fibrosis. Proc Am Thorac Soc. 2007;4:1-9.

[4]Modi AC, Quittner AL. Validation of a disease-specific measure of health-related quality of life for children with cystic fibrosis. J Pediatr Psychol. 2003;28(8):535-45.

11 LIST OF APPENDICES

Appendix A: Schedule of Assessments

Table 11-1 Study VX15-440-101: Schedule of Assessments for Part 1 (Cohort 1A)

Event/Assessment[a]	Screening	Treatment Period[b]						Safety Follow-up
	Days -28 to -1[d]	Day 1	Day 8 (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	ETT Visit[c]	28 (± 7) Days After Last Dose
Informed consent	X							
Randomization[e]		X						
Demographics	X							
Medical history	X							
Ophthalmological history	X							
CFQ-R[f,g]		X		X	X	X	X[h]	X
Weight[i]	X	X	X	X	X	X	X	X
Height	X							

[a] All assessments will be performed before dosing, unless noted otherwise. Assessments that are collected before and after dosing will only be collected once if study drug is not administered on the day of the visit (i.e., if subject prematurely discontinued study drug treatment).

[b] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 8.1.3 of the protocol.

[c] If the subject prematurely discontinues study treatment, an ETT Visit should be scheduled as soon as possible after the decision to terminate study drug treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

[d] All screening results must be reviewed by an appropriately qualified member of the investigator's team before randomization, unless noted otherwise.

[e] Randomization may occur on the previous day (Day -1) after all inclusion and exclusion criteria have been confirmed.

[f] CFQ-R must be completed before the start of any other assessments scheduled at that visit.

[g] The predose assessment on Day 1 may be performed on the previous day (Day -1) if randomization has occurred.

[h] Subjects will complete the CFQ-R at the ETT Visit only if it has been 2 weeks or more since their last visit.

[i] Weight and height will be measured with shoes off.

Table 11-1 Study VX15-440-101: Schedule of Assessments for Part 1 (Cohort 1A)

Event/Assessment[a]	Screening	Treatment Period[b]						Safety Follow-up
	Days -28 to -1[d]	Day 1	Day 8 (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	ETT Visit[c]	28 (± 7) Days After Last Dose
Vital signs[j]	X	X	X	X	X	X	X	X
Pulse oximetry	X	X	X	X	X	X	X	X

[j] Vital signs and pulse oximetry will be collected after the subject has been seated for at least 5 minutes.

Table 11-1 Study VX15-440-101: Schedule of Assessments for Part 1 (Cohort 1A)

Event/Assessment[a]	Screening	Treatment Period[b]						
	Days -28 to -1[d]	Day 1	Day 8 (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose
Physical examination[k]	Complete	Abbreviated		Abbreviated	Abbreviated		Abbreviated	Complete
Ophthalmologic examination[l]	X							
Standard 12-lead ECG[m]	X	X	X	X	X	X	X	X
Sweat chloride[g,n]	X	X	X	X	X	X	X	X
Spirometry[o]	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X
Pregnancy test (all females of childbearing potential)	Serum	Urine			Urine		Serum	Serum
CFTR genotype[p]	X							
FSH[q]	X							

[k] Complete and abbreviated PEs are described in Section 11.7.3 of the protocol. Symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator or healthcare provider.

[l] The ophthalmological examination can be performed at any time during the Screening Period through the Day 1 Visit (before the first dose of study drug). The screening ophthalmological examination does not have to be performed if there is documentation of an examination that met protocol criteria and was within 3 months before the date of informed consent, or if there is documentation of bilateral lens removal for the subject.

[m] All standard 12-lead ECGs will be performed after the subject has been seated for at least 5 minutes. On Days 1 and 15, ECGs will be collected before dosing and 4 hours (± 1 hour) after dosing. At all other visits, ECGs will be collected before dosing (as applicable). ECGs collected on Day 1 before dosing will be performed in triplicate.

[n] Sweat chloride will be measured in all subjects. If the value cannot be determined from the screening test, a sweat chloride value documented in the subject's medical record may be used to establish eligibility.

