VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX15-770-124 (Final Analysis)

A Phase 3, 2-Part, Open-label Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have an Ivacaftor-responsive *CFTR* Mutation

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Version: Version 3.0
Version Date of SAP: 07 December 2022

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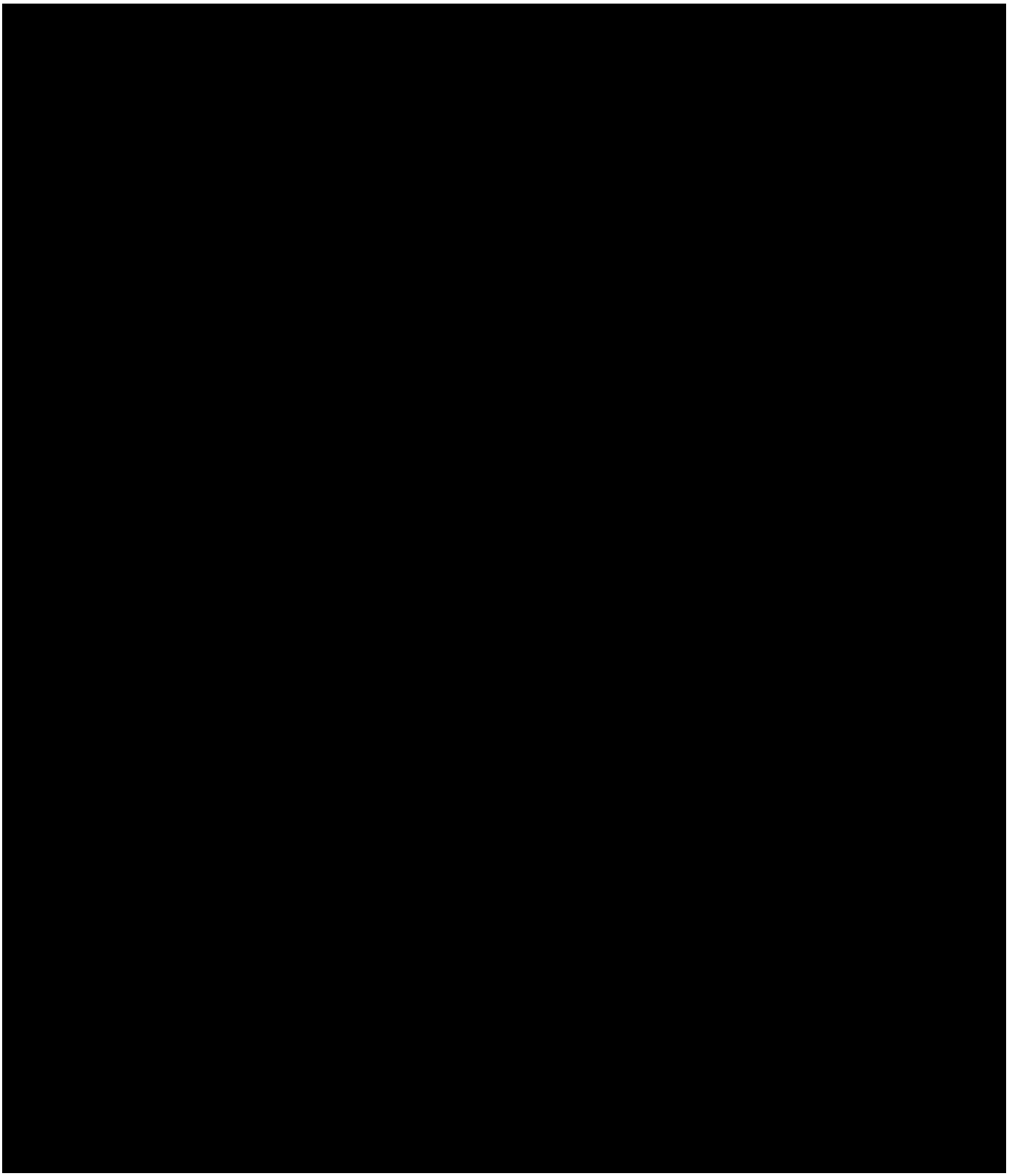


3 INTRODUCTION

This statistical analysis plan (SAP) Methods for the final analysis of Study VX15-770-124 is based on the approved clinical study protocol (CSP), Version 4.0, dated 01 April 2021, final electronic case report form (eCRF) completion guidelines, Version 7.0, dated 18 April 2022, and approved eCRF, Version 10.0, dated 28 March 2022.

Study VX15-770-124 is a Phase 3, 2-Part, Open-label Study to evaluate the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in subjects with cystic fibrosis who are less than 24 months of age at treatment initiation and have an Ivacaftor (IVA)-responsive *CFTR* mutation. This SAP (Methods) documents the planned final statistical analysis of efficacy and safety endpoints defined in the study protocol of VX15-770-124.

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 clinical database lock has occurred will be documented in the clinical study report for this study.

The analysis addressing the pharmacokinetic (PK) objective of the study will be described in the Clinical Pharmacology Analysis Plan (CPAP) which will be developed separately by the Clinical Pharmacology department at Vertex Pharmaceuticals Incorporated (Vertex).

