VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan for Part A (Methods)

Protocol Number VX14-661-110 Version 3.0

A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With VX-661 in Combination With IVA in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the *F508del-CFTR* Mutation

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3 INTRODUCTION

Study VX14-661-110 (Study 110) is a Phase 3, Open-label, rollover study to evaluate the safety and efficacy of long-term treatment with VX-661 in combination with ivacaftor (IVA) in subjects aged 12 years and older with cystic fibrosis, homozygous or heterozygous for the *F508del-CFTR* mutation.

This SAP will focus on the safety and efficacy analysis for all the subjects enrolled in Part A. As there is no subject enrolled in Part A Observational Cohort, the methods pertain to Part A Treatment Cohort, unless specified otherwise.

The Vertex Biometrics department or a designated Contract Research Organization (CRO) will perform the statistical analysis of the safety and efficacy data. SAS® Version 9.4 Software (SAS Institute, Cary, North Carolina, USA) or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets). This SAP will be finalized and approved prior to the final clinical data lock.

4 STUDY OBJECTIVES

4.1 Primary Objective

Part A

To evaluate the long-term safety and tolerability of VX-661/IVA in subjects with CF, homozygous or heterozygous for the *F508del-CFTR* mutation who are in the Treatment Cohort

4.2 Secondary Objectives

Part A

Treatment Cohort

To evaluate the long-term efficacy of VX-661/IVA for subjects in the Treatment Cohort

Observational Cohort

To evaluate the post-treatment safety of VX-661/IVA for subjects in the Observational Cohort

5 STUDY ENDPOINTS

5.1 Primary Endpoints

Part A

Treatment Cohort

Safety and tolerability of long-term treatment of VX-661/IVA based on adverse events (AEs), ophthalmologic exams (subjects <18 years of age [age on the date of informed consent/assent in the parent study]), clinical laboratory values (serum chemistry, hematology, coagulation, lipids, vitamins, and urinalysis), standard digital electrocardiograms (ECGs), vital signs, and pulse oximetry.

5.2 Secondary Endpoints

Part A

Treatment Cohort

- Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$)
- Relative change from baseline in $ppFEV_1$
- Number of pulmonary exacerbations (PEx)
- Absolute change from baseline in body mass index (BMI)
- Absolute change from baseline in BMI z-score for subjects aged <20 years
- Absolute change from baseline in Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain score
- Absolute change from baseline in body weight
- Absolute change from baseline in body weight z-score for subjects aged <20 years
- Absolute change from baseline in height z-score for subjects aged <20 years
- Time-to-first PEx
- Pharmacokinetic (PK) parameters of VX-661, a VX-661 metabolite (M1-661), IVA, and an IVA metabolite (M1-IVA)

Observational Cohort

- Safety, as determined by related serious adverse events (SAEs)

[redacted]

6 STUDY DESIGN

6.1 Overall Design

This is a Phase 3, multicenter, open-label, rollover study in subjects with CF who are homozygous or heterozygous for the *F508del-CFTR* mutation and who participated in Studies VX13-661-103 (Study 103), VX14-661-106 (Study 106), VX14-661-107 (Study 107), VX14-661-108 (Study 108), VX14-661-109 (Study 109), VX14-661-111 (Study 111), Study 112, VX16-661-114 (Study 114), or other Vertex studies investigating VX-661/IVA. The study is designed to evaluate the safety and efficacy of long term treatment of VX-661/IVA.

A schematic of the study design is shown in Figure 6-1 Study Design.

Part A

Part A consists of a Treatment Cohort and an Observational Cohort (see definitions below). Subjects from Studies 103, 106, 107, 108, 109, 111, and other eligible Vertex studies investigating VX-661/IVA, may enroll in Part A. The Treatment Cohort and the Observational Cohort will be open to enrollment in parallel. The analyses specified in this SAP focus on the Part A Treatment Cohort only.

Treatment Cohort

Subjects who completed study drug treatment (i.e., VX-661/IVA, IVA monotherapy, or placebo) during the Treatment Period in the parent study who meet the eligibility criteria (Study Protocol Sections 9.1 and 9.2) will be offered the opportunity to enroll in Study 110. Subjects who permanently discontinue study drug treatment or who withdrew consent during the parent studies are not eligible for enrollment in the Treatment Cohort.

Subjects in the Treatment Cohort will receive VX-661 100 mg/IVA 150-mg fixed-dose combination (FDC) tablet daily (qd) in the morning and IVA 150-mg tablet qd in the evening. The Treatment Period will be approximately 96 weeks.

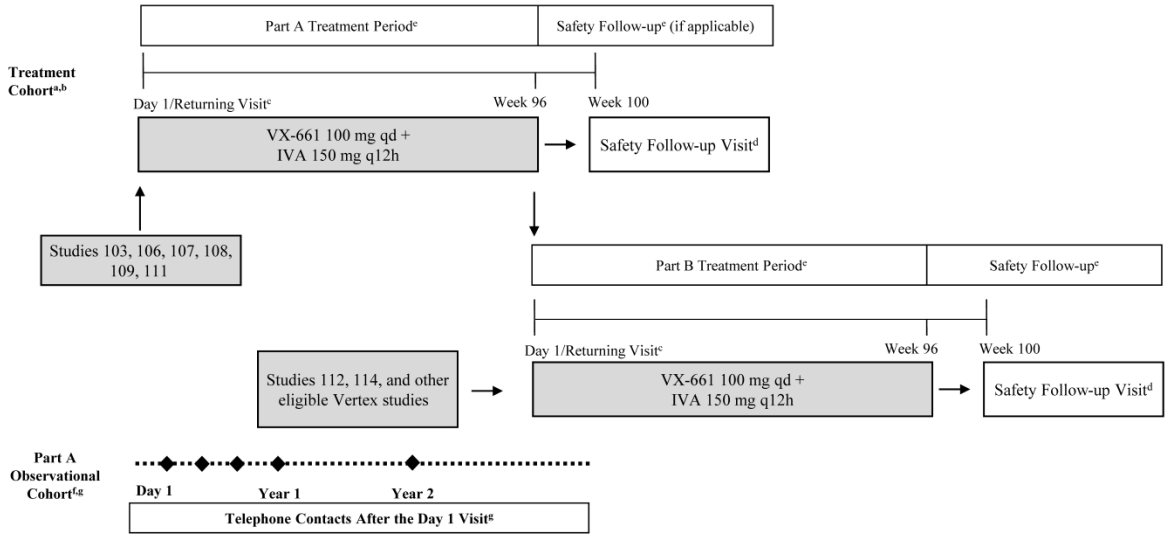
Subjects may screen for another qualified Vertex study while participating in the Treatment Cohort. Subjects who completed at least 4 weeks of treatment before discontinuing Study 110 to participate in another qualified Vertex study, and who meet the eligibility criteria (Study Protocol Sections 9.1 and 9.2), will be offered the opportunity to re-enroll in the Treatment Cohort of Study 110. Subjects who re-enroll will resume treatment with VX-661/IVA at the next study day after their previous treatment discontinuation from Study 110 (e.g., a subject who discontinued at Study Day 50 would resume treatment at Study Day 51). Subjects who discontinue Study 110 more than once to participate in another qualified Vertex study may not re-enroll in Study 110 a second time.

