VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX15-770-126
Final Analysis

A Phase 3, 2-Arm, Open-label Study to Evaluate the Safety and Pharmacodynamics of Long-term Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have an Approved Ivacaftor-Responsive Mutation

[redacted]

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2 MODIFICATIONS

2.1 Modifications to the Approved Clinical Study Protocol

In calculating normalized measures of growth (weight-for-age z-scores, length-for-age z-scores, and weight-for-length-for-age z-scores), WHO reference standards are used instead of CDC reference standards, per CDC recommendations. The reference for z-scores has been updated accordingly.

Per Administrative Letter dated 31 October 2017, in the Schedule of Assessments tables for same-day and gap-transition subjects from Study 124 Part B, an 'X' was inadvertently omitted from the row "12-lead ECGs" for the column "Weeks 12, 36, 60, and 84 (+/- 7 Days)" under "Treatment Period (Day 1 through Week 96)." Data from 12-lead ECGs at these visits will be presented.

Per Administrative Letter dated 07 October 2022, text identified below is revised to clarify that the Follow-up Ophthalmologic Examination (OE) is not required for subjects who rolled over from Study VX15-770-124 and who initiate treatment with commercially available ivacaftor, because safety information for these patients will be collected and reported as part of the post-marketing process. This clarification is being provided to maintain consistency with the Safety Follow-up visit for these subjects, which is not required for the same reason. Text identified below is copied from the indicated section of the protocol with clarifying text provided in italics and deleted text in strikethrough font.

Section 2 Protocol Synopsis Study Design
Subjects who receive commercially available ivacaftor will be discontinued from study drug dosing and will complete the ETT Visit ~~and the Follow-up OE~~; the Safety Follow-up Visit *and 24-Week Follow-up OE* will not be required

Section 9.1.1.4 Ivacaftor Arm Follow-up Ophthalmologic Examination (All Subjects)
There will be a Follow-up OE 24 weeks + 14 days after the last dose of ivacaftor for all subjects *except for subjects who initiate treatment with commercially available ivacaftor within 3 weeks of the final scheduled treatment visit or ETT Visit.*

Section 9.1.1.5 Ivacaftor Arm Early Termination of Treatment (All Subjects)

Subjects who receive commercially available ivacaftor will be discontinued from ivacaftor dosing and will complete the ETT Visit ~~and Follow-up OE~~; the Safety Follow up Visit *and Follow-up OE* will not be required.

Section 9.7 Removal of Subjects

During the course of study conduct, if ivacaftor is approved and available for the treatment of CF in populations enrolled in this study, and if a subject chooses to move onto commercially available ivacaftor, the ETT Visit (Section 9.1.1.5) will be completed before dosing with commercial drug begins, and the Safety Follow-up Visit and Follow-up OE will not be required.

Table 3-1 Footnote "a"

The ETT Visit is to be scheduled as soon as possible after the last dose of ivacaftor. If the ETT Visit occurs 3 weeks or later after the last dose of ivacaftor, the Safety Follow up Visit will not be required. Subjects who elect to receive commercially available ivacaftor will be discontinued from ivacaftor dosing and will complete the ETT Visit ~~and Follow-up OE.~~

Table 3-1 Footnote "b"

For subjects who elect to receive commercially available ivacaftor, the Safety Follow-up Visit *and Follow-up OE* will not be required.

Additional Clarifications

The following are provided to correct minor inconsistencies:

Table 3-1 Footnote "d"

Study Drug Dose Determination is not to be performed at the Week 96 Visit because it is the final visit of the treatment period.

Tertiary Endpoint "weight-for-length-for-age z-score"

The term "weight-for-length-for-age z-score" is not the appropriate name for this endpoint. The correct name is "weight-for-length z-score" in the following sections of the protocol: Sections 2 Synopsis (Assessments); 7.1.3 Tertiary Endpoints; 9.2.3 Rationale for Study Assessments (Measures of Nutritional Status); 11.5.1 Measures of Nutritional Status; and 12.3.3.3 Analysis of Tertiary Variables.

In addition, the final analysis will be based on the combined subjects from Study 124 Parts B and A/B, and subjects not from Study 124 Parts B and A/B.

2.2 Modifications to the Approved Statistical Analysis Plan

Not applicable.

3 INTRODUCTION

This statistical analysis plan (SAP) Methods is for the final analysis for the VX15-770-126 study and is based on the approved clinical study protocol (CSP), dated 05 October 2017, version 2.0.

Study VX15-770-126 is a phase 3, 2-arm, open-label study to evaluate the safety and pharmacodynamics of long-term ivacaftor treatment in subjects with cystic fibrosis who are less than 24 months of age at treatment initiation and have an approved ivacaftor-responsive mutation.

This SAP (Methods) documents the planned final statistical analysis of efficacy and safety endpoints defined in the study protocol of VX15-770-126.

The Vertex Biometrics Department will perform the final statistical analysis of the efficacy and safety 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).

The SAP (Methods) for the final analysis will be finalized and approved before the database lock for the final analysis. Any changes made to the SAP Methods after the database lock has occurred will be documented in the clinical study report for the final analysis.

4 OBJECTIVES

4.1 Primary Objective

Ivacaftor Arm:

To evaluate the safety of long-term ivacaftor treatment in subjects with CF who are <24 months of age at treatment initiation and have an approved ivacaftor-responsive mutation.

Observational Arm:

To evaluate the long-term safety after discontinuation of ivacaftor treatment in subjects with CF who were <24 months of age at treatment initiation and have an approved ivacaftor-responsive mutation.

4.2 Secondary Objectives

Ivacaftor Arm:

To evaluate the pharmacodynamics (PD) of long-term ivacaftor treatment in subjects with CF who are <24 months of age at treatment initiation and have an approved ivacaftor-responsive mutation.

Observational Arm:

Not applicable.

4.3 Tertiary Objectives

Ivacaftor Arm:

To evaluate the efficacy of long-term ivacaftor treatment in subjects with CF who are <24 months of age at treatment initiation and have an approved ivacaftor-responsive mutation.

Observational Arm:

Not applicable.

5 STUDY ENDPOINTS

5.1 Efficacy Endpoint

5.1.1 Primary Efficacy Endpoint

Not applicable.

5.1.2 Secondary Efficacy/Pharmacodynamic Endpoints

Ivacaftor Arm:

Absolute change from baseline in sweat chloride through Week 96

Observational Arm:

Not applicable.

5.1.3 Tertiary Endpoints

Ivacaftor Arm:

- Absolute change from baseline through Week 96 for the following endpoints:
  - Weight
  - Length (assessed as height, as age appropriate)
  - Weight-for-length
  - Weight-for-age z-score
  - Length-for-age z-score
  - Weight-for-length z-score
  - BMI
  - BMI-for-age z-score
  - Lung clearance index (LCI) at qualified study sites
  - Fecal elastase-1
  - Markers of intestinal inflammation
  - Qualitative microbiology cultures
- Annualized rate of pulmonary exacerbations
- Rate of CF-related hospitalizations

Observational Arm:

Not applicable

5.2 Safety Endpoints

Ivacaftor Arm:

Safety, as determined by adverse events (AEs), laboratory values (serum chemistry and hematology), 12-lead ECGs and vital signs, and ophthalmologic examinations (OEs)

Observational Arm:

