VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Vertex Study Number: VX14 661 109 (Final Analysis)

A Phase 3, Randomized, Double-Blind, Ivacaftor-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Heterozygous for the *F508del-CFTR* Mutation and a Second *CFTR* Allele With a Gating Defect That Is Clinically Demonstrated to be Ivacaftor Responsive.

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1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
bpm	beats per minute
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire – Revised
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
CRF	case report form
CRO	contract research organization
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDC	VX-661 100-mg/IVA 150-mg fixed-dose tablet
$FEF_{25-75\%}$	forced expiratory flow, midexpiratory phase
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
HNV_{FEV}	Hankinson predicted value of FEV_1 (L)
$HNV_{FEF25-75\%}$	Hankinson predicted value of $FEF_{25-75\%}$ (L/sec)
HNV_{FVC}	Hankinson predicted value of FVC (L)
IVA	ivacaftor
LS means	Least squares means
LFT	liver function test
max	maximum value
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
min	minimum value
MMRM	mixed model repeated measure
N	number of subjects
PD	pharmacodynamic/pharmacodynamics
[redacted]	
PK	pharmacokinetic/pharmacokinetics
ppFEV1	percent predicted FEV1
[redacted]	
PT	preferred term
q12h	every 12 hours

Abbreviation	Term
QRS	Q, R, and S-wave define the QRS-complex in an ECG
QT	QT interval: The duration of ventricular depolarization and subsequent repolarization; it is measured from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate with Fridericia's correction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
[redacted]	
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WNV_{FEV}	Wang predicted value of FEV_1 (L)
$WNV_{FEF25-75\%}$	Wang predicted value of $FEF_{25-75\%}$ (L/sec)
WNV_{FVC}	Wang predicted value of FVC (L)
WHODDE	World Health Organization Drug Dictionary Enhanced

4 INTRODUCTION

This statistical analysis plan (SAP) Methods for the final analysis is based on the approved clinical study protocol (CSP), dated 18 APR 2017, Version 4.0, final electronic case report form (eCRF) completion guidelines, Version 1.0, dated 16 JUL 2015, and approved eCRF, Version 2.0, dated 29 OCT 2015.

Study VX14 661 109 is a Phase 3, randomized, double-blind, ivacaftor-controlled, parallel-group, multicenter study in subjects aged 12 years and older with CF who are heterozygous for the *F508del CFTR* mutation and a second *CFTR* allele with a gating defect that is clinically demonstrated to be ivacaftor responsive (see Appendix A).

This study is designed to compare active treatment of VX-661 (100 mg daily [qd]) and ivacaftor (150 mg every 12 hours [q12h]) combination therapy with ivacaftor monotherapy (150 mg q12h).

The treatment regimens will be as follows:

- VX-661/ivacaftor combination therapy
  - Morning dose: 1 tablet of fixed-dose combination of VX-661 100 mg/ivacaftor 150 mg and 1 tablet of placebo visually matched to ivacaftor
  - Evening dose: 1 tablet of ivacaftor 150 mg
- Ivacaftor monotherapy
  - Morning dose: 1 tablet of placebo visually matched to the fixed-dose combination tablet and 1 tablet of ivacaftor 150 mg
  - Evening dose: 1 tablet of ivacaftor 150 mg

This SAP (Methods) documents the planned final statistical analysis of efficacy and safety endpoints defined in the study protocol of VX14-661-109, and describes the corresponding data presentations. It also documents additional efficacy and safety analyses not specified in the protocol, which will provide supportive information to the scientific understanding of the drug entity. The study will also evaluate some exploratory endpoints described in the study protocol. Summary statistics will be provided by visit for selected exploratory endpoints. Additional analyses of these endpoints will be documented separately in the exploratory analysis plan (EAP).

The study will also evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of VX-661/ivacaftor in this subject population. PK and PD analyses will be documented separately in the clinical pharmacology analysis plan (CPAP) for the study.

The Vertex Biometrics Department will perform the final statistical analysis of the efficacy and safety data; SAS® Version 9.2 Software (SAS Institute, Cary, North Carolina, USA) or higher will be used to generate all statistical outputs (tables, figures, listings and datasets).

The SAP (Methods) for the final analysis will be finalized and approved before 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.

5 STUDY OBJECTIVES

5.1 Primary Objective

The primary objective of the study is to evaluate the efficacy of VX-661 in combination with ivacaftor in subjects with CF who are heterozygous for the *F508del* mutation on the *CFTR* gene and a second *CFTR* allele with a gating defect that is clinically demonstrated to be ivacaftor responsive.

5.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate the safety of VX-661 in combination with ivacaftor
- To investigate the pharmacokinetics (PK) of VX-661 and its metabolite M1 (M1-661), and ivacaftor and its metabolite M1 (M1-ivacaftor)

6 STUDY ENDPOINTS

6.1 Efficacy Endpoint

The Ivacaftor Run-in Period will have a total duration of 4 weeks and is designed to establish a reliable on-treatment (ivacaftor monotherapy) baseline for all subjects for the Active Comparator Treatment Period. The analysis period for the efficacy evaluation is the Active Comparator Treatment Period. The baseline for evaluating the efficacy of VX-661/ivacaftor combination therapy over ivacaftor monotherapy is defined in Section 9.1.

6.1.1 Primary Efficacy Endpoint

Absolute change in percent predicted forced expiratory volume in 1 second (FEV_1) from baseline through Week 8 in the Active Comparator Treatment Period

6.1.2 Key Secondary Efficacy Endpoints

- Relative change in percent predicted FEV_1 from baseline through Week 8 in the Active Comparator Treatment Period
- Absolute change in Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain score from baseline through Week 8 in the Active Comparator Treatment Period

6.1.3 Secondary Efficacy Endpoints

- Absolute change in sweat chloride from baseline through Week 8 in the Active Comparator Treatment Period
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values (hematology, serum chemistry, lipid panel, vitamin levels, coagulation studies,

and urinalysis), standard digital electrocardiograms (ECGs), vital signs, pulse oximetry, and spirometry.

- PK parameters of VX-661, M1-661, ivacaftor, and M1-ivacaftor

[redacted]

6.2 Safety Endpoints

Safety analyses will be based on the Safety Set with the associated TE Period and performed separately for the Ivacaftor Run-in Period and the Active Comparator Treatment Period, as appropriate.

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

- Incidence of treatment-emergent adverse event (TEAEs)
- Clinical laboratory values (i.e., hematology, serum chemistry, lipid panel, vitamin levels, coagulation studies, and urinalysis)
- ECGs
- Vital signs
- Pulse oximetry
- Spirometry

7 STUDY DESIGN

7.1 Overall Design

This is a Phase 3, randomized, double-blind, ivacaftor-controlled, parallel-group, multicenter study in subjects aged 12 years and older with CF who are heterozygous for the *F508del-CFTR* mutation and a second *CFTR* allele with a gating defect that is clinically demonstrated to be ivacaftor responsive (Section 8 of protocol; Appendix A).

This study is designed to compare active treatment of VX-661 (100 mg daily [qd]) and ivacaftor (150 mg every 12 hours [q12h]) combination therapy with ivacaftor monotherapy (150 mg q12h).

The treatment regimens will be as follows:

- VX-661/ivacaftor combination therapy

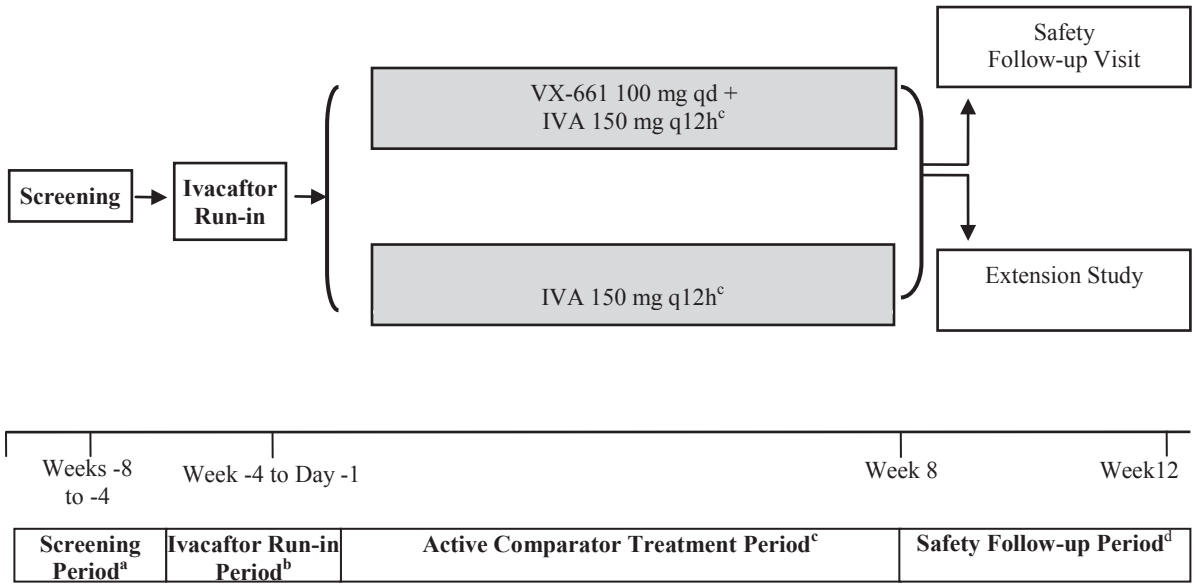
  - Morning dose: 1 tablet of fixed-dose combination of VX-661 100 mg/ivacaftor 150 mg and 1 tablet of placebo visually matched to ivacaftor
  - Evening dose: 1 tablet of ivacaftor 150 mg
- Ivacaftor monotherapy
  - Morning dose: 1 tablet of placebo visually matched to the fixed-dose combination tablet and 1 tablet of ivacaftor 150 mg
  - Evening dose: 1 tablet of ivacaftor 150 mg

This study includes a Screening Period (approximately 28 days), an Ivacaftor Run-in Period (approximately 4 weeks), an Active Comparator Treatment Period (up to 8 weeks), and a Safety Follow-up Visit (approximately 28 days after last dose). Following the Ivacaftor Run-in Period, approximately 160 subjects will be randomized in a ratio of 1:1 to receive either VX-661/ivacaftor combination therapy or ivacaftor monotherapy for 8 weeks during the Active Comparator Treatment Period. The randomization will be stratified by age at the Screening Visit (<18 versus ≥18 years of age), type of mutation on the second *CFTR* allele (*R117H* versus other allowed mutations; Appendix A), and percent predicted FEV_1 severity determined at the end of the Ivacaftor Run-in Period (<70 versus ≥70; see Figure 7-1). Of the randomized subjects, approximately 15% will carry an *R117H* mutation on the second *CFTR* allele. Week 8 is the conclusion of the Active Comparator Treatment Period of the study.

Subjects who complete the Week 8 Visit, regardless of whether they have prematurely discontinued study drug treatment, will be offered the opportunity to enroll in an extension study, if they meet the eligibility criteria.

All subjects randomized in the Active Comparator Treatment Period will be required to complete study assessments for all scheduled visits through Week 8, regardless of whether they have prematurely discontinued study treatment (Section 8 of protocol).

Figure 7-1 Schematic View of the Study Design



FEV_1: forced expiratory volume in 1 second; IVA: ivacaftor; q12h: every 12 hours; qd: once daily.

[a] Approximately 200 subjects will be stratified by age at the Screening Visit (<18 versus ≥18 years of age), type of mutation on the second *CFTR* allele (*R117H* versus all other allowed mutations), and percent predicted FEV_1 severity determined at the end of the Ivacaftor Run-in Period (<70 versus ≥70) and will be randomized (1:1) before the first dose of study drug at Day 1.