4 STUDY OBJECTIVES

4.1 Primary Objectives

Part A:

- To evaluate the safety of ivacaftor treatment in subjects with cystic fibrosis (CF) who are <24 months of age at treatment initiation and have a CF transmembrane conductance regulator (*CFTR*) gene gating mutation
- To evaluate the pharmacokinetics (PK) of ivacaftor and metabolites hydroxymethyl-ivacaftor (M1) and ivacaftor carboxylate (M6) in subjects with CF who are <24 months of age at treatment initiation and have a *CFTR* gating mutation

Part B:

- To evaluate the safety of ivacaftor treatment in subjects with CF who are <24 months of age at treatment initiation and have a *CFTR* gating mutation

Part A/B:

- To evaluate the safety of ivacaftor treatment in subjects with CF who are 1 to <4 months of age at treatment initiation and have an ivacaftor-responsive *CFTR* mutation (consistent with the approved mutations in the region)
- To evaluate the PK of ivacaftor and the ivacaftor metabolites M1 and M6 in subjects with CF who are 1 to <4 months of age at treatment initiation

and have an ivacaftor-responsive *CFTR* mutation (consistent with the approved mutations in the region)

4.2 Secondary Objectives

Part B:

- To evaluate the PK of ivacaftor and metabolites M1 and M6 in subjects with CF who are <24 months of age at treatment initiation and have a *CFTR* gating mutation
- To evaluate the pharmacodynamics (PD) of ivacaftor treatment in subjects with CF who are <24 months of age at treatment initiation and have a *CFTR* gating mutation

Part A/B Cohort 8:

- To evaluate the PD of ivacaftor treatment in subjects with CF who are 1 to <4 months of age at treatment initiation and have an ivacaftor-responsive *CFTR* mutation (consistent with the approved mutations in the region)

5 STUDY ENDPOINTS

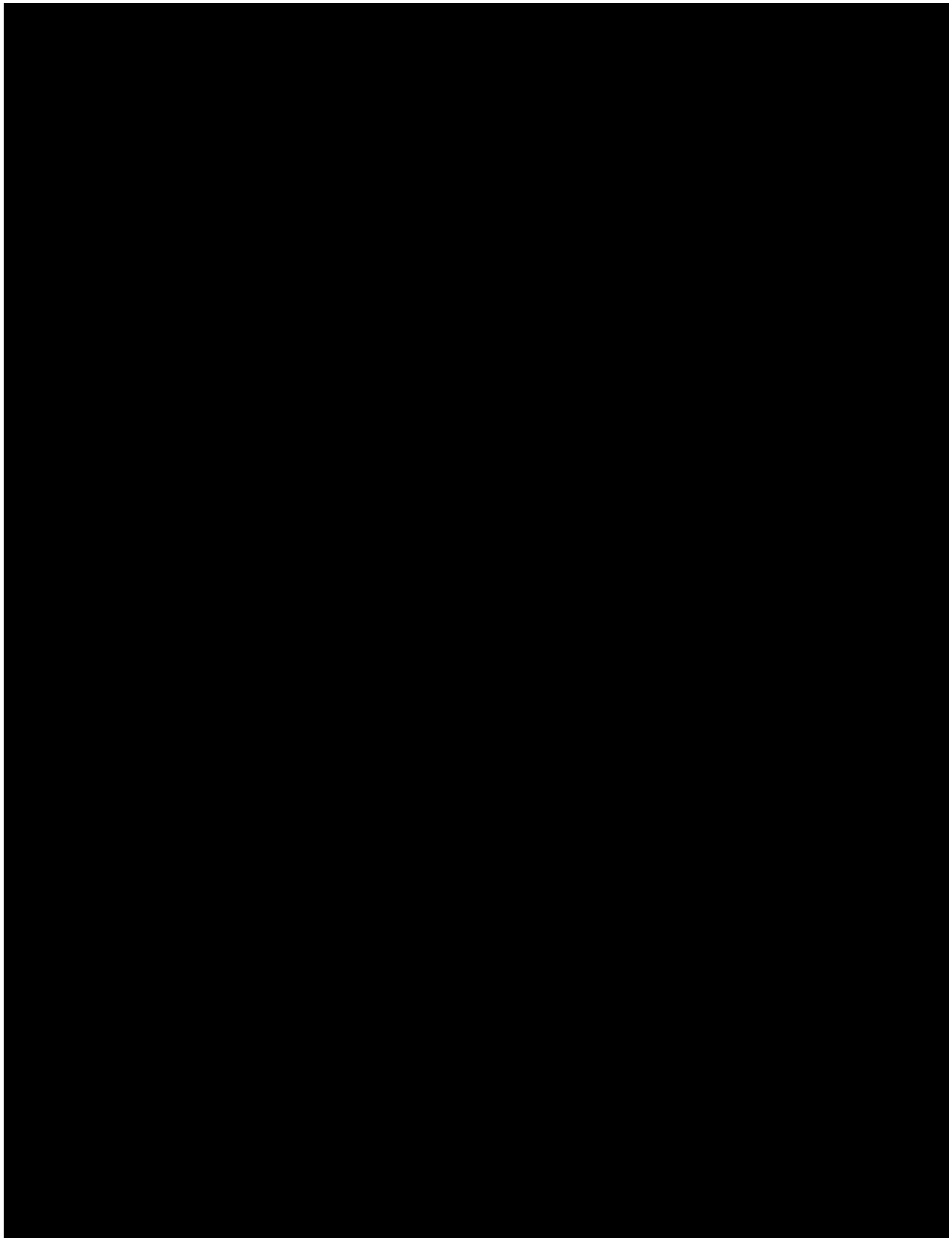
5.1 Efficacy Endpoint (Part B and Part A/B Cohort 8)

5.1.1 Primary Efficacy Endpoint

Not applicable

5.1.2 Secondary Efficacy Endpoint

Absolute change from baseline in sweat chloride



5.2 Safety Endpoints

Primary Endpoint for Part A	• Safety, as determined by adverse events, clinical laboratory values (serum chemistry and hematology), standard 12-lead electrocardiograms (ECGs), vital signs, and ophthalmologic examinations (OEs)
Primary Endpoint for Part B	• Safety, as determined by adverse events, clinical laboratory values (serum chemistry and hematology), ECGs, vital signs, and OEs
Primary Endpoint for Part A/B Cohort 8	• Safety, as determined by adverse events, clinical laboratory values (serum chemistry and hematology), standard 12-lead ECGs, vital signs, and OEs