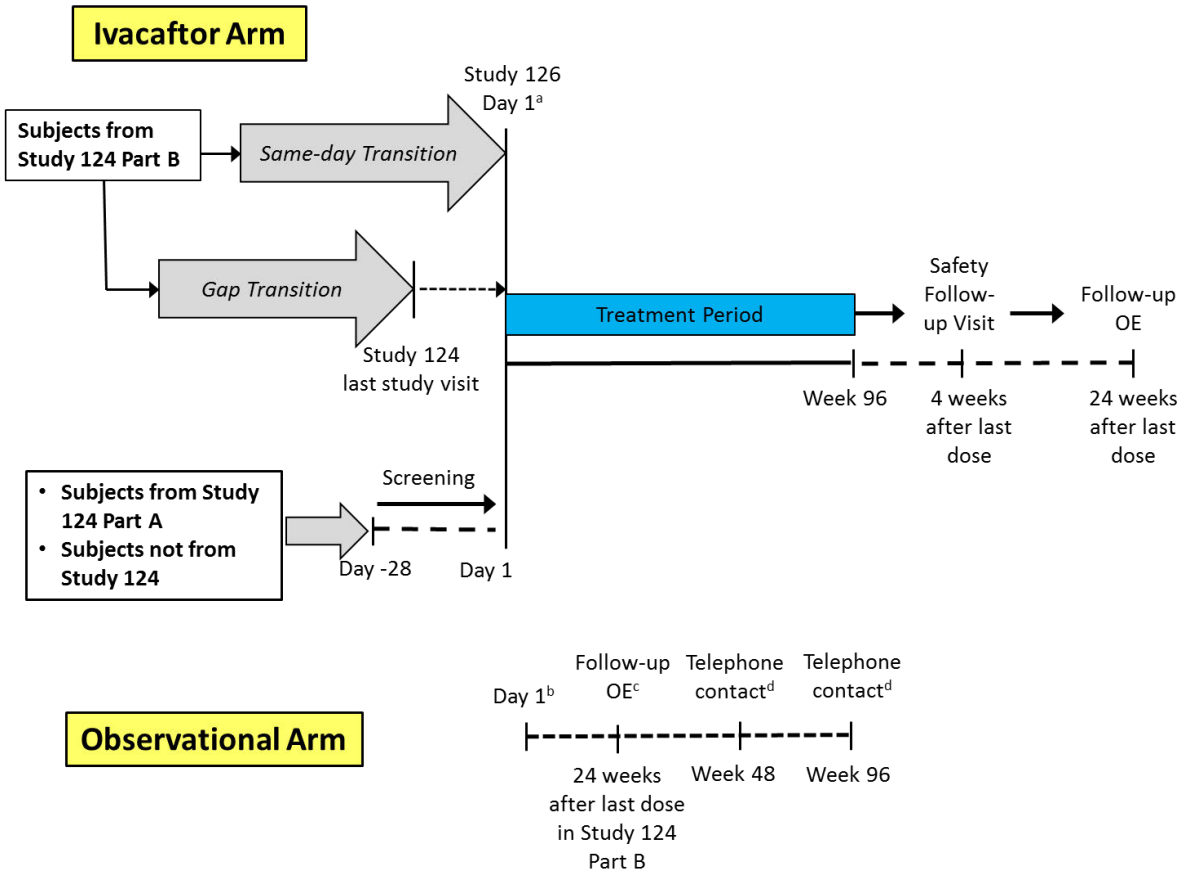
Safety after stopping ivacaftor treatment in Study VX15-770-124 (Study 124) Part B as determined by serious adverse events (SAEs) and results from an OE approximately 24 weeks after the last dose of ivacaftor in Study 124 Part B

6 STUDY DESIGN

6.1 Overall Design

This is a Phase 3, 2-arm, multicenter study with an open-label ivacaftor arm and an observational arm. The study design is shown in Figure 6-1.

Figure 6-1: VX15-770-126 Study Design



[a] For subjects who have a Same-day Transition, the Week 24 Visit of Study 124 Part B or Part A/B will be the same day as the Day 1 Visit of Study 126. For subjects who have a Gap Transition, the last study visit of Study 124 Part B or Part A/B will not be the same day as the Day 1 Visit of Study 126.
[b] Day 1 for subjects in the observational arm can be the last study visit of Study 124 Part B.
[c] The Follow-up OE in the observational arm can be performed in Study 124.
[d] Only for subjects who received at least 4 weeks of study drug in Study 124 Part B.

6.2 Sample Size and Power

The study is not powered to detect a significant treatment effect. The study will enroll approximately 75 subjects.

6.3 Randomization

Not applicable; treatment dose assignments in this study are determined by age and weight.

6.4 Blinding and Unblinding

Not applicable; this is an open-label study.

7 ANALYSIS SETS

7.1 Ivacaftor Arm Analysis Set

7.1.1 All Subjects Set

The All Subjects Set will be defined as all subjects who are enrolled in the current study. This analysis set will be used for all individual subject data listings and the disposition summary table, unless specified otherwise.

7.1.2 Full Analysis Set

The Full Analysis Set (FAS) will be defined as all subjects who are enrolled and receive at least 1 postbaseline efficacy assessment in the current study. The FAS will be used for all efficacy analyses, unless specified otherwise.

7.1.3 Safety Set

The Safety Set will be defined as all subjects who receive at least 1 dose of study drug in the current study. The Safety Set will be used for all safety analyses, unless specified otherwise.

7.2 Observational Arm Analysis Set

As no subjects enrolled in the Observational Arm, the Observational Arm Analysis Set will not be defined. Statistical Analysis

8 STATISTICAL ANALYSIS

8.1 General Considerations

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

All individual subject data for subjects who are enrolled in the current study will be presented in individual subject data listings.

As no subjects are enrolled in the Observation Arm, all analyses will be done for subjects from the Ivacaftor Arm only. All analysis will be performed for the Ivacaftor Arm overall, unless otherwise specified.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), standard error (SE), median, minimum value (min), and maximum value (max). 95% confidence intervals (CI) may be provided as appropriate.

Categorical variables will be summarized using counts and percentages. 95% CI may be provided as appropriate.

Baseline value is defined in two different ways:

Study 124 baseline: the baseline value for rollover subjects (who participated in Study 124 Part B or Part A/B) is defined as the baseline measurement from Study 124 Part B or Part A/B. That is, the most recent non-missing measurement collected on or before the initial

administration of study drug in Study 124 Part B or Part A/B. Note that this definition is consistent with the definition of baseline in Study 124 and applies to both scheduled and unscheduled measurements; if an unscheduled value is the most recent non-missing measurement, it will be used as baseline.

Study 126 baseline: the baseline value for IVA-naïve subjects (who did not participate in Study 124 Part B or Part A/B) is defined as the most recent non-missing measurement collected on or before the initial administration of study drug in the current study, including both the scheduled and unscheduled measurements.

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

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

Treatment-emergent (TE) Period

For the Ivacaftor Arm, the TE period will include the time period starting from the first dose date of the study drug in the current study to the Safety Follow-up Visit, or the last dose date + 28 days for subjects who do not have a Safety Follow-up Visit. The TE period will be used for safety analyses unless specified otherwise.

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

- In scheduled visit windows per specified visit windowing rules
- In the derivation of baseline/last on-treatment measurements.
- In the derivation of maximum/minimum on-treatment values and maximum/minimum change from baseline values for safety analyses.
- In individual subject data listings as appropriate.

Visit windowing rules: The analysis visit windows for protocol-defined visits in the Ivacaftor Arm are provided in Appendix B. The windows will be applied using the following rules 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 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 Safety Follow-Up (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 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, with the exception of the ETT visit occurs 21 days or later after the last dose, which will be treated as SFU visit.
- Assessments at the 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.

Visit windowing rules will not be used for the Observational Arm as they will not add value.

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

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

Multiplicity: No multiplicity adjustment will be performed for hypothesis testing.

8.2 Background Characteristics

Background characteristics will be analyzed for the total subjects in the Ivacaftor Arm.

8.2.1 Subject Disposition

Ivacaftor Arm:

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

- Enrolled (All Subjects Set)
- Enrolled and Dosed (Safety Set)
- Enrolled and having at least 1 post baseline efficacy assessment (FAS)
- Completed treatment
- Prematurely discontinued treatment and the reason for discontinuation
- Completed study
- Prematurely discontinued study and the reason for discontinuation
- Last treatment visit completed (Day 1, Week 2, Week 4, Week 8, Week 12, Week 18, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96)

A listing will be provided for subjects who discontinued treatment or who discontinued study with reasons for discontinuation.