Observational Cohort

Subjects <18 years of age (age on the date of informed consent/assent in the parent study) who received at least 4 weeks of study drug in the parent study, who are not eligible for the Treatment Cohort or who elect not to enroll in the Treatment Cohort, and meet eligibility criteria (Study Protocol Section 9.1) will be offered the opportunity to enroll in the Observational Cohort.

Subjects in the Observational Cohort will not receive study drug and will have regularly scheduled telephone calls for approximately 2 years after their last dose of study drug in the parent study to assess post-treatment safety of VX-661/IVA combination therapy.

Figure 6-1 Study Design



ivacaftor; q12h: every 12 hours; qd: daily.

Notes: All subjects will receive a VX-661 100 mg/ivacaftor 150-mg fixed dose combination tablet qd in the morning and an ivacaftor 150-mg tablet qd in the evening.

[a] Subjects enrolled in parent studies may be eligible to enroll in the Part A Treatment Cohort or Part B if they completed study drug treatment in the parent study and meet the eligibility criteria for the Part A Treatment Cohort or Part B. Subjects who complete Part A of Study VX14-661-110 may continue into Part B of the study.

[b] Subjects may be eligible to re-enroll in the Part A Treatment Cohort or Part B if they completed the last required visit of another qualified Vertex study and meet eligibility criteria for re-enrollment.

[c] Subjects who re-enroll in the Part A Treatment Cohort or in Part B will complete the Returning Visit and resume treatment with VX-661/IVA on the next study day after their previous treatment discontinuation from Study VX14-661-110.

[d] The Safety Follow-up Visit in the Part A Treatment Cohort is scheduled to occur 28 (± 7 days) after the last dose of study drug in Part A (Section 8.1.1.2) for subjects who do not enroll in Part B. The Safety Follow-up Visit in Part B is scheduled to occur 28 (± 7 days) after the last dose of study drug in Part B. Exceptions are explained elsewhere in the protocol.

[e] During the course of study conduct, if VX-661 in combination with ivacaftor is approved and available for the treatment of CF in populations enrolled in Study VX-661-110, subjects with the approved *CFTR* genotypes may be discontinued from this rollover study at the discretion of the sponsor. If a subject is continuing onto commercially available VX-661/ivacaftor, the Early Treatment Termination Visit will be completed before dosing with commercial drug begins, and the Safety Follow-up Visit will not be required. Alternatively, if local health authorities decline to approve, or if clinical benefit is not demonstrated for the use of VX-661 in combination with ivacaftor for the treatment of CF in populations enrolled in Study VX-661-110, subjects with the relevant *CFTR* genotypes may be discontinued after communication to investigators and IRBs/IECs of the risks/benefits related to the safety and efficacy observed for the subset of subjects. If subjects are discontinued from the study, an Early Treatment Termination Visit should occur within 7 days of the last dose of study drug and a Safety Follow-up Visit should occur within 28 (± 7) days after the last dose of study drug.

[f] Subjects <18 years of age (age on the date of informed consent/assent in the parent study) who are not eligible for the Treatment Cohort, or elect not to enroll in the Treatment Cohort, may be eligible for the Observational Cohort.

[g] A telephone contact will be made every 3 to 4 months during the first year and at approximately 2 years (± 4 weeks).

6.2 Sample Size and Power

Part A

Treatment Cohort

1,044 eligible subjects are enrolled from the following parent studies:

- 23 subjects from Study 103.
- 464 subjects from Study 106.
- 159 subjects from Study 107.

- 227 subjects from Study 108.
- 138 subjects from Study 109.
- 33 subjects from Study 111.

Observational Cohort
No patient enrolled in observational cohort.

6.3 Randomization

Randomization is not required because all subjects will receive the same open-label active study drug in the Treatment Cohort.

6.4 Blinding and Unblinding

This will be an open-label study. However, subjects should not be informed of their study-related spirometry results during the study regardless of whether the subject has prematurely discontinued treatment.

7 ANALYSIS SETS

The **All Subjects Set** is defined as all subjects who have signed inform consent (enrolled) or have received at least 1 dose of study drug in Part A. This analysis set will be used in subject data listings and disposition summary tables, unless otherwise specified.

7.1 Efficacy Analysis Sets

The **Full Analysis Set** (FAS) is defined as all enrolled subjects who have received at least 1 dose of study drug in Part A and have one of the following mutations: *F508del/F508del (F/F)* and *F508del/Residual function (F/RF)*. The FAS is to be used in the efficacy analyses unless otherwise specified.
Study 106 and 108 were the basis for the approval of TEZ/IVA. Although Study 107 and 109 subjects were rolled over to FAS in Study 110, after the study results were available, subjects from Study 107 and 109 were early discontinued from Study 110. Thus, the efficacy analysis will focus on the **106/110 Efficacy Set (ES)** and **108/110 ES**, defined as all the FAS subjects rolling over from Study 106 and 108 respectively.
As shown in Table 7-1, treatment group assignment is based on the randomized treatment in parent study. For 108/110 ES, the randomized treatment assignment in Period 2 will be used to assign subjects to a treatment group in Study 110.

Table 7-1 Treatment Group for Efficacy Analysis Sets

Treatment Group	Description
TEZ/IVA	Subjects randomized to TEZ/IVA in parent study
PBO-TEZ/IVA	Subjects randomized to placebo in parent study
IVA-TEZ/IVA	Subjects randomized to IVA in parent study

7.2 Pulmonary Exacerbation Analysis Sets

106/110 PEx Analysis Set and **108/110 PEx Analysis Set** are defined in **Error! Reference source not found.**. They include the subjects who received TEZ/IVA in parent study or Part A.