[o] Spirometry may be performed pre- or post-bronchodilator at the Screening Visit. Spirometry will be performed pre-bronchodilator, before the morning dose of study drugs, and should be performed at approximately the same time at every other study visit. On Days 1 and 15, spirometry will also be performed pre-bronchodilator 5 hours (± 1 hour) after study drug administration.

[p] *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used to establish eligibility.

[q] FSH will be measured for any suspected postmenopausal female subjects with at least 12 months of continuous spontaneous amenorrhea.

Table 11-1 Study VX15-440-101: Schedule of Assessments for Part 1 (Cohort 1A)

Event/Assessment[a]	Screening	Treatment Period[b]						Safety Follow-up
	Days -28 to -1[d]	Day 1	Day 8 (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	ETT Visit[c]	28 (± 7) Days After Last Dose
G6PD activity test[r]	X							
[redacted]								
Serum chemistry and hematology	X	X	X	X	X	X	X	X
Coagulation	X	X		X	X			X
PK sampling[t]		X	X	X	X	X	X	
Study drug dosing[u]		Day 1 through Day 29						
AEs, medications[v], treatments, and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit							

[r] A single blood sample will be collected for the G6PD activity test.

[redacted]

Blood samples will be collected for PK analysis of VX-440, TEZ, M1-TEZ, IVA, and M1-IVA. On Day 1, samples will be collected before dosing (0 hours) and at 1, 2, 4, and 6 hours after dosing (relative to the morning dose). On Days 8 and 29, a predose sample will be collected before the morning dose of study drug. On Day 15, samples will be collected before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing. At the Day 43 and the ETT Visits, a single blood sample for PK analysis will be collected.

[u] The last dose of study drug will be the morning dose on Day 29.

[v] Refer to Section 9.4 of the protocol for details.

Table 11-2 Study VX15-440-101: Schedule of Assessments for Part 1 (Cohort 1B)

Event/Assessment[a]	Screening	Treatment Period[b]					
	Days -28 to -1[d]	Day 1	Day 15 (± 2 day)	Day 29 (± 2 day)	Day 43 (± 3 days)	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose
Informed consent	X						
Randomization[e]		X					
Demographics	X						
Medical history	X						
Ophthalmological history	X						
CFQ-R[f,g]		X	X	X	X	X[h]	X
Weight[i]	X	X	X	X	X	X	X
Height	X						
Vital signs[j]	X	X	X	X	X	X	X
Pulse oximetry	X	X	X	X	X	X	X

[a] All assessments will be performed before dosing, unless noted otherwise. Assessments that are collected before and after dosing will only be collected once if study drug is not administered on the day of the visit (i.e., if subject prematurely discontinued study drug treatment).

[b] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 8.1.3 of the protocol.

[c] If the subject prematurely discontinues study drug treatment, an ETT Visit should be scheduled as soon as possible after the decision to terminate study drug treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

[d] All screening results must be reviewed by an appropriately qualified member of the investigator's team before randomization, unless noted otherwise.

[e] Randomization may occur on the previous day (Day -1) after all inclusion and exclusion criteria have been confirmed.

[f] CFQ-R must be completed before the start of any other assessments scheduled at that visit.

[g] The predose assessment on Day 1 may be performed on the previous day (Day -1) if randomization has occurred.

[h] Subjects will complete the CFQ-R at the ETT Visit only if it has been 2 weeks or more since their last visit.

[i] Weight and height will be measured with shoes off.

[j] Vital signs and pulse oximetry will be collected after the subject has been seated for at least 5 minutes.

Table 11-2 Study VX15-440-101: Schedule of Assessments for Part 1 (Cohort 1B)

Event/Assessment[a]	Screening	Treatment Period[b]					
	Days -28 to -1[d]	Day 1	Day 15 (± 2 day)	Day 29 (± 2 day)	Day 43 (± 3 days)	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose
Physical examination[k]	Complete	Abbreviated	Abbreviated	Abbreviated		Abbreviated	Complete
Ophthalmologic examination[l]	X						
Standard 12-lead ECG[m]	X	X	X	X	X	X	X
Sweat chloride[g,n]	X	X	X	X	X	X	X
Spirometry[o]	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X
Pregnancy test (all females of childbearing potential)	Serum	Urine		Urine		Serum	Serum
CFTR genotype[p]	X						
FSH[q]	X						

[k] Complete and abbreviated PEs are described in Section 11.7.3 of the protocol. Symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator or healthcare provider.

