VERTEX PHARMACEUTICALS INCORPORATED

Final Analysis Statistical Analysis Plan

(Methods)

Protocol Number VX15-809-111

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Efficacy of Lumacaftor/Ivacaftor Combination Therapy in Subjects With Cystic Fibrosis Who Have an *A455E-CFTR* Mutation

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[redacted]

[redacted]

3 INTRODUCTION

This SAP describes the planned final analyses for the Study VX15-809-111 data and is based on the following:

- approved clinical study protocol (Version 2.0, dated 17 February 2017)
- approved electronic case report form (eCRF) (Version 3.0, dated 06 January 2017)

Study VX15-809-111 is a Phase 2, randomized, double-blind, placebo-controlled, crossover study to evaluate the efficacy of LUM/IVA in subjects with cystic fibrosis (CF), 12 years of age and older who have at least one *A455E* mutation.

[redacted]

This SAP (Methods) documents the planned final statistical analyses for efficacy and safety endpoints defined in the VX15-809-111 protocol , and describes the corresponding data presentations. Analyses for additional efficacy and safety variables not specified in the protocol

that will provide supportive information to enhance the scientific understanding of the study drug entity are also described.

The Vertex Biometrics Department will oversee the statistical analysis of the efficacy and safety data; SAS (Version 9.2 or higher) will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved before the clinical database lock and treatment unblinding for the study.If methods in this SAP differ from the methods described in the protocol, the SAP prevails.

4 STUDY OBJECTIVES

4.1 Primary Objective

To evaluate the efficacy of LUM/IVA in subjects with CF 12 years of age and older who have at least one *A455E* mutation.

[redacted]

5 STUDY ENDPOINTS

5.1 Primary Endpoint

Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) through 8 weeks of treatment.

[redacted]

6 STUDY DESIGN

6.1 Overall Design

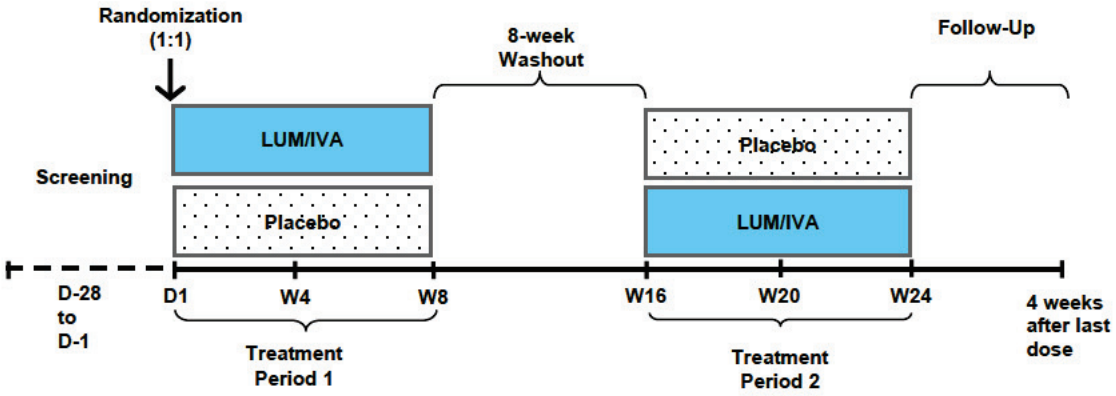
This is a Phase 2, randomized, double-blind, placebo-controlled, crossover study with 2 treatment sequences (Figure 1). The crossover design includes two 8-week treatment periods separated by an 8-week (± 7 days) washout period. There will be 7 to 9 study visits, not including the Screening Period. The total study duration for each subject will be approximately 32 weeks, including the Screening and Follow-up periods. Approximately 20 subjects will be included in this study.

Subjects will be randomized 1:1 to receive 1 of 2 treatment sequences:

- Sequence 1: LUM/IVA in Treatment Period 1; washout; placebo in Treatment Period 2
- Sequence 2: placebo in Treatment Period 1; washout; LUM/IVA in Treatment Period 2

It is recommended that subjects maintain a stable CF medication regimen during the study, as described in Section 9.3.1 of the protocol.

Figure 1 Study Design



This study includes a Screening Period (approximately 28 days), Treatment Period 1 (8 weeks), Washout Period (8 weeks), Treatment Period 2 (8 weeks), and a Safety Follow-up Visit (approximately 28 days after the last dose of study drug).Subjects who are less than 18 years of age at the Screening Visit will undergo an ophthalmologic examination during the Screening Period unless there is documentation of an acceptable ophthalmologic examination that was conducted within 3 months before the Screening Visit. Repetition of Screening Assessments for subjects who did not meet eligibility criteria is not permitted, with the exceptions described in Section 8.1.1.1 of the protocol.