8.2.2 Demographics and Baseline Characteristics

Demographics, medical history, and baseline characteristics will be summarized based on the Safety Set. For rollover subjects, the demographics and baseline characteristics from the Study 124 will be used.

Demographic data will include the following:

- Age (in months)
- Sex (female and male)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not collected per local regulations)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, not collected per local regulations, and Other)

Baseline characteristics will include the following:

- Weight (kg)
- Length (cm)
- Weight-for-length
- BMI (kg/m^2)
- Weight-for-age z-score
- Length-for-age z-score
- Weight-for-length z-score

Disease characteristics will include the following:

- Age at CF diagnosis
- Maternal/pregnancy history: complications in pregnancy, gestational age at delivery, method of delivery
- Number of CF-related hospitalizations from birth to screening
- Number of pulmonary exacerbations requiring antibiotics that occurred from birth to screening
- Number of pulmonary exacerbations requiring IV antibiotics that occurred from birth to screening
- Does subject have abnormal liver function tests (LFTs) documented since birth?
- Any use (yes or no) of the following medications from birth to screening will be assessed: inhaled tobramycin, inhaled aztreonam, inhaled colimycin, inhaled hypertonic saline, dornase alfa, ibuprofen, azithromycin, and pancreatic enzyme replacement therapy.
- Historical pancreatic test measurements

8.2.3 Prior and Concomitant Medications

Medications will be coded using the World Health Organization-Drug Dictionary Enhanced (WHO-DDE).

Medications used in the study will be identified as prior, concomitant, or both according to the rules given below.

Medications used in the study will be classified as follows:

- **Prior medication**: any medication that started before the first dose of ivacaftor in the current study, regardless of when it ended
- **Concomitant medication**: medication received at or after dosing of ivacaftor in the current study, or medication that was received before dosing with ivacaftor in the current study and continued after dosing of ivacaftor
- **Post-treatment medication**: medication continued or newly received after the TE period.

If medication start date is on or after the date of the first dosing of ivacaftor in the current study, the medication will be summarized as concomitant medication regardless of whether the medication end date is missing or not. If the medication end date is before the date of the first dosing of ivacaftor in the current study, then the medication will be summarized as prior medication regardless of whether the medication start date is missing or not. If medication started before the first dosing of ivacaftor in the current study and continued after dosing of ivacaftor, the medication will be summarized as prior medication and separately as concomitant medication.

Prior medications and concomitant medications will be summarized descriptively using frequency tables by Preferred Name.

Both prior and concomitant medications will be based on the Safety Set, with concomitant medications provided for the final analysis.

Post-treatment medications will be provided in data listings only.

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

Note that for rollover subjects from Study 124 Part B or Part A/B, only medications entered in the current study will be summarized.

8.2.4 Study Drug Exposure

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

Exposure summaries will be based on the Safety Set.

8.2.5 Study Drug Compliance

Study drug compliance based on the number of sachets taken will be calculated as: 100 × [(total number of sachets dispensed) – (total number of sachets returned)]/(total number of sachets planned to be taken per day × duration of study drug exposure in days in the current study). The maximum percentage of sachets taken will be 100%.

Study drug compliance based on study drug exposure will be calculated as: 100 × [1 − (total number of days of any study drug interruption) / (duration of study drug exposure in days)].

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

Study drug compliance summaries will be based on the FAS.

8.2.6 Important Protocol Deviations

Important protocol deviations (IPD) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being

IPD rules will be developed and finalized before database lock.

The protocol deviations that 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 excluded concomitant medications
- Subject received the wrong treatment or incorrect doses
- Subject remained in study despite meeting withdrawal criteria

Occurrence of any of these events may be considered as potential IPDs, but the study team will categorize them as IPDs if they have the potential to affect interpretation of study results or a subject's rights, safety, or well-being. .

IPDs will be presented as an individual subject data listing only.

8.2.7 COVID-19 Impacted Visits

A listing containing subjects' visits impacted due to COVID-19 will be provided.

8.3 Efficacy Analysis

Statistical methodology will be restricted to descriptive statistics only. Unless specified otherwise, all efficacy analyses described in this section will be based on the FAS, for the Ivacaftor Arm overall.

The analysis will include all available measurements per the visit windowing rules described in Appendix B.

8.3.1 Analysis of Primary Efficacy Variable

Not applicable.

8.3.2 Analysis of Secondary Efficacy/Pharmacodynamic Variable

The sweat chloride test is a standard diagnostic tool for CF, serving as a biomarker of CFTR activity.

Sweat chloride will be collected at visits as indicated in Appendix A. Absolute change from baseline in sweat chloride will be calculated as: $mean(SW_{Left}, SW_{Right}) - SW_{Base}$, where SW_{Left} and SW_{Right} are the measurements obtained on the left and right arms, respectively, at a particular visit and SW_{base} is the mean of right and left baseline measurements at baseline. If 1 of the 2 measurements at a time point is missing, the other will be used as the mean.

Note: A volume of ≥15 μL is required for an accurate determination of sweat chloride. Any results reported having volume <15 μL will not be included in analysis. In addition, sweat chloride with concentration >160 mmol/L will not be included in analysis.

Defintion of Baseline: Only results obtained from sample collections completed prior to the first administration of study drug (in Study 124 for Study 124 baseline, and in Study 126 for Study 126 baseline) will be considered as baseline results. If sweat chloride collection was completed for 1 arm prior to the first dose and completed for the other arm after the first dose, the baseline will consist of a single measurement. If both sweat collections were completed after the first dose, the baseline sweat chloride result will be considered missing for analysis purposes.

If sweat chloride was not performed at baseline or if the volume of sweat obtained from both arms was insufficient for analysis (<15 μL), or if the concentration of sweat chloride from both arms was >160 mmol/L, the most recent historical sweat chloride result may be used to impute the missing baseline value.

Sweat chloride results (including changes from baseline) will be analyzed as a continuous variable using descriptive summary statistics by visit.

8.3.3 Analysis of Tertiary Efficacy Variables

8.3.3.1 Definition of Variables

For the normalization of annual period the following formula will be used: Normalized Variable = Variable x 365.25 / (date of last dose – date of first dose +1).

The time-to-first pulmonary exacerbation (in days) is calculated as: first pulmonary exacerbation date (postdose in the current study) – first dose date + 1.

The time-to-first CF-related hospitalization (in days) is calculated as: first CF-related hospitalization date (postdose in the current study) – first dose date + 1.

Weight-for-age z-scores, length-for-age z-scores, weight-for-length z-scores, and BMI-for-age z-scores will be derived from weight, length, and BMI values using the WHO Child Growth Standards for infants and children[1], for whom population norms are available from 0 to 60 months of age. The same growth standards will be used to calculate percentiles for each measure.

8.3.3.2 Tertiary Analysis

- The following growth parameters will be summarized descriptively as continuous variables by visit (including change from baseline).
    - Weight
    - Length
    - Weight-for-length (expressed as a percentile)
    - BMI
    - Weight-for-age z-score
    - Length-for-age z-score
    - Weight-for-length z-score
    - BMI-for-age z-score

  Summary statistics for weight-for-age, length-for-age, and BMI-for-age percentiles may also be provided to aid interpretation of z-scores.
- $LCI_{2.5}$ will be analyzed as a continuous variable using descriptive summary statistics and results (including changes from baseline) presented by visit. In the event that fewer than 3 subjects have these optional assessments available, listings of results may be provided instead of summary statistics.
- Markers of pancreatic inflammation (fecal elastase-1): These parameters will be summarized descriptively as a continuous parameter and results (including changes from baseline) presented by visit. Shifts from baseline will be summarized by visit.
- Marker of intestinal inflammation (fecal calprotectin). This parameter will be summarized descriptively as a continuous parameter and results (including changes from baseline) presented by visit.
- Qualitative microbiology cultures: the presence of bacteria will be descriptively summarized by subject counts and percentages by visit. Shifts from baseline may be presented, as appropriate.
- Pulmonary exacerbations: Pulmonary exacerbations (PEx) will be identified using the definitions provided in Section 11.5.3 of the protocol, and will be analyzed in 3 ways, as follows:
    - The number of pulmonary exacerbations will be normalized to an annual period to adjust for differences in time spent on study and summarized as a continuous variable using descriptive summary statistics.
    - The number of days with pulmonary exacerbations (cumulative duration) will be normalized to an annual period to adjust for differences in time spent on study and summarized as a continuous variable using descriptive summary statistics.