[l] The ophthalmological examination can be performed at any time during the Screening Period through the Day 1 Visit (before the first dose of study drug). The screening ophthalmological examination does not have to be performed if there is documentation of an examination that met protocol criteria and was within 3 months before the date of informed consent, or if there is documentation of bilateral lens removal for the subject.

[m] All standard 12-lead ECGs will be performed after the subject has been seated for at least 5 minutes. On Days 1 and 15, ECGs will be collected before dosing and 4 hours (± 1 hour) after dosing. At all other visits, ECGs will be collected before dosing (as applicable). ECGs collected on Day 1 before dosing will be performed in triplicate.

[n] Sweat chloride will be measured in all subjects. If the value cannot be determined from the screening test, a sweat chloride value documented in the subject's medical record may be used to establish eligibility.

[o] Spirometry may be performed pre- or post-bronchodilator at the Screening Visit. Spirometry will be performed pre-bronchodilator, before the morning dose of study drugs, and should be performed at approximately the same time at every other study visit. On Days 1 and 15, spirometry will also be performed pre-bronchodilator, 5 hours (± 1 hour) after study drug administration.

[p] *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used to establish eligibility.

[q] FSH will be measured for any suspected postmenopausal female subjects with at least 12 months of continuous spontaneous amenorrhea.

Table 11-2 Study VX15-440-101: Schedule of Assessments for Part 1 (Cohort 1B)

Event/Assessment[a]	Screening	Treatment Period[b]					
	Days -28 to -1[d]	Day 1	Day 15 (± 2 day)	Day 29 (± 2 day)	Day 43 (± 3 days)	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose
G6PD activity test[r]	X						
[redacted]							
Serum chemistry and hematology	X	X	X	X	X	X	X
Coagulation	X	X	X	X			X
PK sampling[t]		X	X	X	X	X	
Study drug dosing[u]		Day 1 through Day 29					
AEs, medications[v], treatments and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit						

r A single blood sample will be collected for the G6PD activity test.

[redacted]

Blood samples will be collected for PK analysis of VX-440, TEZ, M1-TEZ, IVA, and M1-IVA. On Day 1, samples will be collected before dosing (0 hours) and at 1, 2, 4, and 6 hours after dosing (relative to the morning dose). On Day 15, samples will be collected before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing. On Day 29, a predose sample will be collected before the morning dose of study drug. At the Day 43 and the ETT Visits, a single blood sample for PK analysis will be collected.

u The last dose of study drug will be the morning dose on Day 29.

v Refer to Section 9.4 of the protocol for details.

Table 11-3 Study VX15-440-101: Schedule of Assessments for Part 2

	Screening	Run-in Period		Treatment Period[b]			Washout Period			Safety Follow-up
Event/Assessment[a]	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	Day 57 (± 3 days)	ETT Visit[c]	28 (± 7) Days After Last Dose[d]
Informed consent	X									
Randomization[g]				X						
Demographics	X									
Medical history	X									
Ophthalmological history	X									
CFQ-R[h,i]				X	X	X	X	X	X[j]	X
Weight[k]	X	X		X	X	X	X	X	X	X
Height	X									

[a] All assessments will be performed before dosing, unless noted otherwise. Assessments that are collected before and after dosing will only be collected once if study drug is not administered on the day of the visit (i.e., if subject prematurely discontinued study drug treatment).

[b] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 8.1.3 of the protocol.

[c] If the subject prematurely discontinues study treatment, an ETT Visit should be scheduled as soon as possible after the decision to terminate study drug treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

[d] Part 2 subjects who meet criteria specified in Section 8.1.5 of the protocol will not have a Safety Follow-up Visit.

[e] All screening results must be reviewed by an appropriately qualified member of the investigator's team before the subject receives the first dose of TEZ/IVA in the Run-in Period on Day -28, unless noted otherwise.

[f] The Day -14 Visit is only required for subjects who are naïve to TEZ/IVA treatment.

[g] Randomization may occur on the previous day (Day -1) after all inclusion and exclusion criteria and criteria for entry into the Treatment Period have been confirmed. See Section 8.1.3 of the protocol.