During Treatment Period 1 and Treatment Period 2 of each treatment sequence, subjects will take LUM 400 mg q12h/IVA 250 mg q12h dose regimen or the corresponding placebo (Table 6-1).

Table 6-1 Study Drug

Drug Name	Formulation/ Route	Formulation Strength	Storage Condition
Lumacaftor/ivacaftor (fixed dose)	Fixed-dose tablet/ Oral	Supplied as 200-mg lumacaftor/ 125-mg ivacaftor tablets	Store at ≤30°C (86°F)
Placebo (appearance matched to lumacaftor/ ivacaftor tablets)	Tablet/oral	No active drug	Store at ≤30°C (86°F)

6.2 Sample Size and Power

No formal sample size calculation is conducted for this study of exploratory nature. The planned sample size of approximately 20 subjects is based on the number of subjects expected to be available for participation.

Assuming an estimated standard deviation (SD) of the paired differences of 8.00 in $ppFEV_1$, the available sample size of 20 subjects produces a 2-sided 95% CI of the mean treatment difference with precision (margin of error) of 3.74 percentage points. In addition, Table 6-2 displays a list of treatment differences detectable under various scenarios of power and significance level, with total sample sizes of 15 and 20.

Table 6-2 Difference Detectable Under Various Scenarios of Power, Alpha, and N

Power		90%	90%	90%	90%	80%	80%	80%	80%
Alpha		10%	10%	5%	5%	10%	10%	5%	5%
	N	20	15	20	15	20	15	20	15
	Difference detectable	5.4	6.4	6.1	7.3	4.6	5.4	5.3	6.3

6.3 Randomization

Approximately 20 subjects who meet eligibility criteria will be randomized (1:1) to 1 of the 2 treatment sequences (Figure 1).

An interactive web or voice response system (IXRS) will be used to assign subjects to treatment sequence in a 1:1 ratio to receive either LUM/IVA during Treatment Period 1 and placebo during Treatment Period 2, or placebo during Treatment Period 1 and LUM/IVA during Treatment Period 2.

The IXRS will use a list of randomization codes generated by a designated vendor [redacted].

6.4 Blinding and Unblinding

This is a double-blind study.

6.4.1 Blinding

This study is double-blind. The subjects and all site personnel, including the investigator, site monitor, and study team, will remain blinded to treatment assignments until database lock. Exceptions are made for the following personnel:

- 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 the fetus in the event of a pregnancy
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy serious adverse event (SAE) processing and reporting regulations
- Unblinded statistician who will prepare the final (production) randomization list (this statistician is not a part of the study team)
- Vertex IXRS Management for IXRS oversight and system administration
- Vertex Clinical Supply Chain
- The bioanalytical laboratory/vendor personnel managed by Vertex Bioanalysis

Vertex Quality Assurance Good Clinical Practice (GCP) personnel and all other Vertex Bioanalysis laboratory personnel will be blinded to the treatment assignment.

Subjects and their parents/caregivers will not be informed of their study-related efficacy results during the study, regardless of whether or not the subject prematurely discontinues treatment.

Spirometry Data Blinding

Despite treatment blinding, knowledge of the spirometry results has the potential to suggest whether a subject has received active study drug or placebo. Therefore, during the conduct of the study, the Vertex study team will have no access to the postdose spirometry data. The vendor for central reading of the spirometry data will only send the blinded spirometry files (blinded treatment group, with real values for screening and baseline, but with dummy values for all the spirometry assessments after baseline) 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 Treatment Period, regardless of whether the subject has prematurely discontinued treatment.

[redacted]

[redacted]

6.4.2 Unblinding

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

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

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

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

7 ANALYSIS SETS

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

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

The FAS is defined as all randomized subjects who have at least one *A455E* mutation and have received at least 1 dose of study drug. The FAS will be used for efficacy analyses.

The Safety Set is defined as all subjects who received at least 1 dose of study drug. The Safety Set will be used for safety analyses.

8 STATISTICAL ANALYSIS

8.1 General Considerations

All individual subject data for those randomized or exposed to study drug will be presented in data listings. Summary and plots of efficacy data will be generated. The Schedule of Assessments is provided in Appendix A. The precision standards are provided in Appendix E.

Continuous variables will be summarized using the following descriptive summarystatistics: 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.

Treatment Emergent (TE) Period:

- TE period for Treatment Period 1 will be from the first dose of study drug in the first period to 28 days after the last dose of Period 1 or the safety evaluation visit (Safety Follow-up Visit, if subject discontinues treatment in Period 1), whichever is latest.
- The TE period for Treatment Period 2 will be from the first dose of study drug in the second period to 28 days after the last dose of Period 2 or the Safety Follow-up Visit , whichever is latest.

Baseline Value: For this crossover study, 2 types of baseline will be defined.