  - The time-to-first pulmonary exacerbation in 96 weeks, total treatment duration will be analyzed using the Kaplan-Meier method (provided the number of subjects with events observed is adequate) and the event-free rate.

- Rate of CF-related hospitalizations will be analyzed in 3 ways, as follows:
  - The number of CF-related hospitalizations will be normalized to an annual period to adjust for differences in time spent on study and analyzed as a continuous variable using descriptive summary statistics.
  - The number of days hospitalized (cumulative duration) will be normalized to an annual period to adjust for differences in time spent on study and summarized as a continuous variable using descriptive summary statistics.
  - The time-to-first CF-related hospitalization in 96 weeks, total treatment duration will be analyzed using the Kaplan-Meier method (provided the number of subjects with events observed is adequate) and the event-free rate.

8.4 Safety Analysis

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

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (hematology and serum chemistry)
- Standard 12-lead electrocardiograms
- PEs (clinically significant abnormalities recorded as medical history or adverse events)
- Vital signs (systolic blood pressure, diastolic blood pressure, temperature, pulse rates, and respiratory rate)
- Ophthalmologic examinations

Unless specified otherwise, safety endpoints will be analyzed based on the Safety Set, for the total subjects in the Ivacaftor arm. Only a descriptive analysis of safety will be performed. All safety data will be presented in individual subject data listings. No statistical hypothesis testing will be conducted.

8.4.1 Adverse Events

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

Pretreatment AE: any AE that started before the first dose date of study drug in Study 126

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

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

For AEs with completely missing or partially missing start dates, if there is no clear evidence that the AEs started before or after study treatment, the AEs will be classified as TEAEs.

Details for imputing missing or partial start dates of AEs are described in Appendix D.

AE summary tables will be presented for TEAEs only and will include the following:

- All TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation.
- Serious TEAEs
- Related (defined as missing, possibly related, or related) TEAEs
- Serious Related TEAEs

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

In addition, a listing containing individual subject AE data for TEAEs leading to treatment interruption, TEAEs leading to discontinuation, SAEs, and deaths will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in an individual subject data listing.

8.4.2 Clinical Laboratory

For treatment-emergent laboratory measurements, the raw values and change from baseline values of the continuous hematology and chemistry results will be summarized in SI units by visit.
For selected LFT parameters, the number and percentage of subjects meeting at least 1 threshold analysis criterion event, during the TE period, will be summarized. The threshold analysis criteria are provided in Appendix E.

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

8.4.3 Electrocardiogram

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

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE period for the Treatment Period will be summarized. The threshold analysis criteria are provided in Appendix E.

8.4.4 Vital Signs

For treatment-emergent vital signs measurements, the raw values and change from baseline values will be summarized by visit: systolic and diastolic blood pressure (mm Hg), body temperature (°C), heart rate (beats per minute), respiratory rate (breaths per minute) and oxygen saturation (%).

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

8.4.5 Physical Examination

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

8.4.6 Ophthalmological Examination

The ocular safety profile of ivacaftor will be assessed in terms of the following analyses:

- Incidence of cataracts or lens opacities based on results from dilated slit-lamp examination
- Red reflex

Results of ophthalmologic examinations (incidence of cataracts or lens opacities) will be summarized as a categorical variable and results will be presented.

Lens refracting power and red reflex will be listed as appropriate.

9 SUMMARY OF INTERIM AND IDMC ANALYSES.

9.1 Interim Analysis

Not applicable.

9.2 IDMC Analysis

Data will be reviewed by an independent data monitoring committee (IDMC) to ensure the safety of the subjects in the study. Procedural details of the IDMC's structure and function, frequency of meetings, and data planned for review will be included in the IDMC charter. The IDMC charter will be finalized before the first IDMC review meeting.

10 REFERENCES

1. World Health Organization Growth Standards. Growth charts available at: https://www.cdc.gov/growthcharts/who_charts.htm

11 LIST OF APPENDICES

Appendix A: Schedule of Assessments

Table 11-1 Schedule of Assessments for VX15-770-126 (Ivacaftor Arm: Same-day Transition Subjects From Study 124 Part B)

		Treatment Period (Day 1 Through Week 96)		ETT Visit[a]	Safety Follow-up Visit[b]	24-Week Follow-up OE
Event/Assessment	**Day 1[c]**	**Weeks 12, 36, 60, and 84 (± 7 Days)**	**Weeks 24, 48, 72, and 96 (± 7 Days)**	**As Soon as Possible After the Last Dose**	**4 Weeks (± 7 Days) After the Last Dose**	**24 Weeks (+ 14 Days) After the Last Dose**
Informed consent	X					
Confirm eligibility	X					
Clinic visit	X	X	X	X	X	
Study drug dose determination[d]	X	X	X			
Length and weight[e]	X	X	X	X	X	
Physical examination[f]	X	X	X	X	X	
Vital signs[g]	X	X	X	X	X	

[a] The ETT Visit is to be scheduled as soon as possible after the last dose of ivacaftor. If the ETT Visit occurs 3 weeks or later after the last dose of ivacaftor, the Safety Follow-up Visit will not be required. Subjects who elect to receive commercially available ivacaftor will be discontinued from ivacaftor dosing and will complete the ETT Visit and Follow-up OE.

[b] For subjects who elect to receive commercially available ivacaftor, the Safety Follow-up Visit will not be required.

[c] The Day 1 Visit will be the same day as the Week 24 Visit of Study 124 Part B. Any Study 126 Day 1 assessments performed at the Week 24 Visit of Study 124 Part B do not need to be repeated. Day 1 results should be taken from the Week 24 Visit in Study 124 (if applicable) on which these data are available (including demographics and medical history), except for the signing of informed consent, confirmation of eligibility, and IVRS/IWRS contact.

[d] The ivacaftor dose for each subject will be reassessed based on body weight and adjusted if necessary (see CSP Section 9.4).

[e] Length and weight measurements will be performed predose through the Week 24 Visit (see CSP Section 11.5.1).

[f] Full physical examinations will be performed at the ETT and Safety Follow-up Visits; abbreviated physical examinations will be performed at all other study visits.

[g] Vital signs and ECGs will be taken predose through the Week 24 Visit. Following the Week 24 Visit, vital signs and ECGs may be taken pre- or post-dose. Vital signs include blood pressure (systolic and diastolic), temperature, heart rate, respiratory rate, and pulse oximetry (see CSP Section 11.6.3).

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Table 11-1 Schedule of Assessments for VX15-770-126 (Ivacaftor Arm: Same-day Transition Subjects From Study 124 Part B)

		Treatment Period (Day 1 Through Week 96)		ETT Visit[a]	Safety Follow-up Visit[b]	24-Week Follow-up OE
Event/Assessment	**Day 1[c]**	**Weeks 12, 36, 60, and 84 (± 7 Days)**	**Weeks 24, 48, 72, and 96 (± 7 Days)**	**As Soon as Possible After the Last Dose**	**4 Weeks (± 7 Days) After the Last Dose**	**24 Weeks (+ 14 Days) After the Last Dose**
12-lead ECGs[g, h]	X		X	X	X	
Serum chemistry and hematology	X	X	X	X	X	
Ophthalmologic examination[i]	X		X	X[j]		X
Fecal sample collection[k]	X		X	X		
Sweat chloride test[l]	X		X			
Qualitative microbiology cultures	X		X			
Multiple breath washout (optional)[m]	X		X[n]			
Study drug administration[o]	X	X	X			
Study drug count	X	X	X	X		
Pulmonary exacerbations, CF-related hospitalizations	*Continuous from signing of ICF through the last dose of study drug*					

[h] All 12-lead ECGs will be taken predose at the Day 1, Week 12 and Week 24 Clinic Visits. At all visits, ECGs will be taken before any other procedures that may affect heart rate, such as blood draws (see CSP Section 11.6.4).