Table 7-2 Treatment Group for PEx Analysis Sets

Analysis Population Name	Treatment Group	Description
106/110 PE Analysis Set	TEZ/IVA	Subjects randomized to TEZ/IVA in Study 106 and received treatment
	PBO-TEZ/IVA	Subjects randomized to placebo in Study 106 and who received TEZ/IVA in Study 110
108/110 PE Analysis Set	TEZ/IVA	Subjects randomized to IVA-TEZ/IVA sequence or PBO-TEZ/IVA sequence in Study 108 and who received treatment in Period 2 of Study 108
	IVA-TEZ/IVA	Subjects randomized to TEZ/IVA-IVA sequence or PBO-IVA sequence in Study 108 and who received treatment in Period 2 of Study 108 and who received TEZ/IVA in Study 110. Subjects in TEZ/IVA-IVA sequence who did not enroll in Study 110 treatment cohort will also be included in this group if they received treatment in Period 1.
	PBO-TEZ/IVA	Subjects randomized to TEZ/IVA-PBO sequence or IVA-PBO sequence in Study 108 and who received treatment in Period 2 of Study 108 and who received TEZ/IVA in Study 110. Subjects in TEZ/IVA-PBO sequence who did not enroll in Study 110 treatment cohort will also be included in this group if they received treatment in Period 1.

7.3 Safety Analysis Set

The **Safety Set** is defined as all subjects who have received at least 1 dose of study drug in Part A irrespective of their genotype. The Safety Set is to be used for the safety analyses unless otherwise specified.

7.4 Parent Study Safety Analysis Set

The safety results from Study 106 will be presented along with Part A results. The definition of **106 Safety Set** is the same as defined in the SAP/CSR for Study 106, i.e., subjects who received at least 1 dose of study drug in Study 106.
The treatment group assignment is the same as in Study 106, as illustrated in Table 7-3.

Table 7-3 Treatment Group for 106 Safety Set	
Treatment Group	**Description**
TEZ/IVA	Subjects who received at least 1 dose of TEZ/IVA in the parent study (including subjects randomized to TEZ/IVA or who received TEZ/IVA by error)
PBO	Subjects who take only placebo during the entire parent study period

8 ANALYSIS PERIODS

8.1 Efficacy Analysis Period

110 Efficacy Analysis Period is defined as the time period from the 1st dose of study drug in Part A to the date of last efficacy assessment in Part A.
For subjects who participate in another qualified Vertex study before completing Study 110 assessments and re-enroll in Study 110, 110 Efficacy Analysis Period will exclude the time between the last dose before the discontinuation from Study 110 and the first dose after re-enrollment in Study 110.

8.2 Pulmonary Exacerbation Analysis Period

PEx Efficacy Analysis Period is defined as the time period from the first dose of TEZ/IVA in parent study (after the washout period, if applicable) or Study 110 Part A to the date of last efficacy assessment in parent study or Study 110 Part A, as highlighted in grey in Table 8-1.
Note for parent Study 108, only Period 2 is pooled.
Similarly, for subjects who participate in another qualified Vertex study before completing Study 110 assessments and re-enroll in Study 110, the PEx Efficacy Analysis Period will exclude the time between the last dose before the discontinuation from Study 110 and the first dose after re-enrollment in Study 110.

Table 8-1 PEx Analysis Period for PEx Analysis Sets			
Analysis Set	**Analysis Period**		
	Parent Study		**Study 110 Part A**
106/110 PEx Analysis Set	TEZ/IVA		TEZ/IVA
	PBO		TEZ/IVA
108/110 PEx Analysis Set	Period 1: TEZ/IVA	Period 2: IVA	TEZ/IVA
	Period 1: IVA	Period 2: TEZ/IVA	TEZ/IVA
	Period 1: TEZ/IVA	Period 2: PBO	TEZ/IVA
	Period 1: PBO	Period 2: TEZ/IVA	TEZ/IVA

	Period 1: IVA	Period 2: PBO	TEZ/IVA
	Period 1: PBO	Period 2: IVA	TEZ/IVA

8.3 Safety Analysis Period

The safety analysis period is defined as Study 110 Treatment-emergent Period in Section 9.1.

8.4 Parent Study Safety Analysis Period

The safety analysis period will be the same as Treatment-emergent period defined in the SAP/CSR for Study 106.

9 STATISTICAL ANALYSIS

9.1 General Considerations

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

Categorical variables will be summarized using counts and percentages.

Visit Windowing Rules: Section 11.1 defines the windows for protocol-defined visits. 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.

The windows will be applied for both scheduled and unscheduled visits. If no measurement is available within a visit window, the assessment will be considered missing for the visit. If there is more than one measurement available within the same visit window, the following rules will be used:

For all safety parameters, if there are multiple measurements within a visit window, then

- The record closest to the target day will be used, with the exception of the threshold analysis in which the worst record will be used.
- If there are multiple records within the same distance of the target day, the latest record will be used.
- The SFU visit will not be windowed; instead, the nominal visit will be used in relevant analyses.

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

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

- Assessments at the Early Treatment Termination (ETT) Visit will follow the windowing rules for regular visits.
- Assessments at SFU Visit will follow the windowing rules for regular visits if they fall within the upper boundary of the window for the last scheduled visit. If assessments occur after the upper boundary of the window for the last scheduled visit, they will be still considered as the SFU Visit.

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.

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

- Derivations of measurements at scheduled visits per specified visit windowing rules;
- Derivations of baseline/last on-treatment measurements;
- Derivations of the maximum/minimum on-treatment values and maximum/minimum changes from baseline values for safety analyses;
- Data listings where appropriate.

Treatment-emergent (TE) Period will include the time from the first active dose of VX-661/ivacaftor or ivacaftor alone (in the parent study or Study VX14-661-110, but after the washout period, if applicable) to the Safety Follow-up Visit in Part A or 28 days after the last dose of the study drug for subjects who do not have a Safety Follow-up Visit or who have their Safety Follow-up Visit more than 35 days after the last dose in Part A of Study VX14-661-110. For subjects who participate in another qualified Vertex study before completing Part A of Study VX14-661-110 (96 weeks) and re-enroll in Study VX14-661-110, the TE Period will exclude the time spent in the other study.
110 Treatment-Emergent (TE) Period is defined as the time from 1st dose of study drug in Part A to SFU in Part A or 28 days after the last dose of the study drug for subjects who do not have a SFU Visit or who have their SFU Visit more than 35 days after the last dose in Part A.
For subjects who participate in another qualified Vertex study before completing Part A (96 weeks) and re-enroll in Study 110, the TE Period will exclude the time spent in the other study.
The **efficacy analysis baseline** is defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in the parent studies for all subjects, except for subjects randomized to the placebo arm in Study 106.