[h] CFQ-R must be completed before the start of any other assessments scheduled at that visit.

[i] The predose assessment on Day 1 may be performed on the previous day (Day -1) if randomization has occurred.

[j] Subjects will complete the CFQ-R at the ETT Visit only if it has been 2 weeks or more since their last visit.

[k] Weight and height will be measured with shoes off.

Table 11-3 Study VX15-440-101: Schedule of Assessments for Part 2

	Screening	Run-in Period		Treatment Period[b]			Washout Period			Safety Follow-up
Event/Assessment[a]	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	Day 57 (± 3 days)	ETT Visit[c]	28 (± 7) Days After Last Dose[d]
Vital signs[l]	X	X		X	X	X	X	X	X	X
Pulse oximetry	X	X		X	X	X	X	X	X	X
Physical examination[m]	Complete	Abbreviated		Abbreviated	Abbreviated	Abbreviated		Abbreviated	Abbreviated	Complete
Ophthalmologic examination[n]	X									
Standard 12-lead ECG[o]	X	X		X	X	X	X	X	X	X
Sweat chloride[i,p]	X		X	X	X	X	X	X	X	
Spirometry[q]	X		X	X	X	X	X	X	X	X
Urinalysis	X	X		X	X	X	X	X	X	X

[l] Vital signs and pulse oximetry will be collected after the subject has been seated for at least 5 minutes.

[m] Complete and abbreviated PEs are described in Section 11.7.3 of the protocol. Symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator or healthcare provider.

[n] The ophthalmological examination can be performed at any time during the Screening Period through the Day 1 Visit (before the first dose of study drug). The screening ophthalmological examination does not have to be performed if there is documentation of an examination that met protocol criteria and was within 3 months before the date of informed consent, or if there is documentation of bilateral lens removal for the subject.

[o] All standard 12-lead ECGs will be performed after the subject has been seated for at least 5 minutes. On Days 1 and 15, ECGs will be collected before dosing and 4 hours (± 1 hour) after dosing. At all other visits, ECGs will be collected before dosing (as applicable). ECGs collected on Day 1 before dosing will be performed in triplicate.

[p] Sweat chloride will be measured in all subjects. If the value cannot be determined from the screening test, a sweat chloride value documented in the subject's medical record may be used to establish eligibility.

[q] Spirometry may be performed pre- or post-bronchodilator at the Screening Visit. Spirometry will be performed pre-bronchodilator, before the morning dose of study drugs, and should be performed at approximately the same time at every other study visit. On Days 1 and 15, spirometry will also be performed pre-bronchodilator, 5 hours (± 1 hour) after study drug administration.

Table 11-3 Study VX15-440-101: Schedule of Assessments for Part 2

	Screening	Run-in Period		Treatment Period[b]			Washout Period			Safety Follow-up
Event/Assessment[a]	**Days -56 to -29[e]**	**Day -28 (± 1 day)**	**Day -14[f] (± 1 day)**	**Day 1**	**Day 15 (± 2 days)**	**Day 29 (± 2 days)**	**Day 43 (± 3 days)**	**Day 57 (± 3 days)**	**ETT Visit[c]**	**28 (± 7) Days After Last Dose[d]**
Pregnancy test (all females of childbearing potential)	Serum	Urine		Urine		Urine		Urine	Serum	Serum
CFTR genotype[r]	X									
FSH[s]	X									
G6PD activity test[t]	X									
[redacted]										
Serum chemistry and hematology	X	X		X	X	X	X	X	X	X
Coagulation	X	X		X	X	X				X
PK sampling[v]				X	X	X	X		X	
TEZ/IVA dosing[w]		Day -28 through Day 57								
VX-440 or placebo dosing[x]				Day 1 through Day 29						

[r] *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before Day -28, a previous *CFTR* genotype laboratory report may be used to establish eligibility.

[s] FSH will be measured for any suspected postmenopausal female subjects with at least 12 months of continuous spontaneous amenorrhea.

[t] A single blood sample will be collected for the G6PD activity test.