[redacted]

6 STUDY DESIGN

6.1 Overall Design

This is a Phase 3, 2-part, open-label study as depicted in Figure 6-1. This study is designed to evaluate the safety, PK, PD, and efficacy of ivacaftor in subjects with CF who are <24 months of age at treatment initiation (Day 1) and have an ivacaftor-responsive *CFTR* mutation on at least 1 allele. Part A is designed to evaluate the safety and PK of multiple-dose administration of ivacaftor in subjects <24 months of age over 4 days of dosing, and to confirm (or adjust if necessary) the doses for Part B. Part B is designed to evaluate the safety, PK, PD, and efficacy of ivacaftor in subjects <24 months of age over 24 weeks. Part A/B Cohort 8 is designed to evaluate the safety, PK, PD, and efficacy of ivacaftor in subjects with CF who are 1 to <4 months of age, ≥38 weeks gestation, weigh at least 3 kg at the time of treatment initiation (Day 1), and have an ivacaftor-responsive *CFTR* mutation (consistent with the approved mutations in the region) on at least 1 allele. Subjects will receive an initial low dose of ivacaftor (based on their Day 1 age and weight) up to Day 15, at which time the dose may be adjusted to better match the median adult exposure. Subjects are intended to remain on that dose until they are 4 months of age and at least 5 kg, after which the recommended age- and weight-appropriate dose(s) will be administrated.

Part A:

Subjects will be enrolled in Part A sequentially in the following cohorts:

- **Cohort 1**: subjects aged 12 to <24 months
- **Cohort 2**: subjects aged 6 to <12 months
- **Cohort 3**: subjects aged 3 to <6 months

Enrollment in Part A will begin with subjects in Cohort 1. Enrollment for subjects in Cohort 2 will begin after a review of safety and PK data for subjects from Cohort 1. Enrollment for subjects in Cohort 3 will begin after a review of safety and PK data for subjects in Cohort 2.

PK data from each completed cohort in Part A will be used to update the population PK model and inform dose selection for the subsequent cohort before that cohort begins enrolling. If PK data from any cohort in Part A are insufficient to confirm the dose for that age group, additional subjects will be enrolled in the cohort until an appropriate dose is confirmed.

Part A of this study includes:

- Screening Period (Day -28 to Day -1)
- Treatment Period (Day 1 to Day 5):
  - 25-mg (for subjects 5 to <7 kg on Day 1), 50-mg (for subjects 7 to <14 kg on Day 1), and 75-mg (for subjects 14 to <25 kg on Day 1) ivacaftor will be administered every 12 hours (q12h) on Days 1 through 3 and 1 morning dose on Day 4. These doses may be amended at any time based on available PK data from previous cohorts, and may result in additional doses or different weight strata. Data from each cohort in Part A will be used to update the population PK model and inform dose predictions for each subsequent (younger) cohort.
  - Study visits will occur on Days 1, 4, and 5.
  - PK samples will be collected before the morning dose on Day 4, between 2 and 4 hours, between 6 to 8 hours, and between 24 and 60 hours after the Day 4 dose.
  - For subjects who prematurely discontinue treatment, a PK blood sample will be collected at the Early Termination of Treatment (ETT) Visit (within 5 days after the last dose of study drug).
- Follow-up Telephone Call (Day 14)
- Follow-up OE (within 8 weeks after the last dose of study drug).

Subjects who prematurely discontinue treatment before their last scheduled dose in Part A will be required to complete the ETT Visit, Follow-up Telephone Call, and Follow-up OE.

Part B:

Subjects will be enrolled in Part B sequentially in the following cohorts based on age at Day 1 of Part B:

- **Cohort 5:** subjects aged 12 to <24 months
- **Cohort 6:** subjects aged 6 to <12 months
- **Cohort 7:** subjects aged 4 to <6 months

Enrollment of subjects in Cohort 5 will begin following an assessment of:
- Safety and PK data from Part A for subjects from Cohort 1 and confirmation of dose for subjects aged 12 to <24 months.

Enrollment of subjects in Cohort 6 will begin after an assessment of:
- Safety and PK data from Part A for subjects from Cohort 2 and confirmation of dose for subjects aged 6 to <12 months.
- Safety data from Week 12 of Part B for at least 5 subjects in Cohort 5.

Enrollment of subjects in Cohort 7 will begin with enrollment of subjects aged 4 to <6 months following an assessment of:
- Safety and PK data from Part A for subjects from Cohort 3 and confirmation of dose in subjects aged 3 to <6 months.
- Safety data from Week 12 of Part B for at least 5 subjects in Cohort 6.

Subjects from Cohorts 2 or 3 who age out of the corresponding age cohort (Cohorts 6 or 7) in Part B at Day 1 may enroll in an older age cohort in Part B with the Vertex medical monitor's permission. Otherwise, subjects who will age out of the corresponding age cohort may enroll in the Extension Study.