- The study baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in the study. The definition will be applied to all demographics, background, and baseline characteristics and also to data analyses, including the primary endpoint analysis.
- The period baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in each Treatment Period. For Treatment Period 2, the period baseline should be from an assessment measured after the end of the TE period for Treatment Period 1.

[redacted]

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

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

Unscheduled Visits: Unscheduled visit measurements will be included in the following:

(1) derivations of measurements at scheduled visits per specified visit windowing rules below;

(2) derivations of baseline/last on-treatment measurements;

(3) derivations of the maximum/minimum on-treatment values and maximum/minimum changes from baseline values for safety analyses;

(4) subject data listings where appropriate.

Visit Windowing Rules: Appendix B defines the windows for protocol-defined visits. 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. If there are no measurements at the scheduled visit:

- 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 24.

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; 3) Safety Follow-up Visit will not be windowed, instead, used per nominal visit in relevant analyses.

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

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

8.2 Background Characteristics

8.2.1 Subject Disposition

Number and percentage of subjects in the following categories will be presented by treatment sequence and overall using All Subjects Set (randomized or dosed), as appropriate:

- All Subjectes Set (randomized or dosed)
- Randomized
- Full Analysis Set (FAS)
- Safety Set
- Completed treatment period 1
- Prematurely discontinued the treatment period 1, and the reasons for discontinuations
- Completed treatment period 2

- Prematurely discontinued the treatment period 2, and the reasons for discontinuations
- Completed study (defined as completed Safety Follow-up Visit)
- Prematurely discontinued the study and the reasons for discontinuations

A listing will be provided for subjects who discontinued treatment or who discontinued study, along with reasons for discontinuations.

8.2.2 Demographics and Baseline Characteristics

Demographic, background (e.g. medical history), and baseline characteristics will be summarized by treatment sequence and overall. Protocol deviations/violations will be provided as a subject data listing only. Important protocol deviations/violations will be identified for analysis purposes.

Demographic data will include but not limited to the following:

- Age at screening
- Age group at screening (>= 12 to < 18, and ≥18 years)
- 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)
- Country

Baseline characteristics will include the following:

- Weight (kg) at study baseline
- Height (cm) at study baseline
- BMI (kg/m^2) at study baseline
- Mutation genotype
- $ppFEV_1$ at study baseline
- $ppFEV_1$ category at study baseline (<40, ≥40 to <70, ≥70 to ≤90, and >90)
- Sweat chloride at study baseline
- CFQ-R at study baseline
- FEV_1 (L) at study baseline
- FVC (L) at study baseline
- Percent predicted FVC at study baseline
- $FEF_{25-75\%}$ (L/sec) at study baseline
- Percent predicted $FEF_{25-75\%}$ at study baseline

- FEV_1/FVC at study baseline

In addition, subject data listings will also be provided for:

- Informed consent
- Inclusion/Exclusion criteria violation (for subjects with any such violations)

8.2.3 Medical History

Medical history will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA).

For the FAS, medical history will be summarized descriptively by treatment sequence, system organ class (SOC) and preferred term (PT) for each treatment sequence and overall. It will be listed too.

8.2.4 Prior and Concomitant Medications

Medications taken during this study will be coded using the World Health Organization Drug Dictionary Enhanced (WHO-DDE) and categorized as follows:

- **Prior medication**: any medication that started prior to the first dose of study drug, regardless of when it ended.
- **Concomitant medication**: medication continued or newly received during the TE period for Treatment Period 1 or Treatment Period 2. If a subject took a medication during a specific Treatment Period, this medication will be attributed to the treatment the subject received during this Treatment Period. As a result, 1 medication could be attributed to more than 1 study drug for an individual subject.
- **Post-treatment medication:** medication continued or newly received after the TE period for Treatment Period 2, or between the TE periods for Treatment Period 1 and Treatment Period 2, or after the TE period for Treatment Period 1 for subjects who do not have Treatment Period 2.

A given medication can be classified as a prior medication, a concomitant medication, or a post-treatment medication; both prior and concomitant; both concomitant and post-treatment; or prior, concomitant, and post-treatment. If a medication has a missing or partial missing start/end date or time and it cannot be determined whether the medication was taken before initial dosing, concomitantly, or post-treatment, it will be considered as prior, concomitant, and post-treatment.

For medications with partial start dates, missing month will be imputed with January and missing day will be imputed with 1. For medications with partial stop dates, missing month will be imputed with December and missing day will be imputed with the last day of the month. For the missing years, 2000 will be used for the start dates and 2050 will be used for the end dates.

The logic to decide the category of a medication is presented in Table 8-1.