[redacted]

Blood samples will be collected for PK analysis of VX-440, TEZ, M1-TEZ, IVA, and M1-IVA. On Day 1, samples will be collected before dosing (0 hours) and at 1, 2, 4, and 6 hours after dosing (relative to morning dose). On Day 15, samples will be collected before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing. On Day 29, a predose sample will be collected before the morning dose of study drug. At the Day 43 Visit, a single blood sample for PK analysis will be collected before the morning dose of TEZ/IVA. At the ETT Visit, a single blood sample for PK analysis will be collected.

[w] The last dose of TEZ/ivacaftor will be the morning dose on Day 57.

[x] The last dose of VX-440 or placebo will be the morning dose on Day 29.

Table 11-3 Study VX15-440-101: Schedule of Assessments for Part 2

Event/Assessment[a]	Screening	Run-in Period		Treatment Period[b]			Washout Period		ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose[d]
	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	Day 57 (± 3 days)		
AEs, medications[y], treatments and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit									

[y] Refer to Section 9.4 of the protocol for details.

Appendix B: Analysis Visit Windows for Safety and Efficacy Assessments

Table 11-5 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window (in study days)
Safety Assessment (Part 1, Cohort 1A)			
Serum Chemistry Hematology Urinalysis Vital Signs (including Weight)	Day 1 (Baseline) Day 8 Day 15 Day 29 Day 43 Safety Follow-up	1 8 15 29 43 57	≤1 Pre-dose [1, 12] (12,22] (22, 36] (36, 50] Use nominal visit
Coagulation	Day 1 (Baseline) Day 15 Day 29 Safety Follow-up	1 15 29 57	≤1 Pre-dose [1, 22] (22, 43] Use nominal visit
Standard 12-Lead ECG	Day 1 (Baseline; before dosing) Day 1 (4 hours after dosing) Day 8 Day 15 (before dosing and 4 hours after dosing) Day 29 Day 43 Safety Follow-up	1 1 8 15 29 43 57	Use nominal visit for all visits
Safety Assessment (Part 1, Cohort 1B)			
Serum Chemistry Hematology Urinalysis Vital Signs (including Weight)	Day 1 (Baseline) Day 15 Day 29 Day 43 Safety Follow-up	1 15 29 43 57	≤1 Pre-dose [1,22] (22, 36] (36, 50] Use nominal visit
Coagulation	Day 1 (Baseline) Day 15 Day 29 Safety Follow-up	1 15 29 57	≤1 Pre-dose [1,22] (22, 43] Use nominal visit
Standard 12-Lead ECG	Day 1 (Baseline; before dosing) Day 1 (4 hours after dosing) Day 15 (before dosing and 4 hours after dosing) Day 29 Day 43 Safety Follow-up	1 1 15 29 43 57	Use nominal visit for all visits
Safety Assessment (Part 2)			

[a] Visit name is used to report data in tables, listings and figures.
[b] Target day time point per protocol is predose, except for ECG measurements.

Table 11-5 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window (in study days)
Serum Chemistry Hematology Urinalysis Vital Signs (including Weight)	Day 1 (Baseline) Day 15 Day 29 Day 43 Day 57 Safety Follow-up	1 15 29 43 57 85	≤1 Pre-dose [1,22] (22, 36] (36, 50] (50, 71] Use nominal visit
Coagulation	Day 1 (Baseline) Day 15 Day 29 Safety Follow-up	1 15 29 85	≤1 Pre-dose [1,22] (22, 57] Use nominal visit
Standard 12-Lead ECG	Day 1 (Baseline; before dosing) Day 1 (4 hours after dosing) Day 15 (before dosing and 4 hours after dosing) Day 29 Day 43 Day 57 Safety Follow-up	1 1 15 29 43 57 85	Use nominal visit for all visits
[redacted]			
Efficacy Assessment (Part 1, Cohort 1A)			