Part B of this study includes:
- Screening Period (Day -28 to Day -1)
- Treatment Period (Day 1 to Week 24):
  - Starting doses in Cohorts 5 and 6 of 25-mg (for subjects 5 to <7 kg on Day 1), 50-mg (for subjects 7 to <14 kg on Day 1), and 75-mg (for subjects 14 to <25 kg on Day 1) ivacaftor will be administered q12h for 24 weeks (or other suitable starting dose based on safety and PK data from Part A). At each study visit the ivacaftor dose for each subject will be reassessed based on body weight and adjusted if necessary.
  - All subjects enrolled in Cohort 7 will receive a 25 mg dose of ivacaftor q12h until the subject reaches the age of 6 months. At each study visit after the age of 6 months, the ivacaftor dose for each subject will be reassessed based on body weight and adjusted, if necessary as above for Cohorts 5 and 6.
  - Study visits will occur on Day 1 and Weeks 2, 4, 8, 12, 18, and 24.
  - PK blood samples will be collected at the following time points:
    - Week 2: before the morning dose, between 2 and 4 hours and between 6 and 8 hours after the morning dose
    - Week 8: before the morning dose and 1 and 4 hours after the morning dose

- Week 24: before the morning dose and between 2 and 4 hours after the morning dose
  - PK blood sampling at Week 24 is optional for subjects who undergo MBW (due to fasting requirements)
- For subjects who prematurely discontinue treatment, a PK blood sample will be collected at the ETT Visit.

- OEs will be performed at screening, Week 12, and Week 24.

All subjects who complete 24 weeks of study drug treatment will be eligible to enroll in the open-label treatment arm of an Extension Study. In this study, subjects will receive 96 additional weeks of ivacaftor treatment. The Follow-up Visit will not be required for subjects who enroll in the treatment arm of this study.

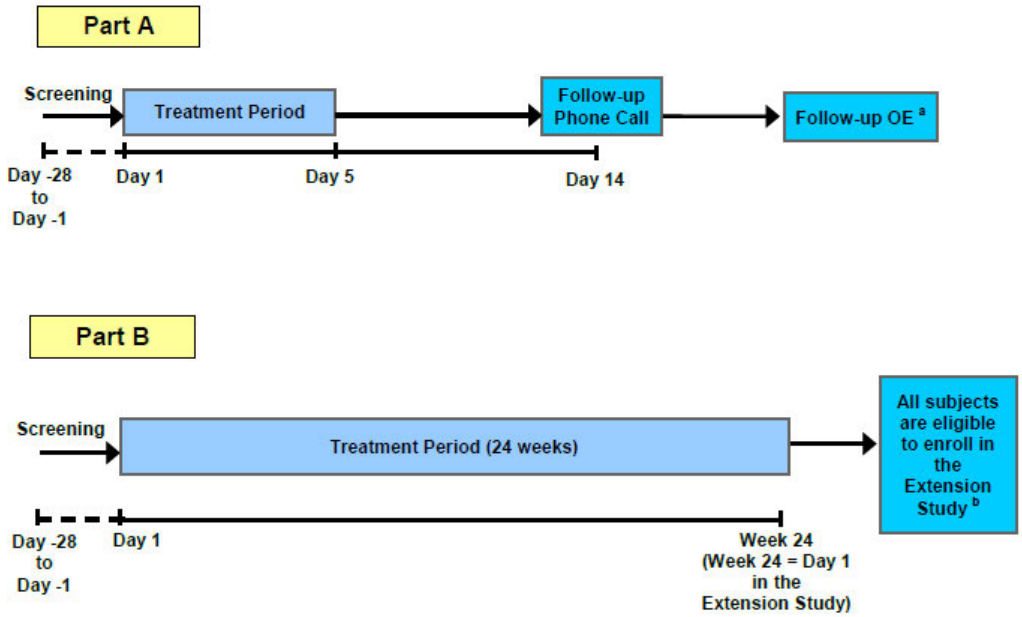
Subjects who complete 24 weeks of study drug treatment who elect not to enroll in the treatment arm of the Extension Study will be required to complete the Follow-up Visit (4 weeks ± 7 days after the last dose of study drug) and will be eligible to enroll in the observational arm of the Extension Study. The Follow-up Visit will not be required in the event that the subject initiates treatment with commercially available ivacaftor within 3 weeks of the Week 24 Visit.

Subjects who prematurely discontinue treatment before their last scheduled dose will be required to complete the ETT Visit, Follow-up Visit, and Follow-up OE. The Follow-up visit will not be required:

- If the ETT Visit occurs 3 weeks or later after the last dose of study drug.
- In the event that the subject initiates treatment with commercially available ivacaftor within 3 weeks of the ETT Visit.

Subjects who prematurely discontinue study drug treatment will be eligible to enroll in the observational arm of the Extension Study. Subjects who are eligible will enroll in the Extension Study as soon as enrollment is open. Subjects enrolling into the Extension Study within 24 weeks after the last dose of study drug are not required to have the Follow-up OE (the OE will be performed in the Extension Study).

Figure 6-1 Schematic of Study Design



OE: ophthalmologic examination
[a] Part A Follow-up OE will occur approximately 8 weeks after last dose of study drug.
[b] All subjects who complete 24 weeks of study drug treatment will be eligible to enroll in the open-label treatment arm of the Extension Study. All other subjects will be eligible to enroll in the observational arm of the Extension Study. Subjects who prematurely discontinue will have the Part B Follow-up OE approximately 24 weeks after last dose of study drug.

Part A/B Cohort 8:

Subjects 1 to <4 months of age, ≥38 weeks gestation, and weighing at least 3 kg at the time of treatment initiation (Day 1), will receive an initial low dose of ivacaftor (5.7 mg q12h or 11.4 mg q12h based on their Day 1 age and weight) from Day 1 up to Day 15 (Figure 6-2). Subjects 3 months of age must weigh ≥5 kg on Day 1. This initial low dose is based on prior age- and weight-based simulations of exposure which accounts for potential variability in metabolic enzyme maturation affecting exposures. The initial dose is expected to result in exposures within or below the adult exposure range. On Day 4, PK samples from each subject will be collected before and after dosing and analyzed to determine the exposure and assess whether the initial dose needs to be adjusted to better match the median adult exposure.