[b] The Ivacaftor Run-in Period has a total duration of approximately 4 weeks and is designed to establish a reliable on-treatment (ivacaftor monotherapy) baseline.

[c] Subjects will receive the same number of tablets each day to maintain the blind during the Active Comparator Treatment Period. Subjects in the VX-661/Ivacaftor Arm will receive 100 mg VX-661 + 150 mg ivacaftor (fixed-dose combination tablet) and a placebo tablet (visually matched to the IVA 150 mg tablet) for the morning dose, and an IVA 150 mg tablet for the evening dose. Subjects in the Ivacaftor Monotherapy Arm will receive placebo tablet (visually matched to the VX-661 100 mg + ivacaftor 150 mg fixed-dose combination tablet) and 150 mg ivacaftor for the morning dose, and 150 mg ivacaftor for the evening dose.

[d] The Safety Follow-up Visit is scheduled to occur 28 (± 7) days after the last dose of study drug. The Safety Follow-up Visit is not required for subjects who complete the Week 8 Visit and have enrolled in the extension study of VX-661 in combination with ivacaftor within 28 days after the last dose of study drug.

7.2 Sample Size and Power

The primary efficacy endpoint is the absolute change in percent predicted FEV_1 from baseline through Week 8 in the Active Comparator Treatment Period.

The null hypothesis to be tested is that the mean absolute change in percent predicted FEV_1 from baseline through Week 8 in the Active Comparator Treatment Period is the same for the VX-661/ivacaftor combination therapy and the ivacaftor monotherapy. Assuming a common standard deviation (SD) of 7 percentage points and a 10% dropout rate, a sample size of 160 subjects will have at least 80% power to detect a treatment difference of 3.4 percentage points between treatment arms in absolute change in percent predicted FEV_1 at a 2-sided 0.05 significance level. A *P* value of 0.05 or less will be interpreted as sufficient evidence to

reject the null hypothesis. The assumption of the main treatment effect of VX-661/ivacaftor combination therapy over ivacaftor monotherapy and a 7 percentage point SD is based on the results from the Phase 2 Study 101, Group 7.

With 160 subjects and assuming 10% lost to follow-up, the study has limited power to detect a treatment effect in CFQ-R respiratory domain score, i.e., a power of 32% to detect a treatment effect (SD) of 4 (16) in absolute change in CFQ-R respiratory domain score. The assumptions regarding the treatment effect of VX-661/ivacaftor combination therapy over the ivacaftor monotherapy and the SD are all based on the within-group treatment effects observed in the Phase 2 Study 101, Group 7.

[redacted]

7.3 Randomization

Following the Ivacaftor Run-in Period, approximately 160 subjects will be randomized in a ratio of 1:1 to receive either VX-661/ivacaftor combination therapy or ivacaftor monotherapy for 8 weeks during the Active Comparator Treatment Period. The randomization will be stratified by age at the Screening Visit (<18 versus ≥18 years of age), type of mutation on the second *CFTR* allele (*R117H* versus other allowed mutations; Appendix A), and percent predicted FEV_1 severity determined at the end of the Ivacaftor Run-in Period (<70 versus ≥70; see Figure 7-1). Of the randomized subjects, approximately 15% will carry an *R117H* mutation on the second *CFTR* allele (Section 8 of protocol).

An interactive web response system (IWRS) will be used to assign subjects to study treatment using a list of randomization codes generated by a designated vendor [redacted], as well as to ensure randomization of approximately 15% of subjects with an *R117H* mutation on the second *CFTR* allele. The Study Biostatistician will be involved in developing the randomization specifications and reviewing the dummy randomization lists, and will remain blinded to the final live unblinded randomization lists and the actual treatment assignments.

The detailed randomization procedure was provided in Appendix B.

7.4 Blinding and Unblinding

This is a double-blind study.

7.4.1 Blinding

The subjects and all site personnel, including the investigator, the site monitor, and the study team, will be blinded 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 their fetus in the event of a pregnancy
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy SAE processing and reporting regulations

- Unblinded statistician preparing the final (production) randomization list who is not part of the study team
- Vertex Clinical Operations IWRS management
- Vertex Clinical Supply Chain
- IDMC
- Vendor preparing the unblinded analysis for the IDMC
- Vendor analyzing PK samples
- Vertex personnel or vendor conducting the population PK analysis
- Vertex 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 Data Blinding

Despite treatment blinding, knowledge of the spirometry results has the potential to suggest whether a subject has been administered active study drug or corresponding active control. Therefore, during the conduct of the study, the Vertex study team will not have access to the postdose spirometry data during the Active Comparator Treatment Period. The vendor for central reading of the spirometry data will only send the blinded spirometry files (blinded treatment group with dummy values for all the spirometry assessment after baseline in the Active Comparator Treatment Period) to Vertex to be used for developing the statistical programs. Furthermore, subjects and their caregivers should not be informed of their study-related spirometry results during the Active Comparator Treatment Period regardless of whether the subject has prematurely discontinued treatment.

Sweat Chloride Data Blinding

Despite treatment blinding, knowledge of the sweat chloride data has the potential to suggest whether a subject has been administered active study treatment or corresponding active control. Therefore, during the conduct of the study, the Vertex study team will not have access to the postdose sweat chloride data; dummy data will be used to develop statistical programs. During the process of locking the clinical database and after all study visits have been completed, treatment-blinded access to the sweat chloride data will be provided to a small group of individuals who are not involved in the study. This group, which will consist of a biostatistician, a statistical programmer, a validation statistical programmer, and a clinical reviewer, will review the sweat chloride data to ensure there are no significant data issues and will use the blinded data set to refine the statistical programs.

7.4.2 Unblinding

At the initiation of the study, the study sites 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 should 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 that it is 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 should 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 Vertex medical monitor or appropriate backup.

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the Vertex medical monitor should be notified within 24 hours of the unblinding event. The reason and the date of the unblinding should 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 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.

8 ANALYSIS SETS

The following analysis sets will be defined in this study: All Subjects Set, Safety Set in the Ivacaftor Run-in Period, Active Comparator Subjects Set, Full Analysis Set (FAS) in the Active Comparator Treatment Period, and Safety Set in the Active Comparator Treatment Period.

The study has two scheduled dosing period:
Ivacaftor Run-in Period starts from the first dose date of open-label ivacaftor monotherapy and ends prior to randomization.
Active Comparator Treatment Period starts after the randomization to either VX-661/Ivacaftor combination therapy or ivacaftor monotherapy and runs from the first dose date of the randomized study drug during the Active Comparator Treatment Period, to the scheduled last dose at the Week 8 visit.

8.1 All Subjects Set

The **All Subjects Set** is defined as all subjects who were enrolled in either the Ivacaftor Run-in Period or the Active Comparator Treatment Period (i.e., all subjects in the study). This analysis set will be used for all individual subject data listings and for the disposition summary table, unless specified otherwise.

The **Active Comparator Subjects Set** includes all subjects randomized or who received at least 1 dose of study drug in the Active Comparator Treatment Period. This analysis set will be used for specific disposition for the Active Comparator Treatment Period and subject listings related to the Active Comparator Treatment Period only.

8.2 Full Analysis Set

The **Full Analysis Set (FAS)** is defined as all randomized subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug during the Active Comparator Treatment Period after randomization. Efficacy analyses will be performed in the FAS in the Active Comparator Treatment Period in which subjects will be analyzed according to their randomized treatment group.

8.3 Safety Set

The **Safety Set**, defined separately for the **Ivacaftor Run-in Period** and the **Active Comparator Treatment Period**, includes all subjects who received at least 1 dose of study drug in the corresponding treatment period. The safety analyses will be performed separately for the Ivacaftor Run-in Period and the Active Comparator Treatment Period; subjects will be analyzed according to the treatment they received.

For the safety analysis, the following analyses period will be defined as below:

- The **pre-treatment period (Ivacaftor Run-in Period only)** is defined as the period after the informed consent/assent date and before the initial dosing of study drug in the Ivacaftor Run-in Period.
- The **Treatment-emergent (TE) Period** will be defined separately for the Ivacaftor Run-in Period and the Active Comparator Treatment Period:
    - The TE Period for the Ivacaftor Run-in Period is defined as the date of the first dose in the Ivacaftor Run-in Period to 1) the last day prior to the first dose of the Active Comparator Treatment Period or 2) either the Safety Follow-up Visit or 28 days (inclusive) after the last dose, whichever is earlier, for subjects who discontinue treatment during the Ivacaftor Run-in Period and are not randomized in the Active Comparator Treatment Period.
    - The TE Period for the Active Comparator Treatment Period is defined as the first dose of the Active Comparator Treatment Period to the Safety Follow-up Visit or 28 days (inclusive) after the last dose, whichever is earlier, in the Active Comparator Treatment Period.

9 STATISTICAL ANALYSIS

9.1 General Considerations

The Schedule of Assessments is provided in Appendix C. 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 subjects who were randomized or recived at least 1 dose of study drug, i.e., All Subjects Set, will be presented in data listings, with indicator of dosing period, i.e., Ivacaftor Run-in Period vs. Active Comparator Treatment Period, as applicable. Listings related to Active Comparator Treatment Period only will be based on the Active Comparator Subjects Set.

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

Categorical variables will be summarized using counts and percentages.

Baseline value, Absolute change from baseline and Relative change from baseline will be defined separately for the Ivacaftor Run-in Period and the Active Comparator Treatment Period:

Baseline value:

- Unless specified otherwise, baseline for the Ivacaftor Run-in Period will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to initial administration of Ivacaftor monotherapy.
- Unless specified otherwise, the baseline for the Active Comparator Treatment Period will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to initial administration of the VX-661/ivacaftor combination therapy or ivacaftor monotherapy (placebo/ivacaftor) during the Active Comparator Treatment Period, but no earlier than the measurement at Week -2.
- For spirometry, the baseline value used for the Active Comparator Treatment Period will be the average of the measurement at Week -2 and the measurement on Day 1 predose. If a subject has an AE leading to an approved extension of the Ivacaftor Run-in Period, and the Week -2 spirometry assessment is between the start and end date (inclusive) of the AE, then the measurement on Day 1 predose will serve as baseline for the Active Comparator Treatment Period.
- For ECG, the baseline will be defined as the average of the non-missing pretreatment measurements (triplicate) on Day 1 (the first day) of the corresponding treatment period.

- For sweat chloride, the baseline value will be the mean of the last values on the left and the right arm prior to the first dose of the study drug of the corresponding treatment period.

Note that references to baseline hereafter should always be interpreted in the context of the corresponding treatment period.

Change (absolute change) from baseline will be calculated as Post-baseline value − Baseline value.

Relative change from baseline will be calculated and expressed in percentage as 100% × (Post-baseline value − Baseline value)/Baseline value.

Treatment-emergent (TE) Period
There are two treatment periods in this study as defined in Section 8.3. The TE periods will be used for safety analyses unless specified otherwise.

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/last on-treatment measurements.
- In the derivation of maximum/minimum on-treatment values and maximum/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 C. The windows will be applied using the following rules for both scheduled and unscheduled visits:

1. If no measurement is available within a visit window, the assessment will be considered missing for the visit;
2. If there is more than one measurement available within the same visit window, use the following rules:

- For all efficacy parameters, if there are multiple measurements within a visit window, the record at the scheduled visit will be used. Otherwise,
    - The record closest to the target day will be used;
    - If there are multiple records with the same distance to the target day, the latest record will be used.
    - Assessments at early treatment termination (ETT) visit will follow the windowing rules for regular visits up to Week 8.
    - Assessments at safety follow-up (SFU) visit will follow the windowing rules for regular visits if they fall within the upper boundary of the window for

Week 8, or remain as SFU if they go beyond the upper boundary of the window for Week 8.