Table 8-1 Logic for Determining the Category of a Medication

Medication start date	Medication end date				
	< Start date ofTE Period 1	≥ Start date of TE Period 1 and ≤ End date of TE Period 1	> End date of TE Period 1 and < Start date of TE Period 2	≥ Start date of TE Period 2 and ≤ End date of TE Period 2	> End date of TE Period 2
< Start date of TE Period 1	P	PC1	PC1A	PC1C2A	PC1C2A
≥ Start date of TE Period 1 and ≤ End date of TE Period 1	-	C1	C1A	C1C2A	C1C2A
> End date of TE Period 1 and < Start date of TE Period 2	-	-	A	C2A	C2A
≥ Start date of TE Period 2 and ≤ End date of TE Period 2	-	-	-	C2	C2A
> End date of TE Period 2	-	-	-	-	A

P – Prior; C1 – Concomitant for the Treatment in Period 1; C2 – Concomitant for the Treatment in Period 2; A – Post-Treatment.

Prior medication summary will be presented by treatment sequence and concomitant medication summary will be presented by treatment. Both prior and concomitant medication will be based on FAS. Medications will be listed by subject.

8.2.5 Study Drug Exposure

Exposure summaries will be based on the FAS and presented by treatment group.

Duration of study drug exposure is defined as follows: last dose date – first dose date + 1 day within the treatment period, regardless of any interruption in dosing between the first and the last dose.

If the last dose date of study drug is missing, the subject's discontinuation or completion date will be used for analysis purposes.

Exposure will be summarized as a continuous variable in weeks, and also in the following categories: ≤2 weeks; >2 and ≤4 weeks;>4 and ≤8 weeks; and >8 weeks, for each treatment group.

8.2.6 Study Drug Compliance

Study drug compliance will be measured by the compliance rate; summarized based on the

FAS and presented by treatment group.

Compliance rate will be calculated as follows:

100 × [1 - (Total number of days study drug interrupted) / (Duration of study drug exposure)].

The total number of days study drug interrupted is defined as the total of number of days the study drug was interrupted in each interruption interval, where number of days study drug interrupted in each interval is defined as the interruption end date - the corresponding interruption start date + 1.

Study drug compliance will be summarized descriptively by the number of subjects (n), mean, SD, SE, median, min, and max and into the categories of <80% and ≥80%.

A list of subjects with <80% compliance rate will be provided.

8.2.7 Important Protocol Deviations

Important protocol deviations (IPDs) 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. IPDs will be identified from the clinical database and/or site deviation log, and IPD rules will be developed and finalized before database lock.

The protocol deviations that may 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 prohibited 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 presented in an individual subject data listing.

8.3 Efficacy Analysis

The primary objective of this study is to evaluate the efficacy of LUMA/IVA. For efficacy analysis, the statistical inference will be based on change from study baseline. Unless otherwise defined, all efficacy analyses described in this section will use the FAS. The efficacy analyses will be performed according to the treatment to which the subject was actually assigned in each period. Data for a period will be used provided that the subject received at least one dose of study drug in that treatment period.

8.3.1 Analysis of Primary Efficacy Variable(s)

The analysis will include all available measurements up to Week 8 [inclusive] during each treatment period, both on-treatment measurements and measurements after treatment discontinuation, per the visit windowing rules (Appendix B).

8.3.1.1 Definition of Variable

The primary efficacy endpoint is the absolute change in $ppFEV_1$ from study baseline through 8 weeks of treatment.

$ppFEV_1$ is the ratio of FEV_1 (L) to the predicted FEV_1 (L), expressed as a percentage. The predicted FEV_1 will be calculated based on the Global Lung Function Initiative (GLI)-2012 multi-ethnic all-age reference equations[3]; details are provided in Appendix D.

8.3.1.2 Primary Analysis

The primary efficacy analysis will be based on a mixed effects model using SAS procedure MIXED. The null hypothesis to be tested is that the mean absolute change from study baseline in $ppFEV_1$ through 8 weeks of treatment is the same for LUMA/IVA and placebo.

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

The primary analysis for the primary efficacy variable will be based on a mixed-effects model for repeated measures (MMRM). The model will include the absolute change from the study baseline in each Treatment Period as the dependent variable, with sequence, treatment, period, visit within period, and treatment-by-visit interaction as fixed effects, study baseline percent predicted FEV_1 as covariate, and subject nested within sequence as the random effect. In the model, visit will be treated as a class variable. An unstructured covariance matrix is assumed for the repeated measurements of the same subject within each treatment period. If there is a convergence problem for the unstructured covariance matrix, an appropriate covariance matrix structure, such as compound symmetry, will be assumed in the primary analysis. Denominator degrees of freedom for the F-test for fixed effects will be estimated using the Kenward-Roger approximation[1]. With a mixed-effects model as the primary analysis model based on maximum likelihood estimation and assuming that data are missing at random conditional on fixed and random effects, no imputation of missing data will be done.

With a mixed-effects model based on a restricted maximum likelihood estimation used for the primary analysis and assuming that, conditional on fixed and random effects, data are missing at random, no imputation of missing data will be performed.