Part A/B Cohort 8 of this study includes:

- Confirmed genotype; genotype testing is expected to be initiated prior to screening and results must be available prior to Day 1
- Screening Period (Day -28 to Day -14)

- Due to limitations in the volume of blood that should be collected from the 1- to <4-month-old age group in a 28-day span, screening should be completed at least 14 days prior to Day 1 (treatment initiation)

- Initial Treatment Period (Day 1 up to Day 15):
  - Subjects will receive an initial low dose of ivacaftor (5.7 mg q12h or 11.4 mg q12h based on their Day 1 age and weight) from Day 1 up to Day 15, as follows:

Age	Weight Range	Starting Dose
1 month	≥3 kg	5.7 mg q12h
2 months	≥3 to <5 kg	5.7 mg q12h
2 months	≥5 kg	11.4 mg q12h
3 months	≥5 kg	11.4 mg q12h

All subjects must have gestational age ≥38 weeks and weigh ≥3 kg. Subjects 3 months of age must weigh ≥5 kg on Day 1.

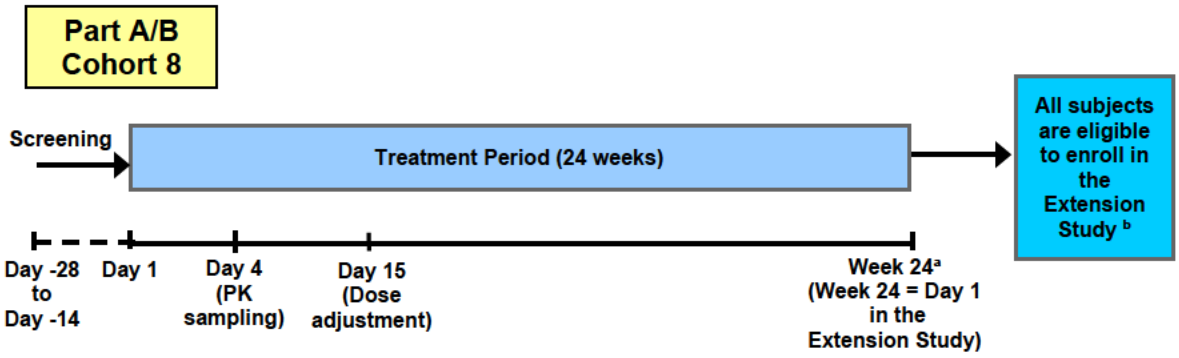
  - Study visits will occur on Days 1, 4, and 15.
  - Follow-up Telephone Call (Day 1 evening)
  - PK samples will be collected before the morning dose on Day 4, between 2 to 4 hours and between 6 to 8 hours after the Day 4 morning dose.
  - The subject's Day 4 PK data will be used to calculate exposure to determine a dose that is expected to bring the exposure for the subject closest to the adult median. This potential dose adjustment will be communicated in writing to the principal investigator for administration to the subject on Day 15.
  - At the Day 15 Visit, a trough PK sample will be collected before the morning dose. The ivacaftor dose will be adjusted if necessary, to either 5.7, 11.4, 17.1, 22.8, or 25 mg, and the adjusted dose will be administered q12h starting with the evening dose on Day 15.
  - If all PK samples collected on Day 4 are missing or cannot be analyzed, PK samples collected on Day 15 will be used to assess whether the initial dose should be adjusted at the Week 4 Visit.

- Subsequent Treatment Period (Day 16 to Week 24):
  - Follow-up Telephone Call (Day 17)
  - Study visits will occur on Weeks 4, 8, 12, 18, and 24.
  - The subject is intended to remain on the same dose from Day 15 until the subject is 4 months of age and at least 5 kg, after which the recommended age- and weight-appropriate dose(s) will be administered.

- PK samples will be collected before the morning dose on Week 8, between 2 to 4 hours and between 6 to 8 hours after the Week 8 morning dose.
- Additional PK samples will be collected before the morning dose on the Week 4, 12, 18, and 24 Visits to characterize the longitudinal PK profile.

- The entire treatment period of the study will be 24 weeks, after which subjects will be eligible to enroll in an Extension Study.
- Subjects who do not enroll in the Extension Study will have a Follow-up Visit within 4 weeks ± 7 days after the last dose of study drug and a Follow-up OE within 12 weeks ± 14 days after the last dose of study drug.

Subjects who prematurely discontinue treatment before their last scheduled dose will be required to complete the ETT Visit, Follow-up Visit, and Follow-up OE. A PK blood sample will be collected at the ETT Visit (if the ETT Visit occurs within 3 days after the last dose of study drug).



OE: ophthalmologic examination

[a] A Follow-up OE will occur approximately 12 weeks after last dose of study drug unless the subject enrolls in the Extension Study.

[b] All subjects who complete 24 weeks of study drug treatment will be eligible to enroll in the open-label treatment arm of the Extension Study. All other subjects will be eligible to enroll in the observational arm of the Extension Study. Subjects who prematurely discontinue will have a Follow-up OE approximately 12 weeks after last dose of study drug.

6.2 Sample Size and Power

The sample size of a minimum of 15 subjects in Part A and 15 subjects in Part B, and 6 up to approximately 10 subjects in Part A/B Cohort 8 is based on the availability of the subject population and PK analysis considerations, and not on any statistical consideration. Therefore, the study is not powered to detect a significant treatment effect.

Part A: A minimum of 15 subjects:

- minimum of 5 subjects aged 12 to <24 months
- minimum of 5 subjects aged 6 to <12 months
- minimum of 5 subjects aged 3 to <6 months

Part B: A minimum of 15 subjects:

- minimum of 5 subjects aged 12 to <24 months
- minimum of 5 subjects aged 6 to <12 months
- minimum of 5 subjects aged 4 to <6 months

Note: Subjects who have an *R117H-CFTR* mutation will only be enrolled in regions where ivacaftor is approved for use in subjects 2 through 5 years of age with an *R117H-CFTR* mutation.