The efficacy analysis baseline for subjects randomized to the Study 106 placebo arm is defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in Study 110.

The **safety analysis baseline**, unless otherwise specified, is defined as the last non-missing assessment prior to the first dose of active treatment (TEZ/IVA or IVA) from the parent study (after the wash-out period, where applicable) or Study 110, whichever is earlier.

9.2 Subject Disposition

The number and percentage (based on All Subjects Set) of subjects in the following categories will be presented:

- All Subjects Set
- Safety Set
- FAS
- Completed treatment regimen
- Prematurely discontinued treatment and the reason for discontinuation
- Completed study
- Prematurely discontinued study and the reason for discontinuation
- Subjects from each of the parent studies
- Subjects rolling over to Part B

The summary tables for these categories (except "Subjects from each of the parent studies") based on 106/110 ES and 108/110 ES will be provided separately.

A listing of subjects who discontinued treatment or who discontinued study will be provided.

9.3 Demographics and Baseline Characteristics

The following demographic data from parent studies will be summarized separately for 106/110 ES and 108/110 ES:

- Age at screening
- Age groups (< 18, and >=18 years)
- Sex
- Ethnicity
- Race
- Geographic region by North America, Europe (including Australia and Israel)

The following baseline characteristics from parent studies will be summarized separately for 106/110 ES and 108/110 ES:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Weight z-score (subjects <20 years old at screening)
- Height z-score (subjects <20 years old at screening)
- BMI z-score (subjects <20 years old at screening)

- Percent predicted FEV_1
- Percent predicted FEV_1 categories (<40, ≥40 to <70, ≥70 to ≤90, >90)
- FEV_1 (L)
- CFQ-R Respiratory

Listings of informed consent, of important protocol deviations/violations will be provided. Medical history, coded by using the Medical Dictionary for Regulatory Activities (MedDRA), will not be summarized because most data were already collected in the parent studies. Only a listing will be presented for the medical history data collected in Part A.

9.4 Prior and Concomitant Medications

Medications used in this study will be coded by using the World Health Organization Drug Dictionary (WHO-DD) and categorized as:

- **Prior medication:** any medication that started before the first dose of study drug in Study Part A, regardless of when the medication ended.
- **Concomitant medication:** medication continued or newly received at, or after, initial dosing of study drug through the end of 110 TE Period.
- **Post-treatment medication:** medication continued or newly received after 110 TE Period.

A given medication can be classified as a prior, a concomitant, 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 partially missing start/end date and it cannot be determined whether it was taken before the first dose, concomitantly, or beyond the TE period, it will be considered as prior, concomitant, and post-treatment.

Medications with missing or partially missing start dates will impute 2000 for the missing year, January for the missing month, and 1 for the missing day. Medications with missing or partially missing stop dates will impute 2050 for the missing year, December for the missing month, and the last day of the month for the missing day. The logic to decide the category of a medication is presented in Table 9-1:

Table 9-1 Logic for Determining the Category of a Medication

Medication start date	**Medication end date**		
	< first dose date of 110 study drug	≥ first dose date of 110 study drug and ≤ End date of 110 TE period	> End date of 110 TE period
< first dose date of study drug	P	PC	PCA
≥ first dose date and ≤ End date of TE period	-	C	CA

> End date of TE period	-	-	A
P: Prior; C: Concomitant; A: Post			

Concomitant medications will be summarized descriptively for Safety Set by: 1) preferred name; and 2) anatomic class (ATC) level 1, ATC level 2, and preferred name.

The medications (prior, concomitant, post-treatment) will be listed.

9.5 Study Drug Exposure and Compliance

The cumulative duration of TEZ/IVA exposure based on 110 TE Period is defined as: last dose date on TEZ/IVA – first dose date on TEZ/IVA + 1 day, regardless of any interruption between the first and last dose. If the last dose date is missing, the subject's last ETT date (for early treatment discontinuations) will be used as a substitute for analysis purposes.
Study drug 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 sum of (number of days of study drug interrupted in each interruption interval), where number of days of study drug interrupted in each interval is defined as the interruption end date - the corresponding interruption start date + 1.

Duration of treatment and dosing compliance for Safety Set will be summarized by descriptive summary statistics: the number of subjects (n), mean, SD, median, min, and max.

Listings of study drug administration, of study drug compliance rates, and of study drug interruptions will be provided.

9.6 Efficacy Analysis

9.6.1 Definitions of Efficacy Endpoints

9.6.1.1 Absolute Change in Percent Predicted FEV1 from Baseline

$ppFEV_1$ is the ratio of FEV_1 (L) to the predicted FEV_1 (L), expressed as a percentage and will be calculated using the Hankinson ([1]) and Wang ([2]) standards with details in Section 11.2.

9.6.1.2 Number of Pulmonary Exacerbations

The definition of a PEx is based on the definition in the individual CSP/CSR. A PEx is defined as a new or change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the following signs/symptoms:

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy

- Temperature above 38°C (equivalent to approximately 100.4°F)
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination of the chest
- Decrease in pulmonary function by 10%
- Radiographic changes indicative of pulmonary infection

The number of PEx is defined as the total number of PEx during the PEx Analysis Period.

9.6.1.3 Absolute Change in BMI from Baseline

BMI will be calculated as:

$$\text{BMI} = \text{Weight (kg)}/(\text{height (m)}^2)$$

9.6.1.4 Absolute Change in CFQ-R Respiratory Domain from Baseline

The CFQ-R is a validated CF-specific instrument that measures quality-of-life domains. Three different versions of CFQ-R forms have been used in the VX-661 program:

- CFQ-R for Children Ages 12 and 13 has a total of 35 questions to form 8 domains. All questions are scored 1, 2, 3, or 4.
- CFQ-R for Adolescents and Adult (subjects 14 years and older) has a total of 50 questions to form 12 domains. Question 43, which is scored 1, 2, 3, 4, or 5, is not used in calculating any domain; all the other 49 questions are scored 1, 2, 3, or 4.
- CFQ-R for Parents/Caregivers (subjects 13 years and younger) has a total of 44 questions to form 11 domains. Question 37, which is scored 1, 2, 3, 4, or 5, is not used in calculating any domains; all the other 43 questions are scored 1, 2, 3, or 4.

For all three CFQ-R versions, to calculate the score for each domain, the response scores on the negatively phrased questions are reversed (reversed scores = 5 – response scores) so that 1 always represents the worst condition and 4 always represents the best condition.