Table 11-5 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window (in study days)
Spirometry Sweat Chloride	Day 1 (Baseline) Day 1 (5 hours after dosing for Spirometry)	1 1	≤1 Pre-dose 1 Post-dose for Spirometry
	Day 8	8	(1, 12]
	Day 15	15	(12,22] (Pre and Post for Spirometry)
	Day 29	29	(22, 36]
	Day 43	43	(36, 50]
	Safety Follow-up	57	Use nominal visit
CFQ-R	Day 1 (Baseline)	1	≤1
	Day 15	15	(1,22]
	Day 29	29	(22, 36]
	Day 43	43	(36, 50]
	Safety Follow-up	57	Use nominal visit
Efficacy Assessment (Part 1, Cohort 1B)			
Spirometry Sweat Chloride CFQ-R	Day 1 (Baseline) Day 1 (5 hours after dosing for Spirometry)	1 1	≤1 1
	Day 15	15	(1,22] (Pre and Post for Spirometry)
	Day 29	29	(22, 36]
	Day 43	43	(36, 50]
	Safety Follow-up	57	Use nominal visit
Efficacy Assessment (Part 2)			
Spirometry Sweat Chloride CFQ-R	Day 1 (Baseline) Day 1 (5 hours after dosing for Spirometry)	1 1	≤1 1
	Day 15	15	(1,22] (Pre and Post for Spirometry)
	Day 29	29	(22, 36]
	Day 43	43	(36, 50]
	Day 57	57	(50, 71]
	Safety Follow-up	85	Use nominal visit
[redacted]			

[a]Visit name is used to report data in tables, listings and figures.
[b]Target day time point is predose.

Table 11-5 Analysis Visit Windows for Safety and Efficacy Assessments

Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window (in study days)

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

1. If no numerical measurement is available within a visit window, the measurement will be considered missing for the visit.
2. If there is more than 1 numerical measurement available within the same visit window, use the following rules:
   a. For efficacy parameters: if there are multiple measurements within a visit window, the measurement at the scheduled visit will be used. Otherwise,
      i. If there are no measurements at the scheduled visit, then the measurement closest to the target day will be used; or
      ii. If there are multiple measurements with the same distance to the target day, the latest measurement will be used.
   b. For safety parameters: if there are multiple measurements within a visit window,
      i. The measurement closest to the target day will be used; or
      ii. If there are multiple measurements within the same distance from the target day, the latest measurement will be used.
      iii. For tables of the extreme lab measurement based on ULN or LLN, convert the lab measurements into times of ULN or LLN first, and then select the extreme measurement.

Derived Variables

1. Age (in years) at first dose date

Obtain age at screening (in days) in yy mm format (e.g., 24 years, 6 months) from screening vital signs page, and add 0.5 month to convert to days.

Obtain screening date from Date of Visit (DOV) page.

Then age (in years) at first dose date = integer part of {[(first dose date-screening date) in days + age at screening (in days)]/365.25}.

Correspondingly, age (in months) at first dose date = integer part of 12*{[(first dose date-screening date) in days + age at screening (in days)]/365.25}.

2. Age (in years) at post-baseline visit (for use in calculation of percent predicted spirometry variables)

Age (in years) at post-baseline visit = integer part of {[(post-baseline visit date – screening date) in days + age at screening (in days)]/365.25}

3. Missing First Dose Date or Last Dose Date

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

If the last dose date is missing at final analysis, use maximum of Early Treatment Termination (ETT) visit date and last study drug administration date from EX SDTM domain (excluding PK dosing dates). When a subject is lost to follow up without ETT, impute the last dose date as the last on-treatment visit date.

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 only 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 (in practical, use Jan. 01, 2000 to impute).
2. Missing or partial medication stop date:
    a. If only 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 (in practical, use Dec. 31, 2050 to impute).

In summary, the prior, concomitant or post categorization of a medication is described below.

Table 11-6 Prior, Concomitant, and Post Categorization of a Medication in Parts 1 and 4

	Medication Stop Date		
Medication Start Date	**< First Dose Date of Study Drug**	**≥ First Dose Date and ≤ End Date of TE Period**	**> End Date of TE Period**
< First dose date of study drug	P	PC	PCA
≥ First dose date and ≤ End date of TE period	-	C	CA
> End date of TE period	-	-	A

P: Prior; C: Concomitant; A: Post

Table 11-7 Prior, Concomitant, and Post Categorization of a Medication in Part 2

	Medication Stop Date			
Medication Start Date	**< First Dose Date of Run-in TE Period**	**≥ First Dose Date and ≤ End Date of Run-in TE Period**	**≥ First Dose Date and ≤ End Date of Treatment TE Period**	**> End Date of Treatment TE Period**
< First dose date of Run-in TE period	P	PC1	PC1C2	PC1C2A
≥ First dose date and ≤ End date of Run-in TE Period	-	C1	C1C2	C1C2A
≥ First dose date and ≤ End date of Treatment TE Period	-	-	C2	C2A
> End date of Treatment TE Period	-	-	-	A