The estimated mean treatment difference overall, a 95% CI, and a 2-sided *P* value will be provided. The estimated mean treatment difference at each visit along with the corresponding 95% CI and *P* value will also be presented.

As a supportive sensitivity analysis, the above MMRM analysis will be repeated using change from period baseline instead of change from study baseline.

The raw values and changes from study baseline will be summarized by treatment group using descriptive statistics at each scheduled visit. In addition, raw values and changes from period baseline will be also summarized by treatment group using descriptive statistics at each scheduled visit. The subgroup summary by mutation groups will also be performed.

[redacted]

8.4 Safety Analysis

All safety analyses will be based on the set of data associated with the TE period for Treatment Period 1 and the TE period for Treatment Period 2. Safety analyses will use the Safety Set. Subjects will be analyzed according to the treatment they actually received in a given treatment period. For safety analysis, the period baseline will be used, as applicable.

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

- Adverse events
- Clinical laboratory data (liver function tests)
- Vital signs
- Pulse oximetry
- Physical examination
- Ophthalmologic examination

Only descriptive analysis of safety will be performed; no statistical testing is planned. All safety data will be presented in individual subject data listings.

For the purpose of safety analysis, the study period will be further divided into 3 segments per the definition of the treatment emergent (TE) period (Section 8.1):

- The **pre-treatment period** is the period after the informed consent/assent date and before the initial dosing of study drug in the study.
- The **treatment-emergent period** (TE period) is defined in Section 8.1.
- The **post-treatment period** is the period after the last date of TE period for Treatment Period 2 to the date of the last study record in the clinical database or the period between the end of TE period for Treatment Period 1 and the start of TE period for Treatment Period 2. For subjects who do not have Treatment Period 2, the period after the last date of TE period for Treatment Period 1 to the date of the last study record in the clinical database will be considered as post-treatment period.

8.4.1 Adverse Events

For analysis purposes, AEs will be categorized as pretreatment AEs, treatment-emergent adverse events (TEAEs), or post-treatment AEs:

- **Pretreatment AE:** any AE that started before initial dosing of study drug in the study.
- **TEAE:** any AE that increased in severity or that was newly developed during the TE period for Treatment Period 1 or Treatment Period 2. If an AE started (or increased in severity) during a specific Treatment Period, this AE will be attributed to the treatment the subject was receiving during the Treatment Period.
- **Post-treatment AE:** any AE that increased in severity or that was newly developed during the post-treatment period.

For AEs with missing or partial start date, if there is no clear evidence that the AEs started (or increased in severity) before the first dose, the start date will be imputed to the first dosing date and the AE assigned to the treatment in Treatment Period 1. As an intermediate step for programming purposes, imputation rules for missing or partially missing AE start/end dates are defined in Appendix C.

By relationship to the study drug regimen, TEAEs will be classified into 4 categories, as defined in Section 13.1.1.5 of the protocol:

- Not related
- Unlikely related
- Possibly related
- Related

By severity, TEAEs will be classified into 4 categories, as defined in Section 13.1.1.4 of the protocol:

- Mild or Grade 1
- Moderate or Grade 2
- Severe or Grade 3
- Life-threatening or Grade 4 or 5

8.4.1.1 Overview of Treatment Emergent AEs

An overview of all TEAEs will be summarized in the following categories:

- Any TEAEs
- TEAEs by relationship
- Related TEAEs
- TEAEs by severity
- Grade 3/4 TEAEs
- Serious TEAEs
- Related Serious TEAEs

- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- TEAEs leading to death

8.4.1.2 TEAEs and TE SAEs by System Organ Class and Preferred Term

The number and percentage of subjects with TEAEs will be summarized by treatment group, MedDRA system organ class (SOC) and preferred term (PT), where multiple occurrences of the same AE or a continuing AE for the same subject will be counted only once. The summary table will be presented in descending order of frequencies in the LUMA/IVA treatment group. TE SAEs will be summarized similarly.

8.4.1.3 TEAEs and TE SAEs by PT

The number and percentage of subjects with TEAEs will be summarized by treatment group and PT, where multiple occurrences of the same AE or a continuing AE for the same subject will be counted only once. TE SAEs will be summarized similarly.

8.4.1.4 Related TEAEs and TE SAEs by SOC, PT

The number and percentage of subjects with related TEAEs will be summarized by treatment group, SOC, and PT, where multiple occurrences of the same AE or a continuing AE for the same subject will be counted only once. The summary table will be presented in descending order of frequencies in the LUMA/IVA treatment group. TEAEs in the following relationship to study drug regimen categories will be considered as related: Related, Possibly Related and Missing. Missing relationships will be summarized separately, as well. TE SAEs will be summarized similarly.