The scaled score for each domain ranges from 0 (worst condition) to 100 (best condition). It is calculated as follows:

$$\text{Scaled score for a domain} = 100 \times (\text{mean(scores of all questions in that domain)} - 1)/3$$

The scaled score for a specific domain will not be calculated if more than half of the questions in the domain have missing scores. [redacted]

Scaled scores will be used in the efficacy analysis.

9.6.1.5 Time to First Pulmonary Exacerbation on TEZ/IVA

The time to first PEx is defined as the number of days from the first dose of TEZ/IVA to the first PEx event during the PEx Analysis Period.

9.6.2 Analysis of Efficacy Endpoints

Most continuous endpoints during 110 Efficacy Analysis Period will be analyzed for subjects in 106/110 ES and 108/110 ES using a mixed-effects model for repeated measures (MMRM) with similar specification as in the parent study SAP/CSR, if applicable. However, these MMRM analysis will be restricted to the last visit at which the total number of subjects is approximately 70% of subjects from the respective parent study.

These continuous endpoints during 110 Efficacy Analysis Period will also be descriptively summarized for subjects in FAS who roll over from Study 103 and 111, where the patients carry *F/F* mutation.

No hypothesis testing will be done for between-group comparisons.

9.6.2.1 Absolute Change in Percent Predicted FEV1 from Baseline

9.6.2.1.1 Subjects in 106/110 ES

The MMRM for 106/110 ES during 110 Efficacy Analysis Period will have the absolute change in $ppFEV_1$ from baseline (including all measurements up to Week 96 [inclusive], both on-treatment measurements and measurements after treatment discontinuation) as the dependent variable and the following fixed effects: treatment (PBO-TEZ/IVA, TEZ/IVA), visit, and treatment-by-visit interaction, sex and age group at screening (<18, ≥18 years old), parent study baseline $ppFEV_1$, and parent study baseline $ppFEV_1$-by-visit interaction.

The repeated-measures analysis will be based on the restricted maximum likelihood (REML) method assuming an unstructured (UN) covariance structure to model the within-subject errors. The denominator degrees of freedom will be based on the method proposed by Kenward-Roger. If the model fails to converge due to the UN covariance assumption, a compound symmetry (CS) covariance structure will be used to model the within-subject errors. In the MMRM approach, assuming that the data are missing at random, no imputation of missing data will be performed.

The number of subjects, least-squares (LS) means at scheduled visits within each treatment group along with the corresponding standard error (SE) and 95% confidence interval (CI) will be presented.

The LS means (±95% CI) for absolute change from baseline at each visit will also be plotted by treatment group.

In addition, the descriptive statistics for observed values and absolute changes from baseline in $ppFEV_1$ by treatment group will be presented at scheduled visits during 110 Efficacy Analysis Period.

9.6.2.1.2 Subjects in 108/110 ES

The analysis for 108/110 ES during 110 Efficacy Analysis Period will be similar to that for 106/110 ES with the exception of different fixed effects: treatment (PBO-TEZ/IVA, IVA-TEZ/IVA, TEZ/IVA), visit, treatment-by-visit interaction and parent study baseline $ppFEV_1$.

Similarly, the results from this MMRM along with descriptive statistics for observed values and absolute changes from baseline will be presented at scheduled visits within each treatment

group, and LS means (±95% CI) for absolute change from baseline at each visit will also be plotted by treatment group.

9.6.2.1.3 Subjects in FAS Who Roll Over from Study 103

For FAS patients rolling over from Study 103, descriptive statistics will be summarized for observed values and absolute changes from baseline in $ppFEV_1$ by treatment group at scheduled visit during 110 Efficacy Analysis Period.

9.6.2.1.4 Subjects in FAS Who Roll Over from Study 111

The analysis for FAS patients rolling over from Study 111 will be similar to that for FAS patients rolling over from Study 103.

9.6.2.2 Number of Pulmonary Exacerbations

9.6.2.2.1 Subjects in 106/110 PEx Analysis Set

The number of PEx during the PEx Analysis Period will be analyzed for 106/110 PEx Analysis Set using a negative binomial regression model and reported as event rate along with the 95% CI. The model will include: treatment (TEZ/IVA, PBO-TEZ/IVA), sex, age group at screening (<18, ≥18 years old), and parent study baseline $ppFEV_1$. The logarithm of PEx analysis period duration will be treated as the offset in this model. If the model does not converge, the negative binomial regression model will be replaced with a Poisson regression model.

Similarly the number of PEx (i) requiring hospitalization, and (ii) requiring IV antibiotic therapy will be analyzed.

9.6.2.2.2 Subjects in 108/110 PEx Analysis Set

The analysis for 108/110 PEx Analysis Set will be similar to 106/110 PE Analysis Set, with the exception of different fixed effects: treatment (TEZ/IVA, IVA-TEZ/IVA, and PBO-TEZ/IVA), residual function mutation (Class V non-canonical splice and Classes II to IV residual function), age group at screening (<18, ≥18 years old), and parent study baseline $ppFEV_1$.

Similarly the number of PEx (i) requiring hospitalization, and (ii) requiring IV antibiotic therapy will be analyzed.

9.6.2.3 Time to First Pulmonary Exacerbation

9.6.2.3.1 Subjects in 106/110 PEx Analysis Set

Time-to-first PEx on TEZ/IVA during PEx Analysis Period will be analyzed and plotted by treatment group using the Kaplan-Meier approach.

Subjects without a PEx by the end of PEx Analysis Period will be censored at the time-point corresponding to the end of PEx Analysis Period.

9.6.2.3.2 Subjects in 108/110 PEx Analysis Set

The analysis of time-to-first PEx for 108/110 PEx Analysis Set will be similar to that for 106/110 PEx Analysis Set.

9.6.2.4 Other Efficacy Endpoints

For all the other efficacy endpoints (including relative change in $ppFEV_1$ from baseline, absolute change in BMI from baseline, absolute change in BMI z- score from baseline, absolute change in CFQ-R Respiratory Domain Score from baseline, absolute change in weight from baseline, absolute change in weight z-score from baseline, absolute change in height z-score from baseline), the analysis will be similar to the analysis of absolute change in $ppFEV_1$ from baseline. Note that for CFQ-R Respiratory Domain Score, the Pooled 'Children Ages 12 and 13' Version and 'Adolescents and Adults' Version is used for MMRM based approach and descriptive summary, 'Parents/Caregivers' Version is also used for descriptive summary.