[i] The OE will be conducted by a licensed ophthalmologist, preferably a pediatric ophthalmologist. The OE may be performed at the study visit or ± 14 days of the clinic visit.

[j] The OE for the ETT Visit will be conducted for all subjects who prematurely discontinue ivacaftor dosing (for any reason) unless performed in the last 12 weeks.

[k] Samples will be analyzed for fecal elastase-1 and other markers of intestinal inflammation, including fecal calprotectin. Samples may be collected up to 24 hours before the study visit (e.g., at home) and brought to the clinic. If the sample is collected in the clinic, the sample may be collected pre- or postdose.

[l] The sweat chloride test must be performed on Day 1 before the ivacaftor dose. At all other visits up to the Week 24 Visit, the sweat chloride test must be performed within ± 2 hours of the ivacaftor dose. After the Week 24 Visit, the sweat chloride test may be performed at any time during the visit.

[m] MBW will be performed on subjects for whom additional or separate informed consent was obtained for the procedures, and only at sites that are adequately trained and qualified to perform MBW (see CSP Section 11.5.6). The Day 1 MBW must be performed within 1 week before the Day 1 Visit. The Week 96 MBW must be performed within 1 week before the last dose. Detailed procedures will be supplied in a separate study manual.

[n] MBW will be performed at the Week 24 and 48 Visits (± 7 days).

[o] The morning dose of study drug will be administered at the Day 1, Week 12 and Week 24 Clinic Visits. After the Week 24 Visit, the morning dose need not be administered at the Clinic Visit. Additional guidance for preparation and administration of study drug is provided in CSP Section 9.4 and the study manual.

Table 11-1 Schedule of Assessments for VX15-770-126 (Ivacaftor Arm: Same-day Transition Subjects From Study 124 Part B)

		Treatment Period (Day 1 Through Week 96)		ETT Visit[a]	Safety Follow-up Visit[b]	24-Week Follow-up OE
Event/Assessment	**Day 1[c]**	**Weeks 12, 36, 60, and 84 (± 7 Days)**	**Weeks 24, 48, 72, and 96 (± 7 Days)**	**As Soon as Possible After the Last Dose**	**4 Weeks (± 7 Days) After the Last Dose**	**24 Weeks (+ 14 Days) After the Last Dose**
Adverse events	*Continuous from signing ICF through the Safety Follow-up Visit (see CSP Section 13.1.1.3)*					*Ocular adverse events only*
Medications and procedures review	*Continuous from signing of ICF through the Safety Follow-up Visit*					

CF: cystic fibrosis; *CFTR*: CF transmembrane conductance regulator gene; ETT: Early Termination of Treatment; ICF: informed consent form; MBW: multiple breath washout; LFT: liver function test; OE: ophthalmologic examination; q12h: every 12 hours.

Table 11-2 Schedule of Assessments for VX15-770-126 (Ivacaftor Arm: Gap Transition Subjects From Study 124 Part B)

		Treatment Period (Day 1 through Week 96)			ETT Visit[a]	Safety Follow-up Visit[b]	24-Week Follow-up OE
Event/Assessment	**Day -28 to Day -1**	**Day 1[c]**	**Weeks 12, 36, 60, and 84 (±7 Days)**	**Weeks 24, 48, 72, and 96 (±7 Days)**	**As Soon as Possible After the Last Dose**	**4 Weeks (±7 Days) After the Last Dose**	**24 Weeks (+ 14 Days) After the Last Dose**
Informed consent[d]	X	X					
Reconfirm eligibility	X	X					
Medical history[e]	X						
Clinic visit	X	X	X	X	X	X	
Study drug dose determination[f]		X	X	X			
Length and weight[g]		X	X	X	X	X	
Physical examination[h]		X	X	X	X	X	
Vital signs[i]		X	X	X	X	X	
12-lead ECGs[i, j]		X		X	X	X	

[a] The ETT Visit is to be scheduled as soon as possible after the last dose of ivacaftor. If the ETT Visit occurs 3 weeks or later after the last dose of ivacaftor, the Safety Follow-up Visit will not be required. Subjects who elect to receive commercially available ivacaftor will be discontinued from ivacaftor dosing and will complete the ETT Visit and Follow-up OE.

[b] For subjects who elect to receive commercially available ivacaftor, the Safety Follow-up Visit will not be required.

[c] The Day 1 Visit will not be the same day as the last study visit of Study 124 Part B. All Day 1 assessments will be conducted on Day 1 with the possible exception of the serum and hematology assessments and the OE, as detailed in footnotes k and m. If the Day 1 Visit is ≤9 days after the last study visit of Study 124 Part B, the subjects must sign the ICF and confirm eligibility before dosing on Day 1.

[d] Subjects must sign the ICF before undergoing any study-related assessments.

[e] Medical history only applies to subjects that complete a Study 124 Safety Follow-up Visit and only for new conditions that start after the Study 124 Safety Follow-up Visit and prior to the Study 126 Screening Visit.

[f] The ivacaftor dose for each subject will be reassessed based on body weight and adjusted if necessary (see CSP Section 9.4).

[g] Length and weight measurements will be performed predose through the Week 24 Visit (see CSP Section 11.5.1).

[h] Full physical examinations will be performed at the ETT and Safety Follow-up Visits; abbreviated physical examinations will be performed at all other study visits.

[i] Vital signs and ECGs will be taken predose through the Week 24 Visit. Following the Week 24 Visit, vital signs and ECGs may be taken pre- or post-dose. Vital signs include blood pressure (systolic and diastolic), temperature, heart rate, respiratory rate, and pulse oximetry (see CSP Section 11.6.3).

[j] All 12-lead ECGs will be taken predose at the Day 1, Week 12 and Week 24 Clinic Visits. At all visits, ECGs will be taken before any other procedures that may affect heart rate, such as blood draws (see CSP Section 11.6.4).

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Table 11-2 Schedule of Assessments for VX15-770-126 (Ivacaftor Arm: Gap Transition Subjects From Study 124 Part B)

		Treatment Period (Day 1 through Week 96)			ETT Visit[a]	Safety Follow-up Visit[b]	24-Week Follow-up OE
Event/Assessment	**Day -28 to Day -1**	**Day 1[c]**	**Weeks 12, 36, 60, and 84 (±7 Days)**	**Weeks 24, 48, 72, and 96 (±7 Days)**	**As Soon as Possible After the Last Dose**	**4 Weeks (±7 Days) After the Last Dose**	**24 Weeks (+ 14 Days) After the Last Dose**
Serum chemistry and hematology	X[k]		X	X	X	X	
Ophthalmologic examination[l]		X[m]		X	X[n]		X
Fecal sample collection[o]		X		X	X		
Sweat chloride test[p]		X		X			
Qualitative microbiology cultures		X		X			

[k] If the Day 1 Visit is conducted ≤9 days after the last study visit of Study 124 Part B, the serum chemistry and hematology assessments performed at the last study visit of Study 124 Part B will not need to be repeated. If the Day 1 Visit is conducted >9 days after the last study visit of Study 124 Part B, the serum chemistry and hematology assessments can be obtained up to 9 days before or at the Day 1 Visit. The results must be reviewed before the first dose of study drug.

[l] The OE will be conducted by a licensed ophthalmologist, preferably a pediatric ophthalmologist. The OE may be performed at the study visit or ± 14 days of the clinic visit.

[m] The OE does not need to be repeated if the subject had an OE in Study 124 Part B within 24 weeks of the Day 1 Visit. Otherwise, an OE must be conducted within 14 days of the Day 1 Visit. Throughout this study, these subjects should have OEs approximately every 24 weeks (± 14 days) from the last OE in Study 124.