- For all safety parameters, if there are multiple measurements within a visit window, then 1) the record closest to the target day will be used; 2) if there are multiple records within the same distance from the target day, the latest record will be used; or 3) SFU visit will not be windowed; instead, it will be used according to the nominal visit in relevant analyses.

Note, spirometry assessments, BMI, weight, and height will be used for both efficacy and safety purposes. Their measurements will follow the visit windowing rules for efficacy parameters.

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: A hierarchical testing procedure will be used to control the Type I error at two-sided $\alpha = 0.05$ among the primary and the key secondary endpoints. The testing hierarchy is as follows:

1. Absolute change in percent predicted FEV_1 from baseline through Week 8
2. Relative change in percent predicted FEV_1 from baseline through Week 8
3. Absolute change in CFQ-R respiratory domain score from baseline through Week 8

9.2 Background Characteristics

9.2.1 Subject Disposition

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

- All Subjects Set (Number only)

Ivacaftor Run-in Period:

- Dosed (Safety Set) in the Ivacaftor Run-in Period
- Completed treatment in the Ivacaftor Run-in Period
- Prematurely discontinued treatment during the Ivacaftor Run-in period and the reasons for treatment discontinuation

Active Comparator Treatment Period:

- Randomized in the Active Comparator Treatment Period (Number only)

- Dosed in the Active Comparator Treatment Period (Number only)
- FAS (randomized, dosed, and with the intended CFTR allele mutation in the Active Comparator Treatment Period; Number only)
- Completed treatment in the Active Comparator Treatment Period
- Prematurely discontinued treatment during the Active Comparator Treatment Period and the reasons for treatment discontinuation
- Completed the study or the Safety Follow-up Visit
- Prematurely discontinued the study, and the reasons for discontinuation, by the following subcategories:
  - Discontinued the study during the Active Comparator Treatment Period
  - Discontinued the study after the Active Comparator Treatment Period
- Last scheduled visit completed for everyone in FAS

For categories related to the Ivacaftor Run-in Period, the number and percentage of subjects in each disposition category will be summarized, with the number in the safety set in the Ivacaftor Run-in Period as the denominator, together with the number of subjects enrolled but never dosed. A listing will be provided for subjects who discontinued treatment during the Ivacaftor Run-in Period or who discontinued the study during the Ivacaftor Run-in Period with the reasons for discontinuation.

The number and percentage of enrolled subjects in the Ivacaftor Run-in Period will be summarized overall using the number of subjects in the All Subjects Set as the denominator. An enrollment listing will be provided, with subjects enrolled ordered by the enrollment date.

For the categories related to the Active Comparator Treatment Period, the number and percentage of subjects in each disposition category will be summarized, with the number of subjects in the FAS as the denominator, except as noted above.

The number and percentage of randomized subjects in the Active Comparator Treatment Period will be summarized by stratification factors, and by country and by site, using the Active Comparator Subjects Set. A randomization listing will be provided with subjects ordered by randomization date.

A listing will be provided for subjects who discontinued treatment during the Active Comparator Treatment Period or who discontinued study during the Active Comparator Treatment period with the reasons for discontinuation.

9.2.2 Demographics and Baseline Characteristics

Demographics, medical history and baseline characteristics will be summarized overall based on the Safety Set in the Ivacaftor Run-in Period and on the FAS by randomized treatment group in the Active Comparactor Treatment Period.

Demographic data will include the following:

- Age (in years)

- Age groups at the Screening visit (<18 versus ≥18 years of age)
- Sex
- 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)
- Geographic region (North America, Europe, Australia)

Baseline characteristics will include the following:

- Type of mutation in the second *CFTR* allele (R117H, Others)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Weight z-score (subjects <20 years old)
- Height z-score (subjects <20 years old)
- BMI z-score (subjects <20 years old)
- type of mutation on the second *CFTR* allele (*R117H* versus other allowed mutations)

Disease characteristics will include the following:

- Percent predicted FEV_1 at screening (<70, ≥70; for Ivacaftor Run-in Period)
- Percent predicted FEV1 at baseline (<40, ≥40 to <70, ≥70 to ≤90, >90; for Active Comparator Treatment Period)
- Percent predicted FEV_1 at baseline
- FEV_1 (L)
- FVC (L)
- Percent predicted FVC
- $FEF_{25-75\%}$ (L/sec)
- Percent predicted $FEF_{25-75\%}$
- FEV_1/FVC
- Sweat Chloride
- CFQ-R respiratory domain
- Received dornase alfa before first dose of study drug (Yes, No)
- Received any inhaled antibiotic before first dose of study drug (Yes, No)
- Received any bronchodilator before first dose of study drug (Yes, No)

Note: On the bronchodilator page, only those coded as bronchodilator will be included.

- Received any inhaled bronchodilator before first dose of study drug (Yes, No)

Note: On the bronchodilator page, only those coded as bronchodilator will be included.

- Received any inhaled hypertonic saline before first dose of study drug (Yes, No)
- Received any inhaled corticosteroids before first dose of study drug (Yes, No)
- Colonization of *Pseudomonas aeruginosa* status before the Ivacaftor Run-in Period (Positive, Negative)

Subjects with exclusionary liver function test results at screening could be retested once within 14 days and were considered eligible if these repeated results met eligibility criteria. Two summaries will be provided: one for the initial liver function testing test only; and one based on the retesting results (if available).

9.2.3 Medical History

Medical history will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized descriptively using the FAS population. Medical history will be summarized descriptively by system organ class (SOC) and preferred term (PT). In addition, the number of subjects reported to have had positive cultures for respiratory pathogens in the 2 years prior to screening (i.e., answered yes on the respiratory microbiology form) will be summarized by test and subcategories within the test. Hospitalization and clinic visit history in the past year will be listed.

9.2.4 Prior and Concomitant Medications

Medication use will be coded using the World Health Organization-Drug Dictionary Enhanced and categorized as:

- **Prior medication:** any medication that started before initial dosing of study drug in the Ivacaftor Run-in Period, regardless of when it ended.
- **Concomitant medication during the Ivacaftor Run-in Period**: medication that continued or that started at or after the first dose of study drug through the end of the TE Period for the Ivacaftor Run-in Period.
- **Concomitant medication during the Active Comparator Treatment Period:** medication that continued or that started at or after the first dose of study drug through the end of the TE Period of the Active Comparator Treatment Period.
- **Post-treatment medication:** medication that continued or that started after the end of the TE Period of the Active Comparator Treatment Period.

A given medication can be classified as a prior medication, a concomitant medication (concomitant medication during the Ivacaftor Run-in Period and/or a concomitant medication during the Active Comparator Treatment Period), or a post-treatment medication; both prior and concomitant; both concomitant and post-treatment; or prior, concomitant, and posttreatment. If a medication has a missing or partially missing start/end date or time and it

cannot be determined whether it was taken before initial dosing, concomitantly, or beyond the TE Period, it will be considered as prior, concomitant, and post-treatment.
Prior medications and concomitant medications in the Ivacaftor Run-in Period will be summarized descriptively based on the Safety Set in that period.

Prior medications and concomitant medication in the Ivacaftor Run-in Period also will be summarized descriptively based on the FAS for the Active Comparator Treatment Period. Concomitant medications in the Active Comparator Treatment Period also will be summarized descriptively based on the FAS.

Post-treatment medications will be listed for each subject.

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

9.2.5 Study Drug Exposure

Duration of study drug exposure (in days) will be calculated as: last dose date – first dose date + 1 day, regardless of study drug interruption.

Exposure will be summaried separated for the Ivacaftor Run-in Period and the Active Comparator Treatment Period based on the corresponding safety set.

9.2.6 Study Drug Compliance

Study drug compliance based on study drug exposure will be calculated as: $100 \times [1 - (\text{total number of days of any study drug interruption}) / (\text{duration of study drug exposure in days})]$.

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

Study drug compliance will be summarized for the Ivacaftor Run-in Period based on the Ivacaftor Run-in Period Safety Set, and for the Active Comparator Treatment period based on the FAS.

9.2.7 Important Protocol Deviations

Important protocol deviations (IPD) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/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:

- Violation of subjects rights, safety or well-being
- Subject entered the study despite violation of any inclusion or exclusion criteria
- Subject was less than 80% compliant with study medications
- Subject received excluded concomitant medications

- Subject received the wrong treatment or incorrect doses
- Subject remained in study despite meeting withdrawal criteria

Occurrence of any of these events should be considered as potential IPDs, but the blinded team should categorize them as IPDs only if they have the potential to affect interpretation of study results.

IPDs (from the clinical database or from the site deviation log) will be summarized descriptively and presented in an individual subject data listing.

9.3 Efficacy Analysis

All efficacy analyses described in this section will be based on the FAS during the Active Comparator Treatment Period, unless specified otherwise. The analysis will include all available measurements through the last assessment, including measurements after treatment discontinuation, per the visit windowing rules described in Appendix D.

Summary statistics may be provided for efficacy endpoints during the Ivacaftor Run-in Period.

9.3.1 Analysis of Primary Efficacy Endpoint(s)

9.3.1.1 Definition

The primary efficacy endpoint is the average absolute change from baseline in percent predicted FEV_1 (with a unit of percentage points) through Week 8 in the Active Comparator Treatment Period.

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 Hankinson[1] and Wang[2] standards with details in Appendix F.

9.3.1.2 Summary in Ivacaftor Run-in Period

Percent predicted FEV_1, both the raw values and their absolute change from baseline, will be summarized by visit for the Ivacaftor Run-in Period (Week -4, Week -2 and Day 1 predose).

9.3.1.3 Primary Analysis

The primary analysis for the primary efficacy endpoint will be based on a mixed model for repeated measures (MMRM) using SAS PROC MIXED in the FAS for the Active comparator Treatment Period. The null hypothesis to be tested is that the average absolute change from baseline in percent predicted FEV_1 through Week 8 is the same for the two treatment arms. The MMRM will be used to test the difference between treatment groups. A *P* value of 0.05 or less will be interpreted as sufficient evidence to reject the null hypothesis.

The model will include absolute change from baseline in percent predicted FEV_1 (including all measurements up to Week 8 [inclusive], both on-treatment measurements and measurements after treatment discontinuation) as the dependent variable, treatment, visit (as a class variable), and treatment-by-visit interaction as fixed effects, with adjustment for age

group at screening (<18 versus ≥18 years of age), type of mutation on the second *CFTR* allele (*R117H* versus Others), and baseline percent predicted FEV_1 value for the Active Comparator Treatment Period as fixed effects, and subject as a random effect. An unconstructed covaraiance structure will be used to model the within-subject errors.

A Kenward-Roger approximation will be used for the denominator degrees of freedom. If there is a convergence problem due to the unstructured covariance matrix, a compound symmetry covariance structure will be used to model the within-subject errors. No imputation of missing data will be done.

The primary result obtained from the model will be the average treatment effect through Week 8 in the Active Comparator Treatment Period. A contrast based on the fixed effects in the model will be used to estimate the average treatment effect across post-baseline visits through Week 8. The contrast will be constructed 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 Week 8.