[redacted]

9.6.2.4.1 Subjects in 106/110 ES and 108/110 ES

The similar analysis will be performed as the analysis of absolute change in $ppFEV_1$ from baseline for 106/110 ES or 108/110 ES during 110 Efficacy Analysis Period. However, in the MMRM models of all other efficacy endpoints, the terms involving parent study baseline $ppFEV_1$ will be replaced by similar terms involving the corresponding endpoint in parent study. Similarly, the results based on MMRM along with descriptive statistics for observed values and absolute changes from baseline will be presented at scheduled visits within each treatment group, and LS means (±95% CI) for absolute change from baseline at each visit will also be plotted by treatment groups.

9.6.2.4.2 Subjects in FAS Who Roll Over from Study 103 and 111

For subjects in FAS who rolled over from Study 103 and 111 respectively, descriptive summary statistics of observed values and absolute or relative changes from baseline in these efficacy endpoints will be provided at scheduled visit during 110 Efficacy Analysis Period.

9.7 Safety Analysis

9.7.1 Adverse Events

For each individual parent study, summary table of treatment emergent AEs during the respective parent study will be included in the Study 110 CSR. The parent studies are 103, 111, 106, 108, 107 and 109.

The analysis of Adverse Events in the rest of section 9.7.1 will be based on the Safety Set during **110 TE Period.**

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

- **Pretreatment AE:** any AE that started before the first dose of study drug in Part A.
- **TEAE:** any AE that increased in severity or that was newly developed at or after the first dose of study drug in Study Part A through the end of 110 TE Period.
- **Post-treatment AE:** any AE that increased in severity or that was newly developed after 110 TE 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 will be considered as TEAE. As an intermediate step for programming purposes, imputation rules for missing or partially missing AE start/end dates are defined in Section 11.4.

TEAEs will be classified into 4 categories of relationship to the study drugs: not related, unlikely related, possibly related, related.

TEAEs will be classified into 4 categories of severity:

- **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.

All the summary tables of TEAEs display counts and exposure-adjusted event rates for the Safety Set in Study 110.

9.7.1.1 Overview of TEAEs

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

- Any TEAEs
- TEAEs by strongest relationship
- Related TEAEs
- TEAEs by maximum severity
- Grade 3/4 TEAEs
- Serious TEAEs
- Related serious TEAEs
- TEAEs leading to treatment discontinuation (this will capture TEAEs leading to discontinuation to either the morning or the evening tablets)
- TEAEs leading to treatment interruption (this will capture TEAEs leading to interruption to either the morning or the evening tablets)
- TEAE leading to death

9.7.1.2 TEAEs, Related TEAEs, Serious TEAEs, Related Serious TEAEs, Grade 3/4 TEAEs

Using MedDRA System Organ Class (SOC) and Preferred Term (PT), the number of subjects and exposure-adjusted event rates for the following TEAEs are summarized based on the Safety Set during 110 TE Period:

- TEAEs by PT and by SOC/PT

- Related TEAEs by SOC/PT
- Serious TEAEs by PT and by SOC/PT
- Related serious TEAEs by SOC/PT
- Grade 3/4 TEAEs by SOC/PT

Multiple occurrences of the same adverse event or a continuing adverse event for the same subject will be counted once. Related adverse events include related, possibly related, and missing categories. The summary tables will be presented in descending order of frequencies in the column based on Safety Set in Study 110.

9.7.1.3 TEAEs Leading to Treatment Discontinuation, Treatment Interruption, Death

The number of subjects and exposure-adjusted event rate for TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption, and TEAEs leading to death will be summarized by SOC/PT for Safety Set during 110 TE Period.

In addition, the following listings will be provided for Safety Set during 110 TE Period:

- Listing of TEAEs leading to treatment discontinuation
- Listing of TEAEs leading to treatment interruption
- Listing of AEs leading to death
- Listing of Serious AEs
- Listing of all AEs by subject
- Listing of TEAEs by preferred term

9.7.1.4 Elevated Transaminase, Respiratory Events or Symptoms

Respiratory events (including symptoms) are defined as any of the following 7 TEAE PTs: Chest Discomfort, Dyspnoea, Respiration abnormal, Asthma, Bronchial hyperreactivity, Bronchospasm, Wheezing.

Respiratory symptoms are defined as any of the following 3 TEAE PTs: Chest Discomfort, Dyspnoea, Respiration abnormal.

Elevated transaminase is defined as the occurrence of any of the following TEAE preferred terms: Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Transaminases abnormal, Transaminases increased, Liver function test abnormal, Liver function test increased, Hyper transaminasaemia, Hepatic enzyme abnormal, Hepatic enzyme increased.
A summary of elevated transaminase, respiratory events and respiratory symptoms counts and exposure-adjusted event rate will be presented by PT for Safety Set during 110 TE Period.

[redacted]

[redacted]

9.7.2 Clinical Laboratory Values

With the threshold criteria for abnormal high/abnormal low listed in Section 11.3, the following summaries for chemistry, LFT, hematology, coagulation, vitamin levels, and lipid panel assessments will be presented for Safety Set during 110 TE Period:

- Raw values and change from baseline will be summarized using SI units by visit.
- Number and percentage of subjects with abnormal assessments meeting the threshold criteria will be summarized during the entire 110 TE Period.
- A summary table for the shift from baseline to post-baseline will be summarized by visit.

Mean value at each visit will be plotted for each LFT parameter.

A listing containing individual subject laboratory assessment values outside the reference ranges will be provided.

Listings of abnormal urinalysis and positive serum/urine pregnancy tests will be provided.

9.7.3 Electrocardiogram

The raw values and change from baseline values will be summarized at each scheduled visit for Safety Set during 110 TE Period: PR, QT, and QTc for HR interval (QTcF), QRS duration, and HR. The number and percentage of subjects with at least 1 threshold analysis event during the entire 110 TE Period will be summarized by treatment group. The threshold analysis criteria are listed in Section 11.3.

9.7.4 Vital Signs

The raw values and change from baseline values will be summarized at each scheduled visit for Safety Set during 110 TE Period: systolic and diastolic blood pressure (mm Hg), body temperature (°C), HR (beats per minute [bpm]), and respiratory rate (breaths per minute). The number and percentage of subjects with at least 1 threshold analysis event during the entire 110 TE Period will be summarized. The threshold analysis criteria are provided in Section 11.3.

9.7.5 Pulse Oximetry

The raw values and change from baseline values will be summarized at each scheduled visit for Safety Set during 110 TE Period for the percent of oxygen saturation by pulse oximetry. The number and percentage of subjects with shift changes from baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the entire 110 TE Period will be tabulated.