Part A/B Cohort 8:

- A minimum of 6 up to approximately 10 subjects aged 1 to <4 months, ≥38 weeks gestation, and at least 3 kg at the time of treatment initiation (Day 1)
- Subjects who have an ivacaftor-responsive mutation on at least 1 allele will be eligible to enroll in regions where ivacaftor is approved (consistent with the approved mutations in the region).

There are estimated to be approximately 1800 CF births per year worldwide. If it is assumed that 61% of these cases are detected by newborn screening (NBS) and 5% carry a gating mutation, then there will be approximately 50 patients available for enrollment in this study each year from NBS (1800 × 0.6 × 0.05). There are estimated to be approximately 70 children between 0 to 2 years of age with a gating mutation not diagnosed by NBS who are available for enrollment in this study each year (1800 × 2 × 0.4 × 0.05). If 15% to 20% of the entire available global patient population is enrolled, this would allow enrollment of approximately 20 subjects per year. There is often a delay in the time it takes for patients to be referred to and evaluated at a CF center following diagnosis, as well as time needed for parents to process the CF diagnosis and to become informed about the disease. Thus, feedback from CF pediatricians indicates there will be some difficulty in enrolling this CF population of <2 year-olds, particularly those <2 to 3 months of age.

Relatively rich PK samples (4 samples at steady-state) will be collected in Part A, which will provide sufficient PK data to inform the population PK model, while accounting for blood volume restrictions in this vulnerable age range. In addition to evaluation of PK in Part A, this study will collect PK samples from all subjects in Part B through 24 weeks. PK evaluation will consist of a population PK approach, utilizing the current population PK model and existing data for patients ≥24 months of age. The between-subject variability estimate for ivacaftor in subjects with CF 2 through 5 years of age from Study 108 is a coefficient of variation (CV) of 34% to 41% for area under the concentration versus time curve (AUC). Based on a review of model-based pediatric simulations with a range of variability, the variability estimate of ivacaftor from Study 108, and the PK collection scheme, the number of subjects planned for enrollment is expected to provide reasonably precise estimates of key PK parameters using a population PK approach. The inclusion of data from pediatric patients ≥24 months of age with the population PK approach is expected to reduce the required sample size.

Given the above feasibility assessment and PK considerations, a minimum of 15 subjects in Part A and 15 subjects in Part B, and 6 up to approximately 10 subjects in Part A/B Cohort 8

is considered an appropriate sample size for evaluation of the PK and safety of ivacaftor in subjects <24 months of age.

For Part A/B Cohort 8, PK samples (3 samples) will be collected on the Day 4 and Week 8 Visits to provide sufficient PK data to assess exposure, while accounting for blood volume restrictions in this vulnerable age range. In addition to evaluation of PK on Day 4, trough PK samples will be collected from all subjects in Part A/B at each visit through 24 weeks.

6.3 Randomization

This study is an open-label study. Randomization is not required because all subjects will be treated identically within a single cohort.

6.4 Blinding and Unblinding

This study is open-labeled and all subjects will receive ivacaftor.

7 ANALYSIS SETS

7.1 All Subjects Set

The All Subjects Set will be defined separately for Part A, and for the combined Part B and Part A/B Cohort 8 as all subjects who are eligible for study enrollment or received at least 1 dose of study drug. This analysis set will be used for all individual subject data listings and the disposition summary table, unless specified otherwise.

7.2 Full Analysis Set (Combined Part B and Part A/B Cohort 8 only)

The Full Analysis Set (FAS) for combined Part B and Part A/B Cohort 8 will be defined as all subjects who are eligible for study enrollment and receive at least 1 dose of study drug in Part B or Part A/B cohort 8.

7.3 Safety Set

The Safety Set will be defined separately for Part A, and for the combined Part B and Part A/B Cohort 8 as all subjects who received at least 1 dose of study drug. The Safety Set will be used for all safety analyses with subjects from Part A, and subjects from combined Part B and Part A/B Cohort 8, unless specified otherwise.

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 were eligible for study enrollment or received at least 1 dose of study drug will be presented in individual subject data listings.

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), and 95% confidence intervals [CI], as appropriate.

Categorical variables will be summarized using counts, percentages, and 95% CI (as appropriate).

Baseline value, unless specified otherwise, will be defined separately for Parts A, and combined Part B and Part A/B Cohort 8 as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the respective study part.

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

Treatment-emergent (TE) Period

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

For the combined Part B and Part A/B Cohort 8 the TE period will include the time period starting from the first dose date of the study drug to the Follow-up Visit, or to the end of study date for subjects who roll over into the Extension Study and for whom the Follow-up Visit is not required. The last dose date + 28 days will be used as the TE period end date for subjects who do not have a Follow-up Visit or an end of study date. 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 (Combined Part B and Part A/B Cohort 8 only).
- In the derivation of baseline measurements.
- In the derivation of maximum/minimum on-treatment values and maximum/minimum change from baseline values for safety analyses.
- In individual subject data listings as appropriate.

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Appendix D. 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; 4) the Follow-Up OE 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 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; it will remain as the SFU if it goes beyond the upper boundary of the window for the last scheduled visit.

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.

All analyses will be done separately for Part A, and combined Part B and Part A/B Cohort 8, as applicable. Unless otherwise specified, summary tables will be presented by cohort and overall.

8.2 Background Characteristics

Background characteristics will be summarized separately for Part A, and for the combined Part B and Part A/B Cohort 8. Summary tables will be presented by cohort and overall.