Descriptive summary statistics, including number of subjects, mean, standard deviation (SD), and LS means, standard error (SE), and 2-sided 95% confidence interval, along with the *P* value will be provided. In particular, the difference in LS means, SE, and the corresponding 2-sided 95% CI will be provided along with the *P* value to assess the average treatment difference between VX-661/ivacaftor combination therapy and Ivacaftor monotherapy through Week 8 in the Active Comparator Treatment Period. Additionally, the *P* value testing the treatment-by-visit interaction will be provided to assess the consistency of treatment effects across different visits.

In addition, the average raw values and average absolute change from baseline in percent predicted FEV_1 through Week 8 (Weeks 2, 4, and 8) will be summarized descriptively (number, mean, SD, SE, median, min, and max). In the raw value summaries, the average raw values through Week 8 will be derived as the arithmetic mean of the available postbaseline measurements at each visit. The average absolute change from baseline in percent predicted FEV_1 through Week 8 will be derived as the arithmetic mean of the absolute change from baseline in percent predicted FEV_1 at each available postbaseline visit.

The cumulative distribution plot of the average absolute change from baseline in percent predicted FEV_1 through Week 8 will be plotted by treatment group. Subjects missing absolute change from baseline in percent predicted FEV_1 at all post baseline visit through Week 8 will have missing average absolute change through Week 8 and will not be included in the related summaries or in the plot.

Absolute change from baseline in percent predicted FEV_1 at each visit

Absolute change from baseline in percent predicted FEV_1 at each postbaseline visit (Weeks 2, 4, and 8) during the Active Comparator Treatment Period will be derived from the main model based on the FAS. Descriptive summary statistics, including number of subjects, mean (SD), and LS means (SE), along with the corresponding 2-sided 95% CIs and the *P* values will be provided. In addition, the difference in LS means (SE) between VX-661/ivacaftor combination therapy and Ivacaftor monotherapy and the corresponding 95% CI will be provided. The LS means (95% CI) at each visit will be plotted by treatment groups.

In addition, the raw values and the absolute change from baseline in percent predicted FEV_1 at each postbaseline visit (Weeks 2, 4, and 8), regardless of the treatment status at the visit, will be summarized descriptively (number, mean, SD, SE, median, min, and max).

[redacted]

9.3.2 Analysis of Key Secondary Efficacy Endpoints

9.3.2.1 Definition of Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are as follows:

- Relative change in percent predicted FEV_1 from baseline through Week 8 in the Active Comparator Treatment Period
- Absolute change in Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain score from baseline through Week 8 in the Active Comparator Treatment Period

Relative change in percent predicted FEV_1 from baseline through Week 8 in the Active Comparator Treatment Period

Relative change in percent predicted FEV_1 at each visit will be defined as the absolute change in percent predicted FEV_1 at each visit divided by the baseline percent predicted FEV_1 in the Active Comparator Treatment Period.

Absolute change in CFQ-R respiratory domain from baseline through Week 8 in the Active Comparator Treatment Period

The CFQ-R is a validated CF-specific instrument that measures quality-of-life domains. The details on the CFQ-R forms and the CFQ-R scoring manual are provided in Appendix G.

9.3.2.2 Analysis of Key Secondary Efficacy Endpoints

Relative change in percent predicted FEV_1 from baseline thorough Week 8 in the Active Comparator Treatment Period

A model similar to the MMRM for the primary analysis of the primary efficacy endpoint will be used. Average relative change from baseline in percent predicted FEV_1 through Week 8 and the relative change from baseline in percent predicted FEV_1 at each post-baseline visit (Weeks 2, 4, and 8), including LS means, standard error (SE), and the 2-sided 95% confidence interval along with the *P* value, will also be derived from the MMRM model for the Active Comparator Treatment Period based on the FAS. The LS means (95% CI) at each visit will be plotted by treatment groups.

In addition, average raw values and average relative change from baseline in percent predicted FEV_1 through Week 8, and raw values and relative change from baseline in percent predicted FEV_1 at each visit (Weeks 2, 4, and 8) will be summarized using descriptive summary statistics.

The cumulative distribution plot of average relative change from baseline in percent predicted FEV_1 through Week 8 will be plotted by treatment groups. In addition, a bar chart showing the percentage of subjects by response categories (<-10%, ≥-10% to < -7.5%, ≥-7.5% to <-5%, ≥-5% to <-2.5%, ≥-2.5% to <0%, ≥0% to <2.5%, ≥2.5% to <5%, ≥5% to <7.5%, ≥7.5% to <10%, ≥10%) of average relative change from baseline in percent predicted FEV_1 through Week 8 will be plotted by treatment groups.

Absolute change in CFQ-R respiratory domain from baseline through Week 8 in the Active Comparator Treatment Period

Analysis for the absolute change from baseline in CFQ-R respiratory domain (Pooled 'Children Ages 12 and 13' Version and 'Adolescents and Adults' Version) through Week 8 will be similar to that used for the primary analysis, with the addition of the baseline CFQ-R respiratory domain score as a covariate. The primary result obtained from this model will be the average treatment effect through Week 8.

Absolute change from baseline in CFQ-R respiratory domain at each postbaseline visit (Week 4 and Week 8) will be derived from the same model. The LS means, SE, 95% CI, and P-values at each visit will be provided; LS means (95% CI) will be plotted by treatment

groups. In addition, average raw values and average absolute change from baseline in CFQ-R respiratory domain through Week 8, and raw values and absolute change from baseline in CFQ-R respiratory domain at each postbaseline visit (Week 4 and Week 8) will be summarized using descriptive summary statistics.

9.3.3 Analysis of Secondary Efficacy Endpoints

9.3.3.1 Definition of Secondary Efficacy Endpoints

Absolute change from baseline in sweat chloride from baseline through Week 8 in the Active Comparator Treatment Period

For each subject and at each time point, 2 sweat chloride measurements will be collected: 1 from the right arm, and 1 from left arm. Only the sweat chloride values obtained from a sample volume ≥15 μL will be used in any analysis.

Note: A volume of ≥15 μL is required for an accurate determination of sweat chloride. Any results reported having volume <15 μL or "Quantity Not Sufficient" (QNS) will be considered missing.

The sweat chloride results for the left and right arms will be averaged and used in the analysis provided that the sweat chloride volumes for the left and right arms are both ≥15 μL; if only 1 arm has a volume ≥15 μL, then only that value will be used. If a subject has replicated measurements at a post-baseline time point, then the median of the values will be used in data analyses.

Note any sweat chloride values reported as <10 mmol/L or >160 mmol/L Values > 160 mmol/L or < 10 mmol/L will be set to missing and excluded from the analysis because these values are considered clinically impossible.

9.3.3.2 Analysis of Secondary Efficacy Endpoints

Absolute change from baseline in sweat chloride from baseline through Week 8 in the Active Comparator Treatment Period

A model similar to the MMRM for the primary analysis of the primary efficacy endpoint will be used with the addition of baseline sweat chloride as a covariate. Average absolute change from baseline in sweat chloride through Week 8 and absolute change from baseline in sweat chloride at each post baseline visit (Weeks 4 and 8), including LS means, standard error (SE), and the 2-sided 95% confidence interval along with the *P* value, will be derived from the main model based on the FAS. The LS means (95% CI) at each visit will be plotted by treatment groups.

In addition, average raw values and average absolute change from baseline in sweat chloride through Week 8, and raw values and absolute change from baseline in sweat chloride at each visit (Week 4 and Week 8) will be summarized using descriptive summary statistics.

[redacted]

[redacted]

9.3.6 Multiplicity Adjustment

A hierarchical testing procedure will be used to control the Type I error at two-sided $\alpha = 0.05$ among the primary and key secondary endpoints. For a test at any step to be considered statistically significant within the testing hierarchy, it must be statistically significant, and all previous tests (if any) within the hierarchy must be statistically significant, at the 0.05 level. The testing hierarchy is as follows:

1. Absolute change in percent predicted FEV_1 from baseline through Week 8
2. Relative change in percent predicted FEV_1 from baseline through Week 8
3. Absolute change in CFQ-R respiratory domain score from baseline through Week 8

9.4 Safety Analysis

Safety endpoints will be analyzed separately for the Ivacaftor Run-in Period and the Active Comparator Treatment Period based on the corresponding Safety Set. Only descriptive summaries of safety will be provided (i.e., no statistical testing will be performed).

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

- Adverse events
- Clinical laboratory values (hematology, serum chemistry, coagulation studies, and urinalysis)
- Standard 12-lead electrocardiograms
- Vital signs
- Pulse oximetry

The safety profile will also include the following safety-supporting data

- Weight
- BMI
- Ophthalmological Examination

9.4.1 Adverse Events

For analysis purposes, AEs will be classified as pretreatment AEs, TEAEs during the Ivacaftor Run-in Period, TEAEs during the Active Comparator Treatment Period, or post-treatment AEs, defined as follows:

- **Pretreatment AE:** any AE that started before initial dosing of study drug in the Ivacaftor Run-in Period.
- **TEAEs during the Ivacaftor Run-in Period**: any AE that increased in severity or that was newly developed at or after initial dosing of study drug through the end of the TE Period for the Ivacaftor Run-in Period.
- **TEAEs during the Active Comparator Treatment Period:** any AE that increased in severity or that was newly developed at or after initial dosing of study drug through the end of the TE Period for the Active Comparator Treatment Period.
- **Post-treatment AEs:** any AE that increased in severity or that was newly developed beyond the TE Period.

For AEs with a missing or partial start date, if there is no clear evidence that the AEs started (or increased in severity) before or after the first dose date for the Active Comparator Treatment Period, the AE will be considered to be a TEAE for the Active Comparator Treatment Period (see Section 11.7). If there is clear evidence that the AE started before the first dose date for the Active Comparator Treatment Period, but there is no clear evidence

that the AE started before or after the first dose date for the Ivacaftor Run-in Period, the AE will be considered to be a TEAE for the Ivacaftor Run-in Period. Similarly, if there is no clear evidence that the AEs started (or increased in severity) before or after the start of the post-treatment period, the start date will be imputed to be the earliest possible time in the TEAE period and the AE will be considered to be a TEAE.

Unless otherwise stated, all TEAE summaries will be provided separately for the Ivacaftor Run-in Period and the Active Comparator Treatment Period. Presented percentages will be calculated based on the number of subjects in the Safety Set of the corresponding period.

Based on the reported severity and relationship to study drugs, TEAEs can be categorized as follows:
By relationship to the study drugs, treatment emergent adverse events (TEAEs) will be classified into 4 categories:

- Not related
- Unlikely related
- Possibly related
- Related.

By severity, TEAEs will be classified into 4 categories:

- Mild (Grade 1): Mild level of discomfort and does not interfere with regular activities
- Moderate (Grade 2): Moderate level of discomfort and significantly interferes with regular activities
- Severe (Grade 3): Significant level of discomfort and prevents regular activities
- Life-threatening (Grade 4 and 5): Any adverse drug experience that places the subject, in the view of the investigator, at immediate risk of death.

9.4.1.1 Overiew of TEAEs

An overview of the TEAE profile will be provided for the total number of TEAEs, and with number and percent of subjects including the following categories:

- All TEAEs
- Serious TEAEs
- Grade 3/4 TEAEs
- TEAEs by relationship
- TEAEs by severity
- TEAEs leading to death
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption

  Note that per protocol, ‘Neither the dosage of individual study drugs nor the combination therapy can be altered, but the investigator can interrupt or stop

treatment with all study drugs' (section 10.4 of protocol). In the rare event when there are different actions applied to VX-661 100-mg/IVA 150-mg fixed-dose tablet (FDC) and to IVA 150-mg tablet, TEAEs leading to treatment discontinuation will include TEAEs leading to withdrawn of both FDC and IVA tablets, or either FDC or IVA tablets. TEAEs leading to treatment interruption will include TEAEs leading to drug interruption for both FDC and IVA tablets, or either FDC or IVA tablets.