9.7.6 Ophthalmologic Examination

The ophthalmologic examination results may be listed for subjects < 18 years old (age on the date of informed consent/assent in the parent study) with cataracts anytime during 110 TE Period.

9.7.7 Pregnancy Tests

Positive urine and serum pregnancy test results during baseline and TE period will be listed.

10 REFERENCES

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11 APPENDICES

11.1 Analysis Visit Window Mapping Rules

Table 11-1 Visit Window Mapping Rules for Safety Measurements

Assessments	Visit	Target Study Day	Visit Window (in study days)

• Standard 12-lead ECG
• Vital signs
• Pulse oximetry
• Labs
  ○ Chemistry
  ○ Hematology
	Day 1	1	[1, 1]

	Day 15	15	[2, 36]
	Week 8	57	[37, 85]
	Week 16	113	[86, 141]
	Week 24	169	[142, 211]
	Week 36	253	[212, 295]
	Week 48	337	[296, 379]
	Week 60	421	[380, 463]
	Week 72	505	[464, 547]
	Week 84	589	[548, 631]
	Week 96	673	[632, 687]
	ETT	N/A	Follow the individual visit window to be mapped to individual visits
	Safety Follow-up Visit	N/A	Nominal (remain as SFU)

• Coagulation
• Lipid Panel
• Labs
  ○ Vitamin Level
  ○ Urinalysis
	Day 1	1	[1, 1]

	Week 8	57	[2, 85]
	Week 16	113	[86, 141]
	Week 24	169	[142, 211]
	Week 36	253	[212, 295]
	Week 48	337	[296, 379]
	Week 60	421	[380, 463]
	Week 72	505	[464, 547]
	Week 84	589	[548, 631]
	Week 96	673	[632, 687]
	ETT	N/A	Follow the individual visit window to be mapped to individual visits
	Safety Follow-up Visit	N/A	Nominal (remain as SFU)

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 measurements.

Table 11-2 Visit Window Mapping Rules for Efficacy Measurements

Assessments	Visit	Analysis Visit	Target Study Day	Visit Window (in study days)
• Spiromtery • CFQ-R	Day 15	Study 110 Day 15	15	[2, 36]
	Week 8	Study 110 Week 8	57	[37, 85]
	Week 16	Study 110 Week 16	113	[86, 141]
	Week 24	Study 110 Week 24	169	[142, 211]
	Week 36	Study 110 Week 36	253	[212, 295]
	Week 48	Study 110 Week 48	337	[296, 379]
	Week 60	Study 110 Week 60	421	[380, 463]
	Week 72	Study 110 Week 72	505	[464, 547]
	Week 84	Study 110 Week 84	589	[548, 631]
	Week 96	Study 110 Week 96	673	[632, 687]
	ETT		N/A	Follow the individual visit window to be mapped to individual visits
	Safety Follow-up Visit	Safety Follow-up Visit	N/A	Follow the individual visit window to be mapped to individual visits if fall within the upper boundary of the window for the last scheduled visit (Day 687); or remain as SFU if otherwise.
• Weight and height • BMI	Week 8	Study 110 Week 8	57	[2, 85]
	Week 16	Study 110 Week 16	113	[86, 141]
	Week 24	Study 110 Week 24	169	[142, 211]
	Week 36	Study 110 Week 36	253	[212, 295]
	Week 48	Study 110 Week 48	337	[296, 379]
	Week 60	Study 110 Week 60	421	[380, 463]
	Week 72	Study 110 Week 72	505	[464, 547]
	Week 84	Study 110 Week 84	589	[548, 631]
	Week 96	Study 110 Week 96	673	[632, 687]
	ETT	ETT	N/A	Follow the individual visit window to be mapped to individual visits
	Safety Follow-up Visit	Safety Follow-up Visit	N/A	Follow the individual visit window to be mapped to individual visits if fall within the upper boundary of the window for the last scheduled visit (Day 687); or remain as SFU if otherwise.

Note:

1. To apply the above visit windows, please first label Day 1 for the date of the first dose in Study 110 drug, and use the nominal visit names to label SFU (for safety).

2. After the 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.

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

   – 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.

   – Assessments at the early treatment termination (ETT) visit will follow the windowing rules for regular visits.

   – 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 the last scheduled visit; it will remain as the SFU if it goes beyond the upper boundary of the window for the last scheduled visit.

4. 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, with the exception of the threshold analysis in which the worst record will be used; 2) if there are multiple records within the same distance of the target day, the latest record will be used; or 3) the SFU visit will not be windowed; instead, the nominal visit will be used in relevant analysis.

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

- On Day 1 & Day 15, ECGs will be collected before dosing and at 1.5 and 4 hours after the morning dose. None of the measures on Day 1 or Day 15 will be mapped into other visits.

  - Day 1 post-dose and Day 15 pre-/post-dose measurements will be analyzed based on nominal visit names.

  - On Day 1, the pre-dose measurements will be performed in triplicate, the average of the triplicate will be used as pre-dose measurement on Day 1. Only pre-dose measurement with nominal visit names related to the triplicate shall be used in this average.

- The visit window in the above table will still apply for the ECG data after Day 15.

11.2 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 provided in [1].

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

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

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 provided in [2].

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.

11.3 Threshold Analysis Criteria

Table 11-3 Threshold Criteria for Clinical Chemistry and Hematology

Parameter	Threshold Criteria
Clinical Chemistry	
CPK	>ULN - ≤ 2.5 x ULN >2.5 - ≤ 5 x ULN >5 - ≤ 10x ULN >10 x ULN
Creatinine	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN
Blood Urea Nitrogen	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN
Sodium	Hyponatremia <LLN - ≥130 mmol/L <130 – ≥120 mmol/L <120 mmol/L
	Hypernatremia >ULN - ≤ 150 mmol/L >150 mmol/L- ≤155 mmol/L >155 mmol/L - ≤ 160 mmol/L >160 mmol/L
Potassium	Hypokalemia <LLN – ≥ 3.0 mmol/L <3.0 – ≥ 2.5 mmol/L <2.5 mmol/L
	Hyperkalemia >ULN – ≤ 5.5 mmol/L >5.5 – ≤ 6.0 mmol/L >6.0 – ≤ 7.0 mmol/L >7.0 mmol/L
Total Cholesterol	>ULN – ≤ 7.75 mmol/L >7.75 – ≤ 10.34 mmol/L >10.34 – ≤ 12.92 mmol/L >12.92 mmol/L