[n] The OE for the ETT Visit will be conducted for all subjects who prematurely discontinue ivacaftor dosing (for any reason) unless performed in the last 12 weeks.

[o] Samples will be analyzed for fecal elastase-1 and other markers of intestinal inflammation, including fecal calprotectin. Samples may be collected (e.g., at home) up to 24 hours before the study visit (e.g., at home) and brought to the clinic. If the sample is collected in the clinic, the sample may be collected pre- or postdose.

[p] At Screening, a sweat chloride test must be performed if the sweat chloride value is not available in the subject's medical records and the value is needed to establish eligibility. For subjects with sweat chloride values documented in their medical records and for whom it is not needed to establish eligibility, the sweat chloride test at screening is not required. For all subjects, except those that completed a baseline sweat chloride test at screening, the Day 1 sweat chloride test will be performed predose. At all other visits up to the Week 24 Visit, the test must be performed within ± 2 hours of the ivacaftor dose. After the Week 24 Visit, the sweat chloride test may be performed at any time during the visit.

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Table 11-2 Schedule of Assessments for VX15-770-126 (Ivacaftor Arm: Gap Transition Subjects From Study 124 Part B)

		Treatment Period (Day 1 through Week 96)			ETT Visit[a]	Safety Follow-up Visit[b]	24-Week Follow-up OE
Event/Assessment	**Day -28 to Day -1**	**Day 1[c]**	**Weeks 12, 36, 60, and 84 (±7 Days)**	**Weeks 24, 48, 72, and 96 (±7 Days)**	**As Soon as Possible After the Last Dose**	**4 Weeks (±7 Days) After the Last Dose**	**24 Weeks (+ 14 Days) After the Last Dose**
Multiple breath washout (optional)[q]		X		X[r]			
Study drug administration[s]		X	X	X			
Study drug count		X	X	X	X		
Pulmonary exacerbations, CF-related hospitalizations	*Continuous from signing of ICF through the last dose of study drug*						
Adverse events	*Continuous from signing ICF through the Safety Follow-up Visit (see CSP Section 13.1.1.3)*						*Ocular adverse events only*
Medications and procedures review	*Continuous from signing of ICF through the Safety Follow-up Visit*						

CF: cystic fibrosis; *CFTR*: CF transmembrane conductance regulator gene; ETT: Early Termination of Treatment; ICF: informed consent form; MBW: multiple breath washout; LFT: liver function test; OE: ophthalmologic examination; q12h: every 12 hours.

[q] MBW will be performed on subjects for whom additional or separate informed consent was obtained for the procedures, and only at sites that are adequately trained and qualified to perform MBW (see CSP Section 11.5.6). If MBW was performed in Study 124 within 28 days of the Day 1 Visit in Study 126, MBW will not need to be repeated on Day 1. If a Day 1 MBW is needed, the MBW must be performed within 1 week before the Day 1 Visit. The Week 96 MBW must be performed within 1 week before the last dose. Detailed procedures will be supplied in a separate study manual.

[r] MBW will be performed at the Week 24 and 48 Visits (± 7 days).

[s] The morning dose of study drug will be administered at the Day 1, Week 12 and Week 24 Clinic Visits. After the Week 24 Visit, the morning dose need not be administered at the Clinic Visit. Additional guidance for preparation and administration of study drug is provided in CSP Section 9.4 and the study manual.

Table 11-3 Schedule of Assessments for VX15-770-126 (Ivacaftor Arm: Study 124 Part A Only Subjects or Subjects Not From Study 124)

	Screening Period[35]	Treatment Period (Day 1 through Week 96)								ETT Visit[36]	Safety Follow-up Visit[37]	24-Week Follow-up OE
Event/Assessment	**Day -28 to Day -1**	**Day 1**	**Day 3 (± 1 Day)**	**Week 2 (± 1 Day)**	**Week 4 (± 5 Days)**	**Weeks 8 and 18 (± 7 Days)**	**Weeks 12 and 24 (± 7 Days)**	**Weeks 36, 60, and 84 (± 7 Days)**	**Weeks 48, 72, and 96 (± 7 Days)**	**As Soon as Possible After the Last Dose**	**4 Weeks (± 7 Days) After the Last Dose**	**24 Weeks (+ 14 Days) After the Last Dose**
Informed consent	X											
Inclusion/exclusion criteria review	X	X										
Clinic visit	X	X		X	X	X	X	X	X	X	X	
Telephone contact			X									
Demographics	X											
Medical history	X											
Historical data	X[38]											
CFTR genotype[39]	X											
Study drug dose determination		X		X	X	X	X	X	X			

[35] Subjects will only be allowed to enroll in Study 126 after an adequate number of subjects have completed the corresponding age cohort in Study 124, in conjunction with feedback from regulatory authorities.

[36] The ETT Visit is to be scheduled as soon as possible after the last dose of ivacaftor. If the ETT Visit occurs 3 weeks or later after the last dose of ivacaftor, the Safety Follow-up Visit will not be required. Subjects who elect to receive commercially available ivacaftor will be discontinued from ivacaftor dosing and will complete the ETT Visit.

[37] For subjects who elect to receive commercially available ivacaftor, the Safety Follow-up Visit will not be required.

[38] Historical data from birth to screening will also be collected before (i.e., at screening) or at Day 1 (see CSP Section 11.2).

[39] For subjects who participated in Study 124 Part A, the *CFTR* genotype result can be taken from Study 124. For all other subjects, the genotype results must be available before the first dose of study drug. If a genotype test has been performed previously and is documented in the subject's medical record, the subject's eligibility must be approved by the Vertex medical monitor. If a historic genotype result is not available at screening or if the

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Table 11-3 Schedule of Assessments for VX15-770-126 (Ivacaftor Arm: Study 124 Part A Only Subjects or Subjects Not From Study 124)

	Screening Period[35]	Treatment Period (Day 1 through Week 96)								ETT Visit[36]	Safety Follow-up Visit[37]	24-Week Follow-up OE
Event/Assessment	**Day -28 to Day -1**	**Day 1**	**Day 3 (± 1 Day)**	**Week 2 (± 1 Day)**	**Week 4 (± 5 Days)**	**Weeks 8 and 18 (± 7 Days)**	**Weeks 12 and 24 (± 7 Days)**	**Weeks 36, 60, and 84 (± 7 Days)**	**Weeks 48, 72, and 96 (± 7 Days)**	**As Soon as Possible After the Last Dose**	**4 Weeks (± 7 Days) After the Last Dose**	**24 Weeks (+ 14 Days) After the Last Dose**
Length and weight[40]	X	X		X	X	X	X	X	X	X	X	
Physical examination[41]	X	X		X	X	X	X	X	X	X	X	
Vital signs[42]	X	X		X	X	X	X	X	X	X	X	
12-lead ECGs[42, 43]	X	X			X		X	X	X	X	X	
Serum chemistry and hematology[44]	X			Chem-istry only	LFTs and hema-tology only	X	X	X	X	X	X	

historic genotype result is not approved by the Vertex medical monitor, subjects will be tested for *CFTR* genotype and the results must be reviewed before the first dose of study drug.

40 Length and weight measurements will be performed predose through the Week 24 Visit (see CSP Section 11.5.1).

41 Full physical examinations will be performed at the Screening, ETT, and Safety Follow-up Visits; abbreviated physical examinations will be performed at all other study visits.

42 Vital signs and ECGs will be taken predose through the Week 24 Visit. Following the Week 24 Visit, vital signs and ECGs may be taken pre- or post-dose. Vital signs include blood pressure (systolic and diastolic), temperature, heart rate, respiratory rate, and pulse oximetry (see CSP Section 11.6.3).

43 All 12-lead ECGs will be performed predose at the Day 1, Week 12 and Week 24 Clinic Visits. At all visits, ECGs will be taken before any other procedures that may affect heart rate, such as blood draws (see CSP Section 11.6.4).