8.4.1.5 Grade 3/4 TEAEs by SOC, PT

The number and percentage of subjects with Grade 3/4 TEAEs will be summarized by treatment group, SOC, and PT, where multiple occurrences of the same AE or a continuing AE for the same subject will be counted only once. The summary table will be presented in descending order of frequencies in the LUMA/IVA treatment group. Grade 3/4 TEAEs include severe and life-threatening adverse events.

8.4.2 Clinical Laboratory

For treatment-emergent liver function measurements, the raw values and change from period baseline values will be summarized in SI units by treatment group at each scheduled time point.

The number and percentage of subjects with liver function values meeting the defined threshold criteria during the overall TE period will be summarized. The threshold analysis criteria are provided in Appendix F.

For all LFT results (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], direct bilirubin, total bilirubin, and gamma-glutamyl transferase [GGT]), a listing of subjects with elevated LFT results during the TE period will be presented.

The hematology and chemistry lab results at screening will be listed.

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

8.4.3 Vital Signs

For treatment-emergent vital signs measurements, the raw values and change from period baseline values will be summarized by treatment group at each scheduled time point: systolic and diastolic blood pressure (mm Hg), body temperature (^{o}C), HR (beats per minute), and respiratory rate (breaths per minute). In addition, the mean value at each time point will be plotted by treatment group for systolic and diastolic blood pressure.

8.4.4 Pulse Oximetry

Arterial oxygen saturation by pulse oximetry will be measured at visits noted in Schedule of Assessments. The assessments of pulse oximetry on Day 2 and the day after the Week 16 Visit will be performed only for subjects whose FEV_1 at the Screening Visit is <40% of predicted.

For treatment-emergent pulse oximetry measurements, a listing of raw values and change from baseline will be provided.

8.4.5 Physical Examination

Abnormal physical examination results performed as part of the Screening Period assessment will be presented in subject data listings only. Clinically relevant results identified after screening will be reported as AEs.

8.4.6 Ophthalmologic Examination

The subjects with abnormal ophthalmological examinations for subjects < 18 years old at screening will be presented in an individual subject data listing.

In addition, the ophthalmological history data for all subjects will be listed.

9 SUMMARY OF INTERIM AND IDMC ANALYSES

No formal interim or IDMC analyses are planned for this study.

10 REFERENCES

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11 LIST OF APPENDICES

11.1 Appendix A: Schedule of Assessments

Table 11-11-1 Study VX15-809-111: Screening Period Assessments

Assessment	Screening Period (Day -28 through Day -1)
Informed consent and assent (when applicable)	X
Review inclusion/exclusion criteria	X
Demographics	X
Medical history	X
CFTR genotyping[a]	If deemed necessary by investigator
Ophthalmological history	X
Prior and concomitant medications	X
Ophthalmologic examination[b]	X
Complete physical examination	X
Weight, height[c]	X
Vital signs and pulse oximetry[d]	X
Spirometry[e]	X
[redacted]	
FSH[f]	X
Serum pregnancy test (females of childbearing potential)[g]	X
Hematology	X
Serum chemistry	X
AEs and SAEs	Continuous from signing of the ICF and Assent Form (where applicable) through the Follow-up Visit

[a] It is expected that most subjects will have documentation of *CFTR* genotype in their medical records. If documentation of *CFTR* genotype is not available, or if confirmation of *CFTR* genotype is deemed necessary by the investigator, *CFTR* genotyping will be performed during the Screening Period.

[b] Ophthalmologic examination is required for subjects who are less than 18 years of age at the Screening Visit. If there is documentation of an ophthalmologic examination that met protocol criteria and was conducted within 3 months before the Screening Visit, the subject is not required to have a repeat ophthalmologic examination during Screening.

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

[d] Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) and pulse oximetry will be collected after the subject has been at rest (seated or supine) for at least 5 minutes. Blood pressure will be measured by sphygmomanometer.

[e] At Screening, spirometry may be performed pre- or post-bronchodilator.

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

[g] See Section 11.6.7.1 of the protocol for definition of childbearing potential.

Table 11-11-2 Study VX15-809-111: Treatment Period Assessments

Event/Assessment	Treatment Period 1				Washout Period (No Visit)	Treatment Period 2				Early Termination of Treatment (ETT)
	Day 1	Day 2[a]	Week 4 (± 4 days)	Week 8 (± 7 days)	8 weeks (± 7 days)	Week 16 (± 4 days)	Day after Week 16 Visit[a]	Week 20 (± 4 days)	Week 24 (± 7 days)	
Review inclusion/ exclusion criteria[b]	X									
Randomization	X									
[redacted]										
Vital signs[g]	X	X	X	X		X	X	X	X	X
Pulse oximetry		X					X			
Spirometry[h]	X	X	X	X		X	X	X	X	X
[redacted]										
Urine pregnancy test[i]	X		X	X		X		X	X	X

[a] These visits will be conducted for subjects whose FEV_1 at Screening is <40% of predicted.
[b] Confirmation of subject eligibility will occur before randomization.
[redacted]
[g] Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be collected after the subject has been at rest (seated or supine) for at least 5 minutes. Blood pressure will be measured by sphygmomanometer.
[h] Spirometry will be performed pre-bronchodilator and must be performed before study drug dosing.
[i] Pregnancy tests will be performed for all female subjects of childbearing potential. The urine β-hCG tests on Day 1 and Week 16 must be negative before the study drug is administered.