9.4.1.2 TEAEs by System Organ Class (SOC) and Preferred Term (PT)

Summaries will be presented by MedDRA system organ class (SOC) and preferred term using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once. Only the maximum severity level will be presented in the severity summaries, and the strongest relationship level will be presented in the relationship summaries.

Additonal summary tables may be presented for TEAEs in the Active Comparator Treatment Period only, showing number and percentage of subjects

- Any TEAE by PT
- TEAE with a frequency of ≥5% in any treatment group by PT (Active Comparator Treatment Period)
- TEAE with a frequency of ≥5% in any treatment group by SOC and PT (Active Comparator Treatment Period)
- TEAEs of ≥2% more frequent at the PT level in the VX-661/ivacaftor combination therapy than ivacaftor monotherapy, by PT
- TEAEs of ≥2% more frequent at the PT level in the VX-661/ivacaftor combination therapy than ivacaftor monotherapy, by SOC and PT

9.4.1.3 Respiratory Events and Symptoms

Respiratory symptoms are defined as any TEAEs for the following 3 PTs:

- Chest discomfort
- Dyspnoea
- Respiration abnormal

Respiratory events are defined as any of the afore-mentioned respiratory symptoms, or any TEAEs for the following 4 additional PTs:

- Asthma
- Bronchial hyperreactivity
- Bronchospasm
- Wheezing

A summary of respiratory symptoms and events will be presented by preferred term.

9.4.1.4 Subgroup Analysis

TEAE summaries in the Active Comparator Treatment Period will also be presented by SOC and PT for the following subgroups:

- Age group at screening (<18, and ≥18 years)
- Percent predicted FEV_1 severity at the end of Ivacaftor Run-in Period as a stratification factor per IWRS (<70, and ≥70)
- Region (North America and Others)
- Type of mutation on the second *CFTR* allele (*R117H* versus others)

In addition, a listing containing individual subject adverse event data for TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption, SAEs and all deaths will be provided separately, with a flag indicating the TEAE status for SAEs and deaths.

9.4.1.5 Clinical Laboratory

The analysis of clinical laboratory measurements will be presented separately for the Ivacaftor Run-in Period and by treatment group at each scheduled time point for the Active Comparator Treatment Period based on the corresponding Safety Set.

For treatment-emergent laboratory measurements, the raw values and change from baseline values of the continuous hematology and chemistry results, including coagulation studies will be summarized in SI units by treatment group and visit.

The number and percentage of subjects with at least 1 potentially clinically significant (PCS) laboratory event during the TE period will be summarized overall and by treatment group, including the shift of the PCS event from baseline to postbaseline. The PCS criteria are provided in Appendix I.

For each liver function test (LFT) laboratory test (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT], and total bilirubin), the following additional analyses will be conducted for the Active Comparator Treatment Period:

- A listing of subjects with elevated LFT results during the TE period will be presented. For each subject in the listing, LFT assessments at all time points will be included (scheduled and unscheduled).
- For each of the LFTs, mean values (±SD) will be plotted by visit, and a box plot of the LFT value/ULN will be plotted by visit.
- The incidence of LFTs meeting threshold criteria
- For each of the LFTs, mean values (±SD) will be plotted by visit, and a box plot of the LFT value/ULN will be plotted by visit.
- The incidence of LFTs meeting threshold criteria against the baseline threshold criteria also will be summarized by treatment group, LFT parameters, and visit (only shifts to values worse than baseline will be presented).

- A scatter plot of the maximum ALT value across visits versus the maximum total bilirubin value also will be presented. The ALT and total bilirubin values will be presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3xULN for ALT and a horizontal line corresponding to 2xULN for total bilirubin. A similar graph of maximum AST value versus maximum total bilirubin value will be presented as well.

For the Active Treatment Period, a summary table for the shift from baseline to the value at Week 8 will be presented by treatment group for vitamin levels and lipid panel. A box plot of vitamin levels and lipid panel also will be plotted against visit.
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. Subject with positive preganancy test results will be listed. Abnormal urinalysis results will also be listed in individual subject data listings.

9.4.2 Electrocardiogram

For treatment-emergent ECG measurements, a summary of raw values and change from baseline values for the Active Treatment Period will be provided by treatment group and visit for the following standard 12-lead ECG measurements: RR (ms), HR (bpm), PR (ms), QRS duration (ms), QRS axis (degrees), QT (ms), and QT corrected for HR intervals [QTcF (ms)].

The number and percentage of subjects with at least 1 PCS ECG event during the TE period will be summarized by treatment group and ECG parameters. The PCS criteria are provided in Appendix I.

9.4.3 Vital Signs

The raw values and change from the corresponding treatment period baseline values will be summarized at each scheduled time point during the TE Period based on the corresponding Safety Set in the Ivacaftor Run-in Period and by treatment group in the Active Comparator Treatment Period: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute [bpm]), and respiratory rate (breaths per minute).

9.4.4 Physical Examination

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

9.4.5 Pulse Oximetry

The raw values and change from the corresponding treatment period baseline values will be summarized at each scheduled time point during the TE Period based on the corresponding Safety Set for the Ivacaftor Run-in Period and by treatment groups for the Active Comparator Treatment Period, separately. In addition, the mean value at each visit during the TE Period will be plotted by treatment group for the Active Comparator for the percent of oxygen saturation.

9.4.6 Postdose Spirometry

For the 2-hour and 4-hour postdose spirometry measurements on Day 1 and Day 15, a summary of raw values for percent predicted FEV1 will be provided by treatment group at each time point. The absolute change from the predose value of percent predicted FEV1 on the same day will be provided by treatment group at each time point. In addition, a boxplot by time point will be provided. Within each treatment group, Day 1 and Day 15 values will be presented on the same plot.

The above analyses will be repeated for FEV1.

In addition, the number and percentage of subjects with percent predicted FEV1 decline ≥10, ≥15, and ≥20 percentage points in the absolute change from the predose value will be summarized by treatment group and by assessment day and time.

9.4.7 Ophthalmology Examination

Ophthalmologic findings (cataracts) during the treatment-emergent period will be summarized by treatment group. The numbers and percentages of subjects with a cataract at screening will be presented. The numbers and percentages of subjects with a cataract after the first dose of study drug will be presented.
In addition, ophthalmology examination results will be provided in a data listing for subjects who have developed any cataracts during the treatment-emergent period. Subjects with cataract at screening will also be listed.

10 SUMMARY OF INTERIM AND IDMC ANALYSES

10.1 Interim Analysis

No interim analysis was planned for this study.

10.2 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 conducted regular planned safety reviews of study data as outlined in the IDMC Charter and IDMC Analysis Plan.

11 REFERENCES

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12 LIST OF APPENDICES

Appendix A: SECOND CFTR ALLELE MUTATIONS INCLUDED FOR SUBJECTS WHO ARE HETEROZYGOUS FOR THE F508del-CFTR MUTATION

Per the study eligibility criteria, heterozygous *F508del-CFTR* subjects must have a second *CFTR* allele that encodes a mutation predicted to have residual function. The list below represents acceptable mutations.

CFTR Mutations with a Gating Defect Clinically Proven as Ivacaftor-Responsive

R117H
G178R
S549N
S549R
G551D
G551S
G1244E
S1251N
S1255P
G1349D

Source: CFTR2.org [Internet]. Baltimore (MD): Clinical and functional translation of CFTR. The Clinical and Functional Translation of CFTR (CFTR2), US Cystic Fibrosis Foundation, Johns Hopkins University, the Hospital for Sick Children. Available at: http://www.cftr2.org/. Accessed 15 September 2014

Appendix B : Randomization Procedures

The randomization codes were produced by the designated vendor, [redacted]. In order to protect the study blind and maintain the scientific integrity of the data, no Vertex biostatistician is unblinded to the actual randomization list before database lock. Below is a brief description of the randomization process.

- The study biostatistician created the randomization specification.
- The external designated vendor, [redacted] created the dummy randomization code using the randomization specification.
- The study biostatistician reviewed the dummy randomization code and provided comments to the vendor. After all outstanding issues were resolved the study biostatistician approved the dummy randomization code.
- Upon approval of the dummy randomization, the external designated vendor, [redacted] generated the final randomization list and provided it directly to the Interactive Web Response System (IWRS) vendor, [redacted]

Appendix C: Schedule of Assessments

Table 12-1 and Table 12-2 provide the schedule of assessments during the study from the Screening Period through the Safety Follow-up Visit.

All visits are to be scheduled relative to the Day 1 Visit (first dose of randomized study drug). For example, the Week 8 (± 5 days) Visit would occur after 8 weeks of study drug administration in the Active Comparator Treatment Period has been completed (i.e., Day 57, first day of Week 9).

Table 12-1 Screening Period Assessments – Study VX14-661-109

Event/Assessment	Screening Period (Week -8 Through Week -4)
ICF and assent (when applicable)	X
Demographics	X
Medical history	X
Ophthalmological history	X
CFQ-R[a]	X
[redacted]	
CFTR genotype[b]	X
Height and weight[c]	X
Ophthalmologic examination[d]	X
Complete PE	X
FSH[e]	X
Serum pregnancy test (all females of childbearing potential)[f]	X
Standard digital ECG[g]	X
Vital signs[h]	X
Pulse oximetry[h]	X
Spirometry[i]	X

[a] The CFQ-R, [redacted] must be completed prior to the start of any other assessments scheduled at that visit.

[b] All subjects will be tested for *CFTR* genotype. The results of the confirmatory genotype sample obtained at the Screening Visit must be reviewed before enrollment. In subjects with confirmed *R117H* mutation, linkage to poly-T track polymorphisms will also be determined. Specific instructions will be provided in the Laboratory Manual.

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

[d] An ophthalmologic examination will be conducted on subjects of all ages by an ophthalmologist. The ophthalmologic examination does not need to be repeated if there is documentation of an examination that met the protocol criteria and that was conducted within 3 months before the Screening Period or if there is documentation of bilateral lens removal (Section 11.7.8). Subjects with clinically significant cataracts, lens opacity, Y-suture, or lamellar rings will be excluded from the study.

[e] FSH will be measured for any potentially postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be ≥40 mIU/mL to be considered postmenopausal.

[f] Any female subject who does not meet the criteria for non-childbearing potential is considered to be of childbearing potential and must have a serum pregnancy test.

[g] A standard digital ECG will be performed after the subject has been supine for at least 5 minutes.

[h] Vital signs and pulse oximetry will be collected after the subject has been at rest (seated or supine) for 5 minutes.

[i] Spirometry may be performed pre- or postbronchodilator (Section 11.6.1). Screening spirometry evaluation may be repeated, as specified in Section8.1.1.1.

Table 12-1 Screening Period Assessments – Study VX14-661-109

Sweat chloride[j]	X
Urinalysis	X
Hematology	X
Coagulation	X
Serum chemistry	X
Inclusion/exclusion criteria review	X
Prior and concomitant medications	X
AEs and SAEs	Continuous from signing of ICF and assent (where applicable) through Safety Follow-up Visit[k]

AE: adverse event; CFTR: cystic fibrosis transmembrane conductance regulator; CFQ-R: Cystic Fibrosis Questionnaire-Revised; ECG: electrocardiogram; FSH: follicle-stimulating hormone; ICF: informed consent form; PE: physical examination; [redacted]; SAE: serious adverse event; [redacted].