8.2.1 Subject Disposition

Part A:

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

- Enrolled
- Enrolled and dosed (Safety Set)

The number and percentage (based on the Safety Set) of subjects in each of the following disposition categories will be summarized:

- Last Treatment Visit completed (Day 1, Day 2, Day 3, Day 4, and Day 5).
- Completed treatment
- Prematurely discontinued the treatment and the reason for discontinuation
- Completed study

- Prematurely discontinued the study and the reason for discontinuation

Combined Part B and Part A/B Cohort 8:

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

- Enrolled
- Enrolled and dosed (Safety Set)
- FAS

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

- Last Treatment visit completed (Day 1, Day 4, Day15/Week 2, Week 4, Week 8, Week 12, Week 18 and Week 24).
- Completed treatment
- Prematurely discontinued the treatment and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation
- Enrolled in a rollover extension study

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 for Part A, and combined Part B and Part A/B Cohort 8, respectively, based on the Safety Set.

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:

[redacted]

For the combined Part B and Part A/B Cohort 8 only, the following disease characteristics will also be summarized:

- Age at CF diagnosis
- Maternal/pregnancy history: complications in pregnancy, gestational age at delivery, method of delivery

[redacted]

- Does subject have abnormal liver function tests 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

Medical history will be summarized by MedDRA system organ class (SOC) and preferred term (PT).

No statistical tests will be carried out to evaluate any baseline imbalance between dose groups.

8.2.3 Prior and Concomitant Medications

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

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

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

Post-treatment medication (combined Part B and Part A/B Cohort 8 only): medication continued or newly received after the TE period.

A given medication may be classified as follows: prior, concomitant, post-treatment, both prior and concomitant, both concomitant and post-treatment, or prior, concomitant, and post-treatment.

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

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

For the final analysis, medications received during the period from the first dose of study drug through the end of Part A participation will be summarized as concomitant medications in Part A. A similar rationale will be adopted for concomitant medications in the combined Part B and Part A/B Cohort 8.

Summaries of medications will be based on the Safety Set.

Post-treatment medications will be listed by subject.

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

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 (Combined Part B and Part A/B Cohort 8 only)

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).
The maximum percentage of sachets taken will be 100%.

Note: For Part A/B Cohort 8 only, multiple sachets of 5.7 mg will be used to achieve doses of 11.4, 17.1, and 22.8 mg. Total number of sachets planned to be taken per day to achieve each dose is:

Doses (q12h)	Total number of sachets of planned to be taken per day
5.7mg	2
11.4mg	4
17.1mg	6
22.8mg	8

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, SE, 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 Safety Set.

8.2.6 Important Protocol Deviations/Violations

Important protocol deviations (IPD) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of key study data or that may significantly affect a subject's rights, safety, or well-being. IPD rules will be developed and finalized before database lock.

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

- Violation of subjects rights, safety or well-being
- Subject entered the study despite violation of any inclusion or exclusion criteria
- Subject was less than 80% compliant with study medications
- Subject received excluded concomitant medications
- Subject received the wrong treatment or incorrect doses
- Subject remained in study despite meeting withdrawal criteria

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

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

8.3 Efficacy Analysis (Combined Part B and Part A/B Cohort 8 only)

Statistical methodology will be restricted to descriptive statistics only. All efficacy analyses described in this section will be based on the FAS, unless specified otherwise. Summary tables will be presented by visit for each cohort and overall, for combined Part B and Part A/B Cohort 8 based on the FAS.

8.3.1 Analysis of Primary Efficacy Variable

Not applicable.

8.3.2 Analysis of Secondary Efficacy Variable

The sweat chloride test is a standard diagnostic tool for CF, serving as a biomarker of *CFTR* activity. Collection of sweat samples will be performed at qualified study sites using an approved Macroduct® (Wescor, Logan, UT) collection device. Sweat samples will be sent to a central laboratory for testing and interpretation of results. Individual sweat test results will