P: Prior; C1: Concomitant during the Run-in Period; C2: Concomitant during the Treatment Period; A: Post

Appendix D: Important Protocol Deviation Programming Rules (Based on the Clinical Database)

Important protocol deviations before first dose

1. Inclusion criteria:

   a) I1: Subject (or subject's legally appointed and authorized representative) will sign and date an informed consent form (ICF), and, when appropriate, an assent form.

   b) I3: Subjects will be aged 18 years or older for Parts 1 and 2, [redacted] on the date of informed consent and, when appropriate, date of assent.

   c) I4: Body weight ≥35 kg.

   d) I6: Subjects must have an eligible *CFTR* genotype as noted below. If the screening *CFTR* genotype result is not received before randomization (Parts 1 [redacted]) or before Day -28 (Part 2), a previous *CFTR* genotype laboratory report may be used to establish eligibility. Note: Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.5).

   e) I7: Part 1 [redacted] Heterozygous for *F508del* with a second *CFTR* allele carrying an MF mutation that is not likely to respond to TEZ and/or IVA therapy (Appendix A)

      Part 2: Homozygous for *F508del*

      Parts 1, 2, [redacted] subjects must have an FEV_1 ≥40% and ≤90% of predicted normal for age, sex, and height (equations of the Global Lung Function Initiative [GLI])[13] at the Screening Visit. Spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria[10] for acceptability and repeatability.

2. Exclusion criteria:

   a) E4: History of hemolysis.

   b) E5: G6PD deficiency, defined as G6PD activity less than the lower limit of normal (LLN) or 70% of the mean of the LLN and the ULN, whichever is greater.

   c) E6: Any of the following abnormal laboratory values at screening:

      - Hemoglobin <10 g/dL
      - Total bilirubin ≥2 × ULN
      - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), or alkaline phosphatase (ALP) ≥3 × ULN
      - Abnormal renal function defined as glomerular filtration rate ≤50 mL/min/1.73 m^2 (calculated by the Modification of Diet in Renal Disease Study Equation)[14, 15] for subjects ≥18 years of age and ≤45 mL/min/1.73 m^2

(calculated by the Counahan-Barratt equation)[16] for subjects aged 12 to 17 years (inclusive)

d) E10: A standard digital ECG demonstrating QTc >450 msec at screening. If QTc exceeds 450 msec for the screening ECG, the ECG should be repeated 2 more times during the Screening Period, and the subject will be excluded if the average of the 3 QTc values is >450 msec.

e) E11: History of solid organ or hematological transplantation.

f) E16: Use of restricted medications as defined in the clinical study protocol, within the specified window before the first dose of study drug (Day 1 in Parts 1[redacted], Day -28 in Part 2).

g) E17: Pregnant or nursing females: Females of childbearing potential must have a negative pregnancy test at screening and Day 1.

3. Stratification error based on comparing the IWRS stratification with the clinical database:
   - Age at Screening Visit (<18, ≥18 years) from IWRS versus age at screening visit in the clinical database
   - % predicted FEV_1 at Stratification (<70 , ≥70) from IWRS versus ppFEV_1 at the screening visit or Day -14 (Part 2) of the Run-in Period from the clinical database

Important protocol deviations during the Treatment Period

1. Compliance < 80% based on the number of tablets taken
2. Use of prohibited medications
3. Actual treatment received is different from the randomized treatment

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

Percent predicted values will be calculated for parameters of FEV$_1$, [redacted] 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:

Quanjer GLI-2012 Regression Equations and Lookup Tables. Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Version 7 April 2013. Available at:

http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/quanjer-gli-2012-regression-equations-and-lookup-tables.aspx.

Accessed March 13, 2017.

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

Implementing GLI-2012 regression equations. Philip H. Quanjer, Sanja Stanojevic, Tim J. Cole, Janet Stocks. Version 19 July 2015. Available at:

http://www.ers-education.org/guidelines/global-lung-function-initiative/gli-2012-explained.aspx.