[j] A sweat chloride test must be performed at the Screening Visit if an eligible sweat chloride value is not available in the subject's medical records and the Screening Visit value is needed to establish eligibility. For subjects using sweat chloride values documented in their medical records to establish eligibility, the sweat chloride test at the Screening Visit is optional.

[k] For enrolled subjects who do not have a Safety Follow-up Visit, AEs and SAEs will be collected through the earliest of the following: 28 days after the last dose of study drug; the ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (Section8.1.5); or prior to the first dose of study drug in the extension study.

Table 12-2 Ivacaftor Run-in Period, Active Comparator Treatment Period, ETT, and Safety Follow-up Visit Assessments – Study VX14-661-109

Event/Assessment[a]	Ivacaftor Run-in Period[b]		Active Comparator Treatment Period				ETT Visit[c]	Safety Follow-up Visit 28 days (± 7 Days) After Last Dose[d]
	Week -4 (Day -28 ± 2 Days)	Week -2 (Day -14) (± 2 Days)	Day 1	Week 2 (Day 15) (± 2 Days)	Week 4 (Day 29) (± 5 Days)	Week 8 (Day 57) (± 5 Days)		
Clinic visit	X	X	X	X	X	X	X	X
Inclusion and exclusion criteria review	X							
[redacted]								
Ophthalmologic examination[g]							X	X
Complete PE[h]	X							

[a] All assessments will be performed before dosing unless noted otherwise. Where repeats of the same assessment are required at a given visit, if study drug is not administered on the day of the visit (i.e., study drug interruption or premature discontinuation of study treatment), only 1 set of assessments will be collected. Subjects who prematurely discontinue study drug treatment in the Active Comparator Treatment Period will continue to complete all other scheduled study visits for assessments of efficacy (spirometry, sweat chloride, and CFQ-R) [redacted] as detailed in Section8.1.5.

[b] Ivacaftor Run-in Period is from Week -4 to Day -1 (1 day prior to the Day 1 Visit).

[c] If the subject prematurely discontinues study treatment, an ETT Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 (± 7) days after their last dose of study drug. 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 (Section 8.1.5).

[d] The Safety Follow-up Visit is not required for subjects who complete the Week 8 Visit and have enrolled in the extension study of VX-661 in combination with ivacaftor within 28 days after the last dose of study drug. For subjects who prematurely discontinue study drug dosing, 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.

[e] All questionnaires must be completed before the start of any other assessments scheduled at that visit. The CFQ-R must be completed first, followed by the [redacted] (Section 11.1). Subjects will need to complete a CFQ-R, [redacted] at the ETT Visit (Section 8.1.5).

[redacted]

Subjects <18 years of age at the Screening Visit who discontinue treatment after receiving at least 1 dose of study drug treatment, and subjects <18 years of age at the Screening Visit who complete study drug treatment but do not enroll in a separate extension study of VX-661/ivacaftor within 28 days after the last dose of study drug will have an ophthalmologic examinations conducted by a licensed ophthalmologist at the ETT Visit or Safety Follow-up Visit. The examination may be completed at either the ETT Visit or Safety Follow-up Visit, but must be completed by the date of the Safety Follow-up Visit. Subjects who have documentation of bilateral lens removal are not required to complete the ophthalmologic examination at the ETT Visit or Safety Follow-up Visit. See Section 11.7.8 for further details on ophthalmologic examinations.

Table 12-2 Ivacaftor Run-in Period, Active Comparator Treatment Period, ETT, and Safety Follow-up Visit Assessments – Study VX14-661-109

Event/Assessment[a]	Ivacaftor Run-in Period[b]		Active Comparator Treatment Period				ETT Visit[c]	Safety Follow-up Visit 28 days (± 7 Days) After Last Dose[d]
	Week -4 (Day -28 ± 2 Days)	Week -2 (Day -14) (± 2 Days)	Day 1	Week 2 (Day 15) (± 2 Days)	Week 4 (Day 29) (± 5 Days)	Week 8 (Day 57) (± 5 Days)		
Pregnancy test[i]	X		X		X	X	X	X
Standard digital ECG[j]	X	X	X	X	X	X	X	X
Vital signs[k]	X	X	X	X	X	X	X	X
Pulse oximetry[k]	X	X	X	X	X	X	X	X
Spirometry[l]	X	X	X	X	X	X	X	X
Sweat chloride[m]	X		X		X	X	X	X
Urinalysis	X		X			X	X	X
Hematology	X		X		X	X	X	X
Coagulation	X		X			X	X	X
Serum chemistry	X[n]	X	X[n]	X	X	X	X	X
Lipid panel[o]			X			X	X	X
Vitamin levels			X			X	X	X

h Symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.

i Pregnancy tests will be performed for all female subjects of childbearing potential. A urine β-hCG test will be performed at the Week -4 (before first dose of study drug), Day 1, and Week 4 Visits. A serum pregnancy test will be performed at the Week 8 Visit, at the ETT, and the Safety Follow-up Visit.

j All standard digital ECGs will be performed before dosing and after the subject has been supine for at least 5 minutes. At the Day 1 and Week 2 Visits, ECGs will be collected before dosing and at 1.5, 3, 4, and 6 hours after the morning dose. The ECG will be performed before the morning dose of study drug at Week -4, Week -2, and Week 4. Single ECGs will be performed at Week 8, ETT, and Safety Follow-up Visits. ECGs collected on Week -4 and Day 1 before dosing will be performed in triplicate. Where repeats of the same assessment are required at a given visit, if study drug is not administered on the day of the visit (i.e., study drug interruption or permanent discontinuation of study drug), only 1 ECG will be collected.

k Vital signs and pulse oximetry will be collected before dosing after the subject has been at rest (seated or supine) for at least 5 minutes.

l At all visits, spirometry will be performed for all subjects pre-bronchodilator and before dosing (Section 11.6.1). On Days 1 and 15, subjects <18 years of age at the Screening Visit will have additional spirometry assessments performed at 2 and 4 hours postdose. If more than 1 spirometry assessment is required at a visit, bronchodilators will be withheld until the last scheduled spirometry assessment is completed.

m The sweat chloride collection on dosing days should occur before the morning dose of the study drugs. At each time point, 2 samples will be collected, 1 from each arm (left and right). Collection of sweat chloride will not overlap with any other study assessments.

n Blood samples will be collected before the first dose of study drug.

o Subjects will require 4 hours of fasting before the blood sample for the lipid panel is obtained.

Table 12-2 Ivacaftor Run-in Period, Active Comparator Treatment Period, ETT, and Safety Follow-up Visit Assessments – Study VX14-661-109

Event/Assessment[a]	Ivacaftor Run-in Period[b]		Active Comparator Treatment Period				ETT Visit[c]	Safety Follow-up Visit 28 days (± 7 Days) After Last Dose[d]
	Week -4 (Day -28 ± 2 Days)	Week -2 (Day -14) (± 2 Days)	Day 1	Week 2 (Day 15) (± 2 Days)	Week 4 (Day 29) (± 5 Days)	Week 8 (Day 57) (± 5 Days)		
PK sampling[p]		X		X			X	X
[redacted]								
Randomization[r]			X					
Meal(s) or snack(s) at site[s]	X	X	X	X	X			
Ivacaftor dosing[t]	X							
Randomized treatment dosing[u]			X	X	X			
Study drug count		X	X	X	X	X	X	
Concomitant medications[v]	X	X	X	X	X	X	X	X
Concomitant treatments and procedures	X	X	X	X	X	X	X	X

[p] PK blood samples will be collected at Week -2 (before the morning dose and at 2 and 6 hours after the morning dose) and Week 2 (before the morning dose and at 3 and 8 hours after the morning dose). If study drug is not administered at the Week -2 Visit or Week 2 Visit (i.e., study drug interruption or permanent discontinuation of study drug), a single PK blood sample will still be collected. At the ETT and the Safety Follow-up Visits (as applicable), a PK blood sample will also be collected.

[redacted]

[r] Randomization must occur after all inclusion and exclusion criteria are met, after the 4 weeks Ivacaftor Run-in Period, and before the first dose of study drug on Day 1 of the Active Comparator Treatment Period. Randomization will be done through IWRS.

[s] Fat-containing food such as a "standard CF" high-fat, high-calorie meal or snack, will be provided at the site to subjects after all predose assessments have been completed.

[t] Subjects will receive ivacaftor 150 mg q12h from the Week -4 Visit through the evening of Day -1 (1 day prior to the Day 1 Visit). The study drug should be administered every 12 hours (± 2 hours) within 30 minutes after starting a meal with fat-containing food such as a "standard CF" high-fat, high-calorie meal or snack. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed.

[u] Subjects will receive randomized study treatment from randomization through the evening of the day before the Week 8 Visit. The study drug should be administered every 12 hours (± 2 hours) within 30 minutes after starting a meal with fat-containing food such as a "standard CF" high-fat, high-calorie meal or snack. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed.

[v] Information on concomitant medications is collected through the Safety Follow-up Visit for all subjects. For subjects who discontinue treatment and are followed for certain efficacy assessments after the ETT Visit (see Section 8.1.5), information on concomitant antibiotic therapy for "sinopulmonary signs/symptoms" are collected through the Week 8 Visit, as described in Section 11.6.4.1.1.

Table 12-2 Ivacaftor Run-in Period, Active Comparator Treatment Period, ETT, and Safety Follow-up Visit Assessments – Study VX14-661-109

Event/Assessment[a]	Ivacaftor Run-in Period[b]		Active Comparator Treatment Period				ETT Visit[c]	Safety Follow-up Visit 28 days (± 7 Days) After Last Dose[d]
	Week -4 (Day -28 ± 2 Days)	Week -2 (Day -14) (± 2 Days)	Day 1	Week 2 (Day 15) (± 2 Days)	Week 4 (Day 29) (± 5 Days)	Week 8 (Day 57) (± 5 Days)		
AEs and SAEs	Continuous from signing of ICF and assent (where applicable) through Safety Follow-up Visit[w]							

AE: adverse event; β-hCG: beta-human chorionic gonadotropin; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire–Revised; ECG: electrocardiogram; ETT: Early Treatment Termination; IWRS: interactive web response system; PE: physical examination; PK: pharmacokinetic; [redacted]; SAE: serious adverse event; [redacted]

[w] For enrolled subjects who do not have a Safety Follow-up Visit, AEs and SAEs will be collected through the earliest of the following: 28 days after the last dose of study drug; the ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (Section8.1.5); or prior to the first dose of study drug in the extension study.