Table 11-11-2 Study VX15-809-111: Treatment Period Assessments

Event/Assessment	Treatment Period 1				Washout Period (No Visit)	Treatment Period 2				Early Termination of Treatment (ETT)
	Day 1	Day 2[a]	Week 4 (± 4 days)	Week 8 (± 7 days)	8 weeks (± 7 days)	Week 16 (± 4 days)	Day after Week 16 Visit[a]	Week 20 (± 4 days)	Week 24 (± 7 days)	
Liver function tests (LFTs)[j]	X			X		X			X	X
Ophthalmologic examination[k]									X[l]	X[l]
[redacted]										
Meal(s) or snack(s) at site[n]	X	X	X	X		X	X	X	X	
Study drug dosing	**Day 1 through Week 8** (Last dose of study drug will be administered the day before the Week 8 Visit)				**No study drug**	**Week 16 through Week 24** (Last dose of study drug will be administered the day before the Week 24 Visit)				
Observation 4 h after dosing[o]	X					X				
Concomitant medications	X	X	X	X		X	X	X	X	X
Concomitant treatments and procedures	X	X	X	X		X	X	X	X	X
AEs and SAEs	**Continuous from signing of the ICF and Assent Form (where applicable) through the Follow-up Visit**									

j ALT, AST, GGT, alkaline phosphatase, and bilirubin.
k For subjects who were less than 18 years of age at the Screening Visit.
l Ophthalmologic examination will be performed at the Week 24 Visit, the Early Termination of Treatment Visit, **or** the Follow-up Visit. This examination is not required if the subject received the study drug for a total of less than 4 weeks.
[redacted]
n Fat-containing food such as a standard "CF" high-fat, high-calorie meal or snack will be provided to subjects at the site after all predose assessments have occurred.
o Observation 4 h after dosing will be performed for subjects whose FEV_1 at Screening is <40% of predicted.

Table 11-11-3 Study VX15-809-111: Follow-up Visit Assessments

Event/Assessment	Follow-up 4 weeks (± 7 days) after last dose of study drug
Vital signs[a]	X
[redacted]	
Spirometry[d]	X
[redacted]	
Serum pregnancy test[e]	X
LFTs[f]	X
Ophthalmologic examination[g,h]	X
[redacted]	
Concomitant medications	X
Concomitant treatments and procedures	X
AEs and SAEs	**Continuous from signing of the ICF and Assent Form (where applicable) through the Follow-up Visit**

[a] Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) will be collected after the subject has been at rest (seated or supine) for at least 5 minutes. Blood pressure will be measured by sphygmomanometer.

[redacted]

[d] Spirometry will be performed pre-bronchodilator.

[e] Pregnancy tests will be performed for all female subjects of childbearing potential.

[f] ALT, AST, GGT, alkaline phosphatase, and bilirubin.

[g] For subjects who were less than 18 years of age at the Screening Visit.

[h] Ophthalmologic examination will be performed at the Week 24 Visit, the Early Termination of Treatment Visit, **or** the Follow-up Visit. This examination is not required if the subject received study drug for a total of less than 4 weeks.

[redacted]

11.2 Appendix B: Analysis Visit Windows for Safety and Efficacy Assessments

Table 11-4 Visit Window Mapping Rules (within Period)

Assessments	Period - Visit	Analysis Visit	Target Study Day	Visit Window (in study days)
Vital signs (excluding weight, BMI), and spirometry, per Schedule of Assessments	1 – Day 1	Day 1	1	[1, 1]
	1 – Day 2	Day 2	2	Remain as the nominal visit
	1 – Week 4	Week 4	29	[study day of Day 2 visit +1, 43]
	1 – Week 8	Week 8	57	[44, 71]
	2 – Week 17	Day 1	1	[1, 1] of period 2
	2 – Week 17-2	Day 2	2	Remain as the nominal visit
	2 – Week 20	Week 4	29	[study day of Day 2 visit in period 2 +1, , 43 of period 2]
	2 – Week 24	Week 8	57	[44, 71] of period 2
	Safety Follow-up Visit	Safety Follow-up Visit	NA	For Vital Signs, remain as the nominal visit. For Spirometry, follow the individual visit window to be mapped to individual visits if measured before / on Day 71 or remain as SFU if otherwise.
[redacted]				
Height	1 - Day 1	Day 1	1	[1, 1]