Accessed March 13, 2017 .

GLI-2012 - SAS Macro. Sanja Stanojevic. Version 2, 7 April 2013. Available at:

http://www.ers-education.org/guidelines/global-lung-function-initiative/tools/sas-macro.aspx

Accessed March 13, 2017.

Appendix G: Calculation of BMI z-score for subjects <20 years old at screening

BMI will be calculated from weight and height at baseline and post-baseline time points (Day 15, Week 4, 8, and 12), as applicable for Parts 1, 2 [redacted]

BMI, adjusted for age and sex, will be referred to as BMI-for-age z-score (BMI z-score). BMI z-score will be calculated by using Centers for Disease Control and Prevention (CDC) growth charts. The BMI z-score will be calculated as follows:

$$z = \begin{cases} \dfrac{\left(\dfrac{X}{M}\right)^{L} - 1}{LS}, & L \neq 0 \\ \dfrac{\ln\left(\dfrac{X}{M}\right)}{S}, & L = 0 \end{cases}$$

where X is the derived BMI value in kg/m^2 based on the raw weight and raw height and L, M, and S are selected from the CDC BMI-for-age chart by subject sex and age. The BMIAGE file contains these parameters by sex (1=male, 2=female) and age; it is available at:

http://www.cdc.gov/growthcharts/percentile_data_files.htm.

Additionally, SAS code for calculating percentiles and z-scores is available at:

http://www.cdc.gov/growthcharts/computer_programs.htm.

NOTE: The CDC BMI-for-age charts are designed for use in pediatric populations (2 to 20 years of age); in this analysis plan, BMI z-score will be calculated only for subjects between 2 and <20 years.

Appendix H: Imputation Rules for Missing AE dates

H.1 Parts 1[redacted]

Imputation rules for missing or partial AE start date for Parts 1[redacted] are defined below.

- **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 with no imputation.
    - 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 the AE will be considered as TEAE for the Treatment Period.
    - else the AE will be considered as a pretreatment AE.

H.2 Part 2

Imputation rules for missing or partial AE start date for Part 2 are defined below.

- **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 if AE start year and month are equal to the month and year of first dose date of the Run-in Period, then impute the AE start day as the day of first dose date of the Run-in Period;
  - else impute the AE start day as 1.
- else if the full (or partial) AE end date is NOT before the first dose date of the Run-in Period, then impute the AE start day as the day of first dose date of the Run-in Period;
  - if AE start year and month are equal to the month and year of first dose date of the Run-in Period, then impute the AE start day as the day of first dose date of the Run-in 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 if AE start year is equal to the year of first dose date of the Run-in Period, then impute the AE start month and day as the month and day of first dose date of the Run-in Period;
    - else impute the AE start month as January and day as 1.
  - else if the full (or partial) AE end date is NOT before the first dose date of the Run-in Period, then impute the AE start day as the day of first dose date of the Run-in Period;
    - if AE start year is equal to the year of first dose date of the Run-in Period, then impute the AE start month and day as the month and day of first dose date of the Run-in 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 with no imputation.

  - 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 the AE will be considered as TEAE for the Treatment Period.
  - else if the full (or partial) AE end date is NOT before the first dose date of the Run-in Period, then the AE will be considered as TEAE for the Run-in Period.
  - else the AE will be considered as a pretreatment AE.

Imputation rules for partial AE end date are defined below:

If partial end date, then impute as min (the last day of the month, end of study) if day is missing, or min (Dec, end of study) if month is missing.

Appendix I: Criteria for Threshold Analysis

Table 11-10 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 11-10 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
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
Reticulocytes	<LLN >ULN	No CTCAE

Table 11-11 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
HR	Bradycardia	Per HV grade 2, 3, plus shift change
	<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	
	Tachycardia	Per HV grade 1, 2, 3, plus shift change
	>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	
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		To be applied to any kind of QT correction formula.
Borderline	>450 ms (Male) and <500ms; >470 ms and <500ms (Female)	
Prolonged*	≥500 ms	
Additional	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 11-12 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
HR	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	
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	

Table 11-12 Threshold Analysis Criteria for Vital Signs

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