Appendix D: Analysis Visit Window Mapping Rules for Efficacy and Safety Measurements

Table 12-D Visit Window Mapping Rules

Assessments	Visit	Target Study Day	Visit Window (in study days)
•Weight and height •Vital signs •Pulse oximetry •Labs ○Serum Chemistry	Baseline for the Ivacaftor Run-in Period (Week -4)	-28	[screening visit, 1st dose day for the Ivacaftor Run-in Period]
	Week -2	-14	[1 day after 1st dose day for the Ivacaftor Run-in Period, 1 day prior to 1st dose day for the Active Comparator Treatment Period]
	Baseline for the Active Comparator Treatment Period	1	[1, 1]
	Week 2	15	[2, 22]
	Week 4	29	[23, 43]
	Week 8	57	[44, 71]
	ETT	N/A	Follow the individual visit window to be mapped to individual visits
	Safety Follow-up Visit	N/A	Efficacy assessments: follow the individual visit window to be mapped to individual visits if measured before / on Day 71 or remain as SFU if otherwise. Safety assessments: remain as SFU
•Standard 12-lead ECG •Spirometry	Baseline for the Ivacaftor Run-in Period (Week -4)	-28	Nominal, if no nominal [screening visit, 1st dose day for the Ivacaftor Run-in Period]

	Week -2	-14	Nominal, if no nominal [1 day after 1st dose day for the Ivacaftor Run-in Period, 1 day prior to 1st dose day for the Active Comparator Treatment Period]
	Baseline for the Active Comparator Treatment Period	1	Nominal [1, 1]
	Week 2	15	Nominal, if no nominal [2, 22]
	Week 4	29	[23, 43]
	Week 8	57	[44, 71]
	ETT	N/A	Follow the individual visit window to be mapped to individual visits
	Safety Follow-up Visit	N/A	Efficacy assessments: follow the individual visit window to be mapped to individual visits if measured before / on Day 71 or remain as SFU if otherwise. Safety assessments: remain as SFU
•CFQ-R [redacted]	Baseline for the Ivacaftor Run-in Period (Week -4)	-28	[screening visit, 1st dose day for the Ivacaftor Run-in Period]
	Week -2	-14	[1 day after 1st dose day for the Ivacaftor Run-in Period, 1 day prior to 1st dose day for the Active Comparator Treatment Period]
	Baseline for the Active Comparator Treatment Period	1	[1, 1]
	Week 4	29	[2, 43]
	Week 8	57	[44, 71]
	ETT	N/A	Follow the individual visit window to be mapped to individual visits

	Safety Follow-up Visit [redacted]	N/A	Efficacy assessments: follow the individual visit window to be mapped to individual visits if measured before / on Day 71 or remain as SFU if otherwise. Safety assessments: remain as SFU
•CFQ-R [redacted]	Baseline for the Ivacaftor Run-in Period (Week -4)	-28	[screening visit, 1st dose day for the Ivacaftor Run-in Period]
	Week -2	-14	[1 day after 1st dose day for the Ivacaftor Run-in Period, 1 day prior to 1st dose day for the Active Comparator Treatment Period]
	Baseline for the Active Comparator Treatment Period	1	[1, 1]
	Week 4	29	[2, 43]
	Week 8	57	[44, 71]
	ETT	N/A	Follow the individual visit window to be mapped to individual visits
	Safety Follow-up Visit [redacted]	N/A	Efficacy assessments: follow the individual visit window to be mapped to individual visits if measured before / on Day 71 or remain as SFU if otherwise. Safety assessments: remain as SFU
•Sweat chloride •Hematology [redacted]	Baseline for the Ivacaftor Run-in Period (Week -4)	-28	[screening visit, 1st dose day for the Ivacaftor Run-in Period]
	Baseline for the Active Comparator Treatment Period	1	[1 day after 1st dose day for the Ivacaftor Run-in Period, 1]
	Week 4	29	[2, 43]
	Week 8	57	[44, 71]

	ETT	N/A	Follow the individual visit window to be mapped to individual visits
	Safety Follow-up Visit [redacted]	N/A	Efficacy assessments: follow the individual visit window to be mapped to individual visits if measured before / on Day 71 or remain as SFU if otherwise. Safety assessments: remain as SFU
•Urinalysis •Coagulation	Baseline for the Ivacaftor Run-in Period (Week -4)	-28	[screening visit, 1st dose day for the Ivacaftor Run-in Period]
	Baseline for the Active Comparator Treatment Period	1	[1 day after 1st dose day for the Ivacaftor Run-in Period, 1]
	Week 8	57	[2, 71]
	ETT	N/A	Follow the individual visit window to be mapped to individual visits
	Safety Follow-up Visit	N/A	Efficacy assessments: follow the individual visit window to be mapped to individual visits if measured before / on Day 71 or remain as SFU if otherwise. Safety assessments: remain as SFU
•Lipid panel	Baseline for the Active Comparator Treatment Period	1	[1, 1]
	Week 8	57	[2, 71]
	ETT	N/A	Follow the individual visit window to be mapped to individual visits
	Safety Follow-up Visit	N/A	Safety assessments: remain as SFU

Note:

1. To apply the above visit windows, please first determine the baseline measurements based on the first dose for the Active Comparator Treatment Period and then label Day 1 for the date of the first dose for the Active Comparator Treatment Period. Day 1 will be used to indicate the 1st dose date for the Active Comparator Treatment Period.

2. After baseline for the Active Comparator Treatment Period, please find the first dose for the Ivacaftor Run-in Period and determine the baseline measurements for the Ivacaftor Run-in Period (last non-missing value before the 1st dose of Ivacaftor Run-in Period).

3. Use the nominal visit names to label SFU (for safety).

4. After baseline, and SFU (for safety) measurements are determined; the above visit windows will be applied to determine the analysis visit names for all remaining measures at scheduled or unscheduled visits.

5. If there is no scheduled Day 1 post dose visit, any assessments on Day 1 after the first dose will be considered for the window of next visit.

6. For spirometry and ECG, nominal visit will be used, only when nomial visit is not available, visit windowing rule shall be applied. Instead, nominal visit will be used.

7. For all efficacy parameters, if there are multiple measurements within a visit window, the record at the scheduled visit will be used.

   - If there are no measurements at the scheduled visit, then the record closest to the target day will be used;
   - If there are multiple records with the same distance to the target day, the latest record will be used.

8. For all safety parameters, if there are multiple measurements within a visit window, then 1) the record closest to the target day will be used; or 2) if there are multiple records within the same distance from the target day, the latest record will be used.

9. FEV_1, BMI, Weight and Height are following the efficacy windowing rules.

<u>Special handling for ECG:</u>

- On Day 1 and Week 2, ECGs will be collected before dosing and at 1.5, 3, 4, and 6 hours after the morning dose. None of the measures on Day 1 or Week 2 will be mapped into other visits.
  - Day 1 post-dose and Week 2 pre-/post-dose measurements will be analyzed based on nominal visit names.
  - On Week -4 and Day 1, the pre-dose measurements will be collected as triplets, the average of the triplicate will be used as pre-dose measurement on Week -4 and Day 1 respectively. Only pre-dose measurement with nominal visit names related to the triplets shall be used in this average.
- For other post-dose visits, the visit window in the above table will apply.

Appendix E: 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.
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 summary, the prior, concomitant or post categorization of a medication is described below.

Table 12-E Prior, Concomitant, and Post Categorization of a Medication

	Medication Stop Date			
Medication Start Date	**< First Dose Date of Study Drug in Ivacaftor Run-in**	**≥ First Dose Date and ≤ End Date of Ivacaftor Run-in TE**	**≥ First Dose Date and ≤ End Date of Active Comparator**	**> End Date of Active Comparator TE Period**

	Period	**Period**	**TE Period**	
< First dose date of study drug in Ivacaftor Run-in Period	P	$PC_{IVA\ Run\text{-}in}$	$PC_{IVA\ Run\text{-}in}\ C_{AC}$	$PC_{IVA\ Run\text{-}in}\ C_{AC}\ A$
≥ First dose date and ≤ End date of Ivacaftor Run-in TE period	-	$C_{IVA\ Run\text{-}in}$	$C_{IVA\ Run\text{-}in}C_{AC}$	$C_{IVA\ Run\text{-}in}C_{AC}\ A$
≥ First dose date and ≤ End date of Active Comparator TE period	-	-	C_{AC}	$C_{AC}\ A$
> End date of Active Comparator TE period	-	-		A

A: Post; $C_{IVA\ Run\text{-}in}$: Concomitant for Ivacaftor Run-in Period; C_{AC}: Concomitant for Active Comparator Treatment Period; P: Prior

Appendix F: Coefficients for Hankinson and Wang Methods for Calculating Predicted Spirometry Parameters

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 (L) will be calculated using the Hankinson[1] and Wang[2] standards.

The Hankinson standard will be applied to male subjects 18 years and older and female subjects 16 years and older; the Wang standard will be applied to male subjects 6 to 17 years and female subjects 6 to 15 years of age. During the study, the subjects who have a birthday that would move them from Wang to Hankinson will use the Wang standard before that birthday and the Hankinson standard at or after that birthday.

Hankinson Normal Values (HNVs) will be calculated for FEV_1, forced vital capacity (FVC), forced expiratory flow mid expiratory phase ($FEF_{25-75\%}$), and FEV_1/FVC% using the Hankinson equation:

$$\text{Predicted lung function parameter} = b0 + b1 \times age + b2 \times age^2 + b3 \times height^2$$

In the equation, height is given in centimeters, age is given in years, and the coefficients b_0, b_1, b_2, and b_3 are determined based on subject's sex, race, and age group as shown in **Table 12--**1.

Wang Normal Values (WNVs) will be calculated for FEV_1, FVC, $FEF_{25-75\%}$, and FEV_1/FVC using the Wang equation:

$$\ln(\text{Predicted lung function parameter}) = \alpha + \beta \ln(\text{height})$$

Wang Normal Values (WNVs) will be calculated for FEV_1, FVC, $FEF_{25-75\%}$, and FEV_1/FVC using the Wang equation. In the equation, height is given in meters, and the coefficients α and β are determined based on subject's sex, race, and age as shown in **Table 12--**2 and **Table 12--**3.

If either height or age is missing, and the spirometry measurement is non-missing, the last non-missing value of height and age will be used in the calculation of predicted values.

Table 12-F-1 HNVs Equation Coefficients by Sex, Race, and Age

Parameter	Sex	Race	Age (years)	b_0	b_1	b_2	b_3
HNV_{FEV1}	Male	Caucasian	<20	-0.7453	-0.04106	0.004477	0.00014098
			≥20	0.5536	-0.01303	-0.000172	0.00014098
		African American	<20	-0.7048	-0.05711	0.004316	0.00013194
			≥20	0.3411	-0.02309		0.00013194
		Mexican American	<20	-0.8218	-0.04248	0.004291	0.00015104
			≥20	0.6306	-0.02928		0.00015104
	Female	Caucasian	<18	-0.8710	0.06537		0.00011496
			≥18	0.4333	-0.00361	-0.000194	0.00011496
		African American	<18	-0.9630	0.05799		0.00010846
			≥18	0.3433	-0.01283	-0.000097	0.00010846
		Mexican American	<18	-0.9641	0.06490		0.00012154
			≥18	0.4529	-0.01178	-0.000113	0.00012154
HNV_{FVC}	Male	Caucasian	<20	-0.2584	-0.20415	0.010133	0.00018642
			≥20	-0.1933	0.00064	-0.000269	0.00018642
		African American	<20	-0.4971	-0.15497	0.007701	0.00016643
			≥20	-0.1517	-0.01821		0.00016643
		Mexican American	<20	-0.7571	-0.09520	0.006619	0.00017823
			≥20	0.2376	-0.00891	-0.000182	0.00017823
	Female	Caucasian	<18	-1.2082	0.05916		0.00014815
			≥18	-0.3560	0.01870	-0.000382	0.00014815
		African American	<18	-0.6166	-0.04687	0.003602	0.00013606
			≥18	-0.3039	0.00536	-0.000265	0.00013606
		Mexican American	<18	-1.2507	0.07501		0.00014246
			≥18	0.1210	0.00307	-0.000237	0.00014246
$HNV_{FEF25-75\%}$	Male	Caucasian	<20	-1.0863	0.13939		0.00010345
			≥20	2.7006	-0.04995		0.00010345
		African American	<20	-1.1627	0.12314		0.00010461
			≥20	2.1477	-0.04238		0.00010461
		Mexican American	<20	-1.3592	0.10529		0.00014473
			≥20	1.7503	-0.05018		0.00014473
	Female	Caucasian	<18	-2.5284	0.52490	-0.015309	0.00006982
			≥18	2.3670	-0.01904	-0.000200	0.00006982
		African American	<18	-2.5379	0.43755	-0.012154	0.00008572
			≥18	2.0828	-0.03793		0.00008572
		Mexican American	<18	-2.1825	0.42451	-0.012415	0.00009610
			≥18	1.7456	-0.01195	-0.000291	0.00009610
$HNV_{FEV1/FVC\%}$	Male	Caucasian		88.066	-0.2066		
		African American		89.239	-0.1828		
		Mexican American		90.024	-0.2186		
	Female	Caucasian		90.809	-0.2125		
		African American		91.655	-0.2039		
		Mexican American		92.360	-0.2248		