	Safety Follow-up Visit	Safety Follow-up Visit	NA	Remain as the nominal visit
Other clinical chemisty and hemotology lab except LFTs, urine prenanancy test, pulse oximetry, ophthalmologic examination, physical examination	Any	Any	NA	Remain as the nominal visit

Note:

1. For measurements taken on Day 2 of each treatment period, no visit windowing rule shall be applied. Instead, nominal visit will be used.
2. 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.
3. For all "safety" parameters, such as liver function tests, if there are multiple measurements within a visit window, then
   - the record closest to the target day will be used; or
   - if there are multiple records within the same distance from the target day, the latest record will be used.
4. Spirometry, [redacted] will follow the efficacy windowing rules.
5. For prenanancy test, pulse oximetry, ophthalmologic examination, physical examination, there is no need to derive the mapped analysis visit as they will be listed only.

11.3 Appendix C: Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start date are defined below:

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose date, then:

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

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

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date; otherwise, impute the AE start Month as January and the Day as 1.
- Otherwise, impute the AE start MONTH as January and the DAY as 1.

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

If Year of AE start date is missing:

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

The imputation rule will be applied with respect to treatment start date for both periods, as necessary and applicable, and preference will be given to treatment in period 1 in case the AE is assigned to treatments in both periods. Missing or partially missing AE end date will not be imputed.

[redacted]

11.5 Appendix E: Precisions of Summary Statistics and Derived Variables in TFLs

Continuous Variables

Table 11-5 Precision of special summary statistics for CF studies[j]

Variables	Statistics	Decimal Places
ppFEV1	Mean, LS mean, 95% CI	1
[redacted]		

The precision of the Safety Lab Data will follow the latest standard from the Biometrics Standardization Committee.

The precision of the measurement in raw data for other continuous variables will be used to determine the number of decimal places to present in tables, figures, and derived listings. Minimum and maximum values will be reported with the same precision as the units of measure. The mean, median, SD and SE will be reported to 1 greater decimal place.

Any values that require transformation to standard units (metric or SI) will be converted with the appropriate corresponding precision.

Categorical Variables: Percentages will be presented to 1 decimal place.

[j] The precisions will be reflected in the TFLs.

11.6 Appendix F: Criteria for Potentially Clinically Significant Events (Threshold Analysis Criteria)

Please use relevant threshold analysis criteria from the following tables as it applies to this study.

Table 11-6 Threshold Criteria for Laboratory Tests

Parameter	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	CTCAE grade 1-4

	>8.9 – ≤ 13.9 mmol/L >13.9 – ≤ 27.8 mmol/L >27.8 mmol/L	
Albumin	<35 - ≥ 30 g/L <30 – ≥ 20 g/L <20 g/L	CTCAE grade 1-3
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
Bicarbonate	<LLN >ULN	No CTCAE
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 >20.0 x ULN	FDA DILI Guidance and CTCAE
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

Table 11-7 Threshold Criteria for Vital Signs

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT VITAL SIGNS		
Parameter	**Threshold Criteria**	**Comments**
SBP	SBP increased >140 mmHg >160 mmHg >10 mmHg increase from baseline >20 mmHg increase from baseline >140 mmHg & >10 mmHg increase from baseline >140 mmHg & >20 mmHg increase from baseline >160 mmHg & >10 mmHg increase from baseline >160 mmHg & >20 mmHg increase from baseline	809/770 analyses
	SBP decrease <90 mmHg <80 mmHg >10 mmHg decrease from baseline >20 mmHg decrease from baseline <90 mmHg and >10 mmHg decrease from baseline <90 mmHg and >20 mmHg decrease from baseline <80 mmHg and >10 mmHg decrease from baseline <80 mmHg and >20 mmHg decrease from baseline	Per HV grade 1, 3, plus shift change
DBP	DBP increased >90 mmHg >100 mmHg >5 mmHg increase from baseline >10 mmHg increase from baseline >90 mmHg and >5 mmHg increase from baseline >90 mmHg and >10 mmHg increase from baseline >100 mmHg and >5 mmHg increase from baseline >100 mmHg and >10 mmHg increase from baseline	809/770 analyses

	DBP decreased <60 mmHg <45 mmHg >5 mmHg decrease from baseline >10 mmHg decrease from baseline <60 mmHg and >5 mmHg decrease from baseline <60 mmHg and >10 mmHg decrease from baseline <45 mmHg and >5 mmHg decrease from baseline <45 mmHg and >10 mmHg decrease from baseline	
Weight	Weight gain ≥5 % increase from baseline ≥10 % increase from baseline ≥ 20% increase from baseline	CTCAE grade 1-3
	Weight loss ≥5 % decrease from baseline ≥10 % decrease from baseline ≥ 20% decrease from baseline	CTCAE grade 1-3

[redacted]