44 To minimize blood draws, the Screening Visit and Day 1 clinical laboratory assessments can be combined into a single blood draw taken up to 9 days before the Day 1 dosing. The results must be received and reviewed before the first dose of study drug.

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Table 11-3 Schedule of Assessments for VX15-770-126 (Ivacaftor Arm: Study 124 Part A Only Subjects or Subjects Not From Study 124)

	Screening Period[35]	Treatment Period (Day 1 through Week 96)								ETT Visit[36]	Safety Follow-up Visit[37]	24-Week Follow-up OE
Event/Assessment	**Day -28 to Day -1**	**Day 1**	**Day 3 (± 1 Day)**	**Week 2 (± 1 Day)**	**Week 4 (± 5 Days)**	**Weeks 8 and 18 (± 7 Days)**	**Weeks 12 and 24 (± 7 Days)**	**Weeks 36, 60, and 84 (± 7 Days)**	**Weeks 48, 72, and 96 (± 7 Days)**	**As Soon as Possible After the Last Dose**	**4 Weeks (± 7 Days) After the Last Dose**	**24 Weeks (+ 14 Days) After the Last Dose**
Ophthalmologic examination[45]	X[46]						X		X	X[47]		X
Fecal sample collection[48]	X[49]			X	X	X	X		X	X		
Sweat chloride test[50]	X	X		X			X		X			
Qualitative microbiology cultures		X					X		X			

[45] The OE will be conducted by a licensed ophthalmologist, preferably a pediatric ophthalmologist. The OE may be performed at the study visit or ± 14 days of the clinic visit.

[46] If an OE was conducted in Study 124 Part A within 12 weeks of the Day 1 Visit, the Day 1 Visit OE does not need to be repeated.

[47] The OE for the ETT Visit will be conducted for all subjects who prematurely discontinue ivacaftor dosing in the ivacaftor arm, regardless of the reason for discontinuation. If the ETT Visit occurs within 12 weeks of the subject's last OE, the OE at the ETT Visit will not be required.

[48] Samples will be analyzed for fecal elastase-1 and other markers of intestinal inflammation, including fecal calprotectin. Samples may be collected (e.g., at home) up to 24 hours before the study visit (e.g., at home) and brought to the clinic. If the sample is collected in the clinic, the sample may be collected pre- or postdose.

[49] The fecal sample may be collected at any time during screening.

[50] At Screening, a sweat chloride test must be performed if the sweat chloride value is not available in the subject's medical records and the value is needed to establish eligibility. For subjects with sweat chloride values documented in their medical records and for whom it is not needed to establish eligibility, the sweat chloride test at screening is not required. For all subjects, except those that completed a baseline sweat chloride test at screening, a Day 1 sweat chloride test will be performed predose. At all other visits up to the Week 24 Visit, the test must be performed within a window of ± 2 hours relative to the ivacaftor dose. After the Week 24 Visit, the sweat chloride test may be performed at any time during the visit.

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Table 11-3 Schedule of Assessments for VX15-770-126 (Ivacaftor Arm: Study 124 Part A Only Subjects or Subjects Not From Study 124)

	Screening Period[35]	Treatment Period (Day 1 through Week 96)								ETT Visit[36]	Safety Follow-up Visit[37]	24-Week Follow-up OE
Event/Assessment	**Day -28 to Day -1**	**Day 1**	**Day 3 (± 1 Day)**	**Week 2 (± 1 Day)**	**Week 4 (± 5 Days)**	**Weeks 8 and 18 (± 7 Days)**	**Weeks 12 and 24 (± 7 Days)**	**Weeks 36, 60, and 84 (± 7 Days)**	**Weeks 48, 72, and 96 (± 7 Days)**	**As Soon as Possible After the Last Dose**	**4 Weeks (± 7 Days) After the Last Dose**	**24 Weeks (+ 14 Days) After the Last Dose**
Multiple breath washout (optional)[51]		X					X		X[52]			
Study drug administration[53]		X		X	X	X	X	X	X			
In-clinic observation for 4 hours after administration of the first dose of study drug		X										
Study drug count				X	X	X	X	X	X	X		
Pulmonary exacerbations, CF-related hospitalizations	*Continuous from signing of ICF through the last dose of study drug*											

[51] MBW will be performed on subjects for whom additional or separate informed consent was obtained for the procedures, and only at sites that are adequately trained and qualified to perform this assessment (CSP Section 11.5.6). The Day 1 MBW must be performed within 1 week before the first dose, not postdose. The Week 96 MBW must be performed within 1 week before the last dose, not after the last dose. Detailed procedures will be supplied in a separate study manual.

[52] MBW will be performed at the Week 48 and Week 72 Visits (± 7 days).

[53] The morning dose of study drug will be administered at the Day 1, and 2-, 4-, 8-, 12-, 18-, and 24-Week Clinic Visits. After the Week 24 Visit, the morning dose need not be administered at the Clinic Visit. Additional guidance for preparation and administration of study drug is provided in CSP Section 9.4 and the study manual.

Table 11-3 Schedule of Assessments for VX15-770-126 (Ivacaftor Arm: Study 124 Part A Only Subjects or Subjects Not From Study 124)

	Screening Period[35]	Treatment Period (Day 1 through Week 96)								ETT Visit[36]	Safety Follow-up Visit[37]	24-Week Follow-up OE
Event/Assessment	**Day -28 to Day -1**	**Day 1**	**Day 3 (± 1 Day)**	**Week 2 (± 1 Day)**	**Week 4 (± 5 Days)**	**Weeks 8 and 18 (± 7 Days)**	**Weeks 12 and 24 (± 7 Days)**	**Weeks 36, 60, and 84 (± 7 Days)**	**Weeks 48, 72, and 96 (± 7 Days)**	**As Soon as Possible After the Last Dose**	**4 Weeks (± 7 Days) After the Last Dose**	**24 Weeks (+ 14 Days) After the Last Dose**
Adverse events	*Continuous from signing ICF through the Safety Follow-up Visit (see CSP Section 13.1.1.3)*											*Ocular adverse events only*
Medications and procedures review	*Continuous from signing of ICF through the Safety Follow-up Visit*											

CF: cystic fibrosis; *CFTR*: CF transmembrane conductance regulator gene; ETT: Early Termination of Treatment; ICF: informed consent form; MBW: multiple breath washout; LFT: liver function test; OE: ophthalmologic examination; q12h: every 12 hours.

Appendix B: Analysis Visit Windows for Safety and Efficacy Assessments

Table 11-4 Analysis Visit Windows for Safety and Efficacy Assessments - Rollover Subjects From Study 124 Part B or Part A/B

Assessment	Visit[a]	Target Study Day	Analysis Visit Window (in study days)
Safety Assessments			
Serum Chemistry Hematology Vital Signs	Baseline	Not applicable	parent study baseline
	Week 12	84	[2, 126]
	Week 24	168	[127, 210]
	Week 36	252	[211, 294]
	Week 48	336	[295, 378]
	Week 60	420	[379, 462]
	Week 72	504	[463, 546]
	Week 84	588	[547, 630]
	Week 96	672	[631, max(686, Date of Week 96 + 14)]
	Safety Follow-up Visit	NA	Use nominal visit
Standard 12-Lead ECG	Baseline	Not applicable	parent study baseline
	Week 24	168	[2, 252]
	Week 48	336	[253, 420]
	Week 72	504	[421,588]
	Week 96	672	[589, max(686, Date of Week 96 + 14)]
	Safety Follow-up Visit	NA	Use nominal visit
Ophthalmologic Exam	Baseline	Not applicable	parent study baseline
	Week 24	168	[2, 252]
	Week 48	336	[253, 420]
	Week 72	504	[421, 588]
	Week 96	672	[589, max(686, Date of Week 96 + 14)]
	24-Week Follow-up OE	NA	Use nominal visit
Efficacy Assessments			
Weight Length Weight-for-length BMI Weight-for-age z-score Length-for-age z-score Weight-for-length z-score BMI-for-age z score	Baseline	Not applicable	parent study baseline
	Week 12	84	[2, 126]
	Week 24	168	[127, 210]
	Week 36	252	[211, 294]
	Week 48	336	[295, 378]
	Week 60	420	[379, 462]
	Week 72	504	[463, 546]
	Week 84	588	[547, 630]
	Week 96	672	[631, max(686, Date of Week 96 + 14)]
	Safety Follow-up Visit	NA	Use nominal visit[c]

Fecal elastase-1 Fecal calprotectin Sweat chloride Qualitative Microbiology Multiple Breath Washout	Baseline	Not applicable	parent study baseline
	Week 24	168	[2, 252]
	Week 48	336	[253, 420]
	Week 72	504	[421, 588]
	Week 96	672	[589, max(686, Date of Week 96 + 14)]

[a] Visit name is used to report data in tables, listings and figures.
[b] Target day time point per protocol is predose, except for ECG measurements.
[c] Per section 8.1, it will remain as the SFU if it goes beyond the upper boundary of the window for the last scheduled visit.