Source: Reference 1. (Tables 4, 5 and 6)

Table 12-F-2 WNVs Equation Coefficients by Sex and Age in White Boys and Girls

		FEV_1		FVC		$FEF_{25-75\%}$		FEV_1/FVC	
Sex	**Age**	**α**	**β**	**α**	**β**	**α**	**β**	**α**	**β**
Male	6	-0.109	2.252	-0.024	2.470			-0.078	-0.248
	7	-0.104	2.270	-0.018	2.489			-0.086	-0.220
	8	-0.089	2.257	0.005	2.443	0.264	1.505	-0.091	-0.199
	9	-0.063	2.197	0.017	2.426	0.308	1.443	-0.086	-0.206
	10	-0.057	2.212	0.030	2.407	0.290	1.557	-0.081	-0.209
	11	-0.093	2.324	0.009	2.468	0.242	1.738	-0.101	-0.147
	12	-0.161	2.512	-0.061	2.649	0.165	1.982	-0.101	-0.133
	13	-0.292	2.843	-0.175	2.924	0.007	2.396	-0.116	-0.085
	14	-0.329	2.983	-0.219	3.060	0.014	2.483	-0.106	-0.087
	15	-0.141	2.709	-0.079	2.859	0.241	2.163	-0.060	-0.155
	16	0.062	2.409	0.104	2.591	0.503	1.764	-0.045	-0.178
	17	0.262	2.099	0.253	2.374	0.762	1.368	0.008	-0.272
Female	6	-0.109	1.949	-0.013	2.007			-0.097	-0.055
	7	-0.144	2.243	-0.062	2.385			-0.084	-0.132
	8	-0.137	2.239	-0.055	2.381	0.247	1.668	-0.079	-0.152
	9	-0.123	2.222	-0.039	2.351	0.254	1.710	-0.084	-0.128
	10	-0.161	2.364	-0.068	2.458	0.195	1.933	-0.092	-0.097
	11	-0.223	2.558	-0.120	2.617	0.161	2.091	-0.102	-0.061
	12	-0.264	2.709	-0.174	2.776	0.185	2.120	-0.090	-0.067
	13	-0.153	2.535	-0.061	2.576	0.294	1.976	-0.093	-0.040
	14	0.046	2.178	0.139	2.208	0.450	1.711	-0.096	-0.026
	15	0.148	2.008	0.210	2.099	0.581	1.486	-0.062	-0.093

Source: Reference 2. (Tables 2 and 3)

Table 12-F-3 WNVs Equation Coefficients by Sex and Age in Black Boys and Girls

		FEV_1		FVC		$FEF_{25-75\%}$		FEV_1/FVC	
Sex	**Age**	**α**	**β**	**α**	**β**	**α**	**β**	**α**	**β**
Male	6	-0.166	1.723	-0.088	1.961			-0.091	-0.152
	7	-0.122	1.846	-0.040	2.040			-0.091	-0.153
	8	-0.225	2.271	-0.094	2.323	0.097	1.544	-0.118	-0.104
	9	-0.142	2.059	-0.074	2.308	0.255	1.248	-0.079	-0.218
	10	-0.157	2.117	-0.110	2.417	0.230	1.428	-0.047	-0.303
	11	-0.176	2.166	-0.138	2.453	0.256	1.438	-0.048	-0.263
	12	-0.307	2.548	-0.224	2.710	0.085	1.936	-0.084	-0.162
	13	-0.486	2.962	-0.342	2.975	-0.121	2.476	-0.141	-0.018
	14	-0.472	3.010	-0.337	3.035	-0.115	2.536	-0.123	-0.050
	15	-0.318	2.789	-0.226	2.889	0.170	2.120	-0.070	-0.140
	16	0.074	2.140	0.058	2.425	0.663	1.299	0.018	-0.289
	17	0.053	2.223	0.148	2.310	0.505	1.618	-0.095	-0.087
Female	6	-0.288	2.182	-0.172	2.117			-0.109	0.059
	7	-0.250	2.158	-0.135	2.132			-0.104	-0.030
	8	-0.276	2.295	-0.176	2.362	-0.283	2.990	-0.103	-0.066
	9	-0.294	2.330	-0.200	2.452	0.025	2.062	-0.097	-0.104
	10	-0.344	2.507	-0.230	2.571	0.051	2.028	-0.120	-0.043
	11	-0.308	2.460	-0.204	2.526	0.078	2.006	-0.089	-0.105
	12	-0.219	2.312	-0.107	2.342	0.225	1.804	-0.115	-0.021
	13	-0.117	2.196	-0.042	2.294	0.418	1.504	-0.051	-0.148
	14	0.041	1.920	0.105	2.021	0.574	1.257	-0.063	-0.103
	15	0.203	1.662	0.253	1.787	0.599	1.281	-0.043	-0.139

Source: Reference 2. (Tables 4 and 5)

Appendix I: Threshold Criteria for Clinical Chemistry and Hematology

Threshold Criteria for Clinical Chemistry and Hematology

Parameter	Threshold Criteria	Comments
Clinical Chemistry		
CPK	>ULN - ≤ 2.5 x ULN >2.5 - ≤ 5 x ULN >5 - ≤ 10x ULN >10 x ULN	CTCAE grades 1-4
Creatinine	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN	CTCAE grades 1-4
Blood Urea Nitrogen	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN	Same criteria as creatinine No CTCAE
Sodium	Hyponatremia <LLN - ≥130 mmol/L <130 – ≥120 mmol/L <120 mmol/L	CTCAE grade 1, 3, 4 (No CTCAE grade 2)
	Hypernatremia >ULN - ≤ 150 mmol/L >150 mmol/L- ≤155 mmol/L >155 mmol/L - ≤ 160 mmol/L >160 mmol/L	CTCAE grade 1-4
Potassium	Hypokalemia <LLN – ≥ 3.0 mmol/L <3.0 – ≥ 2.5 mmol/L <2.5 mmol/L	CTCAE grade 1&2, 3, 4 (Grade 1 and 2 are the same)
	Hyperkalemia >ULN – ≤ 5.5 mmol/L >5.5 – ≤ 6.0 mmol/L >6.0 – ≤ 7.0 mmol/L >7.0 mmol/L	CTCAE grade 1-4
Total Cholesterol	>ULN – ≤ 7.75 mmol/L >7.75 – ≤ 10.34 mmol/L >10.34 – ≤ 12.92 mmol/L >12.92 mmol/L	CTCAE grade 1-4
Triglycerides	>1.71 – ≤ 3.42 mmol/L >3.42 – ≤ 5.7 mmol/L >5.7 – ≤ 11.4 mmol/L >11.4 mmol/L	CTCAE grade 1-4
Glucose	Hypoglycemia <3.0 – ≥ 2.2 mmol/L <2.2 - ≥ 1.7 mmol/L <1.7 mmol/L	CTCAE grade 1-4
	Hyperglycemia >ULN - ≤ 8.9 mmol/L >8.9 – ≤ 13.9 mmol/L >13.9 – ≤ 27.8 mmol/L >27.8 mmol/L	CTCAE grade 1-4
Albumin	<35 - ≥ 30 g/L	CTCAE grade 1-3

	<30 – ≥ 20 g/L <20 g/L	
Amylase	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.0 x ULN >2.0 – ≤ 5.0 x ULN >5.0 x ULN	CTCAE grade 1-4
Lipase	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.0 x ULN >2.0 – ≤ 5.0 x ULN >5.0 x ULN	CTCAE grade 1-4
Direct bilirubin	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2 x ULN >2 – ≤ 3 x ULN >3 – ≤ 10 x ULN >10 x ULN	Same Criteria as Total Bilirubin No CTCAE Not in DILI Guidance
GGT	>ULN - ≤ 2.5 x ULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	CTCAE grade 1-4
Calcium	Hypercalcemia >ULN - ≤ 2.9 mmol/L >2.9 – ≤ 3.1 mmol/L >3.1 – ≤ 3.4 mmol/L >3.4 mmol/L	CTCAE grade 1-4
	Hypocalcemia <LLN - ≥ 2.0 mmol/L <2.0 – ≥1.75 mmol/L <1.75 – ≥ 1.5 mmol/L <1.5 mmol/L	CTCAE grade 1-4
Magnesium	Hypermagnesemia >ULN - ≤ 1.23 mmol/L >1.23 – ≤ 3.30 mmol/L >3.30 mmol/L	CTCAE grade 1, 3, 4 No CTCAE grade 2
	Hypomagnesemia <LLN - ≥ 0.5 mmol/L <0.5 – ≥ 0.4 mmol/L <0.4 – ≥ 0.3 mmol/L <0.3 mmol/L	CTCAE grade 1-4
Inorganic phosphate	Hypophosphatemia <0.74 – ≥ 0.6mmol/L <0.6 – ≥ 0.3 mmol/L <0.3 mmol/L	CTCAE grade 1-4
ALT	>ULN - ≤ 3 xULN >3 – ≤ 5 xULN >5 – ≤ 8 xULN >8 – ≤ 20.0 xULN >20.0 x ULN	Per FDA DILI Guidance Jul 2009 and CTCAE
AST	>ULN - ≤ 3 xULN >3 – ≤ 5 xULN >5 – ≤ 8 xULN >8 – ≤ 20.0 xULN	FDA DILI Guidance and CTCAE

	>20.0 x ULN	
ALT or AST	(ALT>ULN and ALT ≤ 3 xULN) or (AST>ULN and AST≤ 3 xULN) (ALT>3 xULN and ALT ≤ 5 xULN) or (AST>3xULN and AST≤ 5 xULN) (ALT>5 xULN and ALT ≤ 8 xULN) or (AST>5xULN and AST≤ 8 xULN) (ALT>8 xULN and ALT ≤ 20 xULN) or (AST>8xULN and AST≤ 20 xULN) ALT>20 xULN 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 and CTCAE
Total Bilirubin	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2 x ULN >2 – ≤ 3 x ULN >3 – ≤ 10 x ULN >10 x ULN	FDA DILI Guidance and CTCAE
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
Hematology		
WBC	WBC decreased <LLN - ≥ 3.0 x 10e9 /L <3.0 – ≥ 2.0 x 10e9 /L <2.0 – ≥ 1.0 x 10e9 /L <1.0 x 10e9 /L	CTCAE grade 1-4
	Leukocytosis >100 x 10e9 /L	CTCAE grade 3 (only Grade available)
Lymphocytes	Lymphocyte decreased <LLN - ≥ 0.8 x10e9 /L <0.8 – ≥ 0.5 x10e9 /L <0.5 – ≥ 0.2 x10e9 /L <0.2 x10e9 /L	CTCAE grade 1-4
	Lymphocyte increased >4 – ≤ 20 x10e9/L >20 x10e9/L	CTCAE grade 2, 3 (only Grades available)
Neutrophils	Neutrophil decreased <LLN - ≥ 1.5 x10e9 /L <1.5 – ≥ 1.0 x10e9 /L <1.0 – ≥ 0.5 x10e9 /L <0.5 x10e9 /L	CTCAE grade 1-4
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