Triglycerides	>1.71 – ≤ 3.42 mmol/L
	>3.42 – ≤ 5.7 mmol/L
	>5.7 – ≤ 11.4 mmol/L
	>11.4 mmol/L
Glucose	Hypoglycemia
	<3.0 – ≥ 2.2 mmol/L
	<2.2 - ≥ 1.7 mmol/L
	<1.7 mmol/L
	Hyperglycemia
	>ULN - ≤ 8.9 mmol/L
	>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
Amylase	>ULN - ≤ 1.5 x ULN
	>1.5 – ≤ 2.0 x ULN
	>2.0 – ≤ 5.0 x ULN
	>5.0 x ULN
Lipase	>ULN - ≤ 1.5 x ULN
	>1.5 – ≤ 2.0 x ULN
	>2.0 – ≤ 5.0 x ULN
	>5.0 x ULN
Direct bilirubin	>ULN - ≤ 1.5 x ULN
	>1.5 – ≤ 2 x ULN
	>2 – ≤ 3 x ULN
	>3 – ≤ 10 x ULN
	>10 x ULN
GGT	>ULN - ≤ 2.5 x ULN
	>2.5 – ≤ 5.0 x ULN
	>5.0 – ≤ 20.0 x ULN
	>20.0 x ULN
Calcium	Hypercalcemia
	>ULN - ≤ 2.9 mmol/L
	>2.9 – ≤ 3.1 mmol/L
	>3.1 – ≤ 3.4 mmol/L
	>3.4 mmol/L
	Hypocalcemia
	<LLN - ≥ 2.0 mmol/L

	<2.0 – ≥1.75 mmol/L
	<1.75 – ≥ 1.5 mmol/L
	<1.5 mmol/L
Magnesium	Hypermagnesemia
	>ULN - ≤ 1.23 mmol/L
	>1.23 – ≤ 3.30 mmol/L
	>3.30 mmol/L
	Hypomagnesemia
	<LLN - ≥ 0.5 mmol/L
	<0.5 – ≥ 0.4 mmol/L
	<0.4 – ≥ 0.3 mmol/L
	<0.3 mmol/L
Inorganic phosphate	Hypophosphatemia
	<0.74 – ≥ 0.6mmol/L
	<0.6 – ≥ 0.3 mmol/L
	<0.3 mmol/L
ALT	>ULN - ≤ 3 xULN
	>3 – ≤ 5 xULN
	>5 – ≤ 8 xULN
	>8 – ≤ 20.0 xULN
	>20.0 x ULN
AST	>ULN - ≤ 3 xULN
	>3 – ≤ 5 xULN
	>5 – ≤ 8 xULN
	>8 – ≤ 20.0 xULN
	>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
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
Total Bilirubin	>ULN - ≤ 1.5 x ULN
	>1.5 – ≤ 2 x ULN
	>2 – ≤ 3 x ULN
	>3 – ≤ 10 x ULN

	>10 x ULN
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN
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
	Leukocytosis >100 x 10e9 /L
Lymphocytes	Lymphocyte decreased <LLN - ≥ 0.8 x10e9 /L <0.8 – ≥ 0.5 x10e9 /L <0.5 – ≥ 0.2 x10e9 /L <0.2 x10e9 /L
	Lymphocyte increased >4 – ≤ 20 x10e9/L >20 x10e9/L
Neutrophils	Neutrophil decreased <LLN - ≥ 1.5 x10e9 /L <1.5 – ≥ 1.0 x10e9 /L <1.0 – ≥ 0.5 x10e9 /L <0.5 x10e9 /L
Hemoglobin	Hgb decreased (anemia) <LLN - ≥ 100 g/L <100 – ≥ 80 g/L < 80 g/L
	Hgb increased >ULN - ≤ 20 g/L above ULN >20 g/L above ULN - ≤ 40 g/L above ULN >40 g/L above ULN
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

Note: Sources utilized for threshold analyses:
- NCI CTC-AE v4.03;
- FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical trials;
- FDA Guidance for Industry – DILI: Premarketing Clinical Evaluation.

Table 11-4 Threshold Criteria for Coagulation

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ECGs Ref.: CPMP 1997 guideline.	
Parameter	**Threshold**
Activated partial thromboplastin time (PTT)	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.5 x ULN >2.5 x ULN
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.5 x ULN >2.5 x ULN

Note: Sources utilized for threshold analyses:
- NCI CTC-AE v4.03;
- FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical trials;
- FDA Guidance for Industry – DILI: Premarketing Clinical Evaluation.

Table 11-5 Threshold Criteria for ECGs

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ECGs Ref.: CPMP 1997 guideline.	
Parameter	**Threshold**
HR	Bradycardia
	<50 bpm
	<45 bpm
	Decrease from baseline ≥10 bpm
	Decrease from baseline ≥20 bpm
	<50 bpm and decrease from baseline ≥10 bpm
	<50 bpm and decrease from baseline ≥20 bpm
	Tachycardia
	>100 bpm
	>115 bpm
	>130 bpm
	Increase from baseline ≥10 bpm
	Increase from baseline ≥20 bpm
	>100 bpm and increase from baseline ≥10 bpm
	>100 bpm and increase from baseline ≥20 bpm
PR	≥240 ms
	≥300 ms
	≥200 ms and increase from baseline ≥40 ms
	≥200 ms and increase from baseline ≥100 ms
QRS	>110 ms
	>160 ms
	Increase from baseline ≥20 ms
	Increase from baseline ≥40 ms
QTc	>450 ms (Male)
	>470 ms (Female)
	≥500 ms
	Increase from baseline >10 ms
	Increase from baseline >20 ms
	Increase from baseline >40 ms
	Increase from baseline >60 ms

Note: Sources utilized for threshold analyses:
- NCI CTC-AE v4.03;

- FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical trials;
- FDA Guidance for Industry – DILI: Premarketing Clinical Evaluation.

Table 11-6 Threshold Criteria for Vital Signs

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT VITAL SIGNS	
Parameter	**Threshold Criteria**
HR	Same PCS as above in ECG category
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
	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
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

	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
	Weight loss
	≥5 % decrease from baseline
	≥10 % decrease from baseline
	≥ 20% decrease from baseline

Note: Sources utilized for threshold analyses:
- NCI CTC-AE v4.03;
- FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical trials;
- FDA Guidance for Industry – DILI: Premarketing Clinical Evaluation

11.4 Imputation Rules for Missing or Partial AE Date

For missing or partial AE start date, use the imputation rules below for the purpose of determining whether an AE is treatment-emergent. The imputed dates will not be displayed in the listing outputs.

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.

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