Table 11-5 Analysis Visit Windows for Safety and Efficacy Assessments – IVA-naïve subjects (Subjects Not From Study 124 Part B or Part A/B)

Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window (in study days)
Safety Assessments			
Serum Chemistry	Baseline	1	≤1
	Week 2	14	[2, 35]
	Week 8	56	[36, 70]
	Week 12	84	[71, 105]
	Week 18	126	[106, 147]
	Week 24	168	[148, 210]
	Week 36	252	[211, 294]
	Week 48	336	[295, 378]
	Week 60	420	[379, 462]
	Week 72	504	[463, 546]
	Week 84	588	[547, 630]
	Week 96	672	[631, max(686, Date of Week 96 + 14)]
	Safety Follow-up Visit	NA	Use nominal visit
Hematology	Baseline	1	≤1
	Week 4	28	[2, 42]
	Week 8	56	[43, 70]
	Week 12	84	[71, 105]
	Week 18	126	[106, 147]
	Week 24	168	[148, 210]
	Week 36	252	[211, 294]
	Week 48	336	[295, 378]
	Week 60	420	[379, 462]
	Week 72	504	[463, 546]
	Week 84	588	[547, 630]

Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window (in study days)
	Week 96	672	[631, max(686, Date of Week 96 + 14)]
	Safety Follow-up Visit	NA	Use nominal visit
Standard 12-Lead ECG	Baseline	1	≤1
	Week 4	28	[2, 56]
	Week 12	84	[57, 126]
	Week 24	168	[127, 210]
	Week 36	252	[211, 294]
	Week 48	336	[295, 378]
	Week 60	420	[379, 462]
	Week 72	504	[463, 546]
	Week 84	588	[547, 630]
	Week 96	672	[631, max(686, Date of Week 96 + 14)]
	Safety Follow-up Visit	NA	Use nominal visit
Liver Function Tests Vital Signs	Baseline	1	≤1
	Week 2	14	[2, 21]
	Week 4	28	[22, 42]
	Week 8	56	[43, 70]
	Week 12	84	[71, 105]
	Week 18	126	[106, 147]
	Week 24	168	[148, 210]
	Week 36	252	[211, 294]
	Week 48	336	[295, 378]
	Week 60	420	[379, 462]
	Week 72	504	[463, 546]
	Week 84	588	[547, 630]
	Week 96	672	[631, max(686, Date of Week 96 + 14)]
	Safety Follow-up Visit	NA	Use nominal visit
Ophthalmologic Exam	Baseline	1	≤1
	Week 12	84	[2, 126]
	Week 24	168	[127, 252]
	Week 48	336	[253, 420]
	Week 72	504	[421, 588]
	Week 96	672	[589, max(686, Date of Week 96 + 14)]
	24-Week Follow-up OE	NA	Use nominal visit
Efficacy Assessments			
Weight Length Weight-for-length BMI Weight-for-age z-score Length-for-age z-score	Baseline	1	≤1
	Week 2	14	[2, 21]
	Week 4	28	[22, 42]
	Week 8	56	[43, 70]
	Week 12	84	[71, 105]
	Week 18	126	[106, 147]

Assessment	Visit[a]	Target Study Day[b]	Analysis Visit Window (in study days)
Weight-for-length z-score BMI-for-age z score	Week 24	168	[148, 210]
	Week 36	252	[211, 294]
	Week 48	336	[295, 378]
	Week 60	420	[379, 462]
	Week 72	504	[463, 546]
	Week 84	588	[547, 630]
	Week 96	672	[631, max(686, Date of Week 96 + 14)]
	Safety Follow-up Visit	NA	Use nominal visit[c]
Fecal elastase-1 Fecal calprotectin	Baseline	1	≤1
	Week 2	14	[2, 21]
	Week 4	28	[22, 42]
	Week 8	56	[43, 70]
	Week 12	84	[71, 105]
	Week 18	126	[106, 147]
	Week 24	168	[148, 252]
	Week 48	336	[253, 420]
	Week 72	504	[421, 588]
	Week 96	672	[589, max(686, Date of Week 96 + 14)]
Sweat Chloride	Baseline	1	≤1
	Week 2	14	[2, 49]
	Week 12	84	[50, 126]
	Week 24	168	[127, 252]
	Week 48	336	[253, 420]
	Week 72	504	[421, 588]
	Week 96	672	[589, max(686, Date of Week 96 + 14)]
Qualitative Microbiology	Baseline	1	≤1
	Week 12	84	[2, 126]
	Week 24	168	[127, 252]
	Week 48	336	[253, 420]
	Week 72	504	[421, 588]
	Week 96	672	[589, max(686, Date of Week 96 + 14)]
Multiple Breath Washout	Baseline	1	≤1
	Week 12	84	[2, 126]
	Week 24	168	[127, 252]
	Week 48	336	[253, 420]
	Week 72	504	[421, 588]
	Week 96	672	[589, max(686, Date of Week 96 +14)]

[a] Visit name is used to report data in tables, listings and figures.
[b] Target day time point per protocol is predose, except for ECG measurements.
[c] Per section 8.1, it will remain as the SFU if it goes beyond the upper boundary of the window for the last scheduled visit.

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

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

Appendix C: Imputation Rules for Missing Prior/Concomitant Medication Dates

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use the informed consent date for non-rollovers and the first dose date for rollovers.
2. Missing or partial medication stop date:
    a. If only DAY is missing, use the last day of the month.
    b. If DAY and Month are both missing, use the last day of the year.
    c. If DAY, Month and year are all missing, use End of Study date.

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

Table 11-5 Prior, Concomitant, and Post Categorization of a Medication

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

A: Post; C: Concomitant; P: Prior

Appendix D: 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.

Appendix E: Criteria for Threshold Analysis

Table 11-6 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Clinical Chemistry (LFT)		
ALT	≤ULN >ULN - ≤2xULN >2xULN - ≤3xULN >3xULN - ≤ 5xULN >5xULN- ≤ 8xULN >8xULN	FDA DILI Guidance
AST	≤ULN >ULN - ≤2xULN >2xULN - ≤3xULN >3xULN - ≤ 5xULN >5xULN- ≤ 8xULN >8xULN	FDA DILI Guidance
ALT or AST	≤ULN >ULN - ≤2xULN >2xULN - ≤3xULN >3xULN - ≤ 5xULN >5xULN- ≤ 8xULN >8xULN	FDA DILI Guidance
Total Bilirubin	≤ULN >ULN - ≤2xULN >2xULN - ≤3xULN >3xULN - ≤ 5xULN >5xULN- ≤ 8xULN >8xULN	FDA DILI Guidance
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	FDA DILI Guidance

Table 11-7 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
QT interval corrected by Fridericia's formula	<=450 msec >450 to <=480 msec >480 to <=500 msec >500 msec	