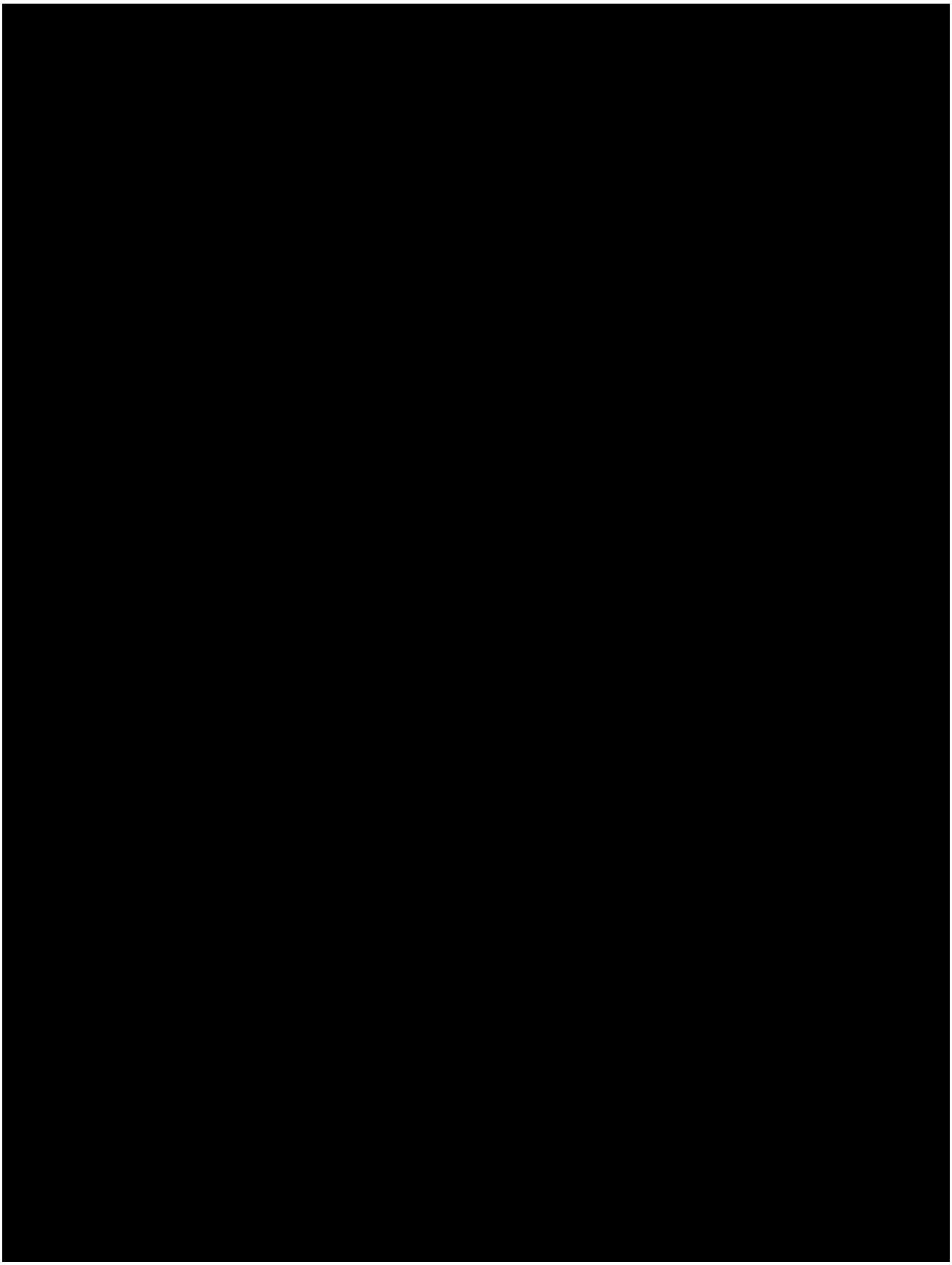
not be disclosed to the study sites. Specific instructions for collection, handling, processing, and shipping of sweat chloride samples to the central laboratory will be provided separately.

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. If 1 of the 2 measurements at a time point is missing, the other will be used as the mean. If both are missing, then sweat chloride is missing for that visit.

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.

Definition of Baseline: Only results obtained from sample collections completed prior to the first administration of study drug 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.

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



8.4 Safety Analysis

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

- Adverse events
- Clinical laboratory values (hematology and serum chemistry)
- OEs
- Physical examinations
- Standard 12-lead electrocardiograms
- Vital signs

Safety endpoints will be analyzed based on the Safety Set, separately for Part A and for the combined Part B and Part A/B Cohort 8. Only a descriptive analysis of safety will be performed. Summary tables will be presented by visit for each cohort, and overall. 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

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

Post-treatment AE (Combined Part B and Part A/B Cohort 8): any AE that worsened (either in severity or seriousness) or that was newly developed beyond the TE period

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

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

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

- All TEAEs
- TEAEs by strongest relationship
- TEAEs by severity
- TEAEs leading to treatment discontinuation
- Serious TEAEs
- Related (defined as possibly related or 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 adverse event data for TEAEs leading to treatment 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 all LFT results, the maximum on-treatment LFTs will be summarized.

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.

Clinically significant abnormal findings will be reported as AEs.

8.4.3 Electrocardiogram

For treatment-emergent ECG measurements, a summary of raw values and change from baseline values will be provided by visit. In addition, the number and percentage of subjects by maximum on-treatment value and by maximum on-treatment increase from baseline in QTc intervals will be presented. A listing of abnormal ECG complexes from the ambulatory recordings will be presented.

8.4.4 Vital Signs

For treatment-emergent vital sign measurements, the raw values and change from baseline values will be summarized by visit: systolic and diastolic blood pressure (mmHg), oral body temperature (°C), pulse oximetry (%), heart rate (beats per minute), and respiration rate (breaths per minute).

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

8.4.5 Physical Examination

Physical examination 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 OEs (incidence of cataracts or lens opacities) will be summarized as a categorical variable and results will be presented by visit.

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

8.4.7 Other Safety Analysis

Not applicable.

9 SUMMARY OF INTERIM AND IDMC ANALYSES

9.1 Interim Analysis

An interim analysis (IA) of safety, PK, and PD data from subjects in Cohorts 1 and 5 was conducted after either of the following:

- All subjects in Cohort 5 have completed their Week 12 Visit and 5 subjects in Cohort 5 have completed their Week 24 Visit
- All subjects in Cohort 5 have completed their Week 24 Visit

An IA of safety, PK, and PD data from subjects in Cohorts 2 and 6 was conducted after:

- All subjects in Cohort 6 have completed their Week 24 Visit

An IA of safety, PK, and PD data from subjects in Cohorts 3 and 7 was conducted after:

- All subjects aged 4 to <6 months in Cohort 7 have completed their Week 24 Visit

An IA of safety, PK, and PD data from subjects in Cohorts 8 was conducted after:

- All subjects aged 1 to <4 months in Cohort 8 have completed their study participation

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

11 LIST OF APPENDICES

Appendix A: Schedule of Assessments

Table 11-1 Study VX15-770-124: Part A (Screening, Treatment, Early Termination of Treatment, and Follow-up Periods)

	Screening Period	Treatment Period					Early Termination of Treatment Visit	Follow-up Telephone Call	Follow-up Ophthalmologic Examination
Event/Assessment	Day -28 to Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Within 5 Days After Last Dose of Study Drug	Day 14 (± 2 Days)	8 Weeks (± 14 Days) After Last Dose of Study Drug
Informed consent[a]	X								
Inclusion/exclusion criteria review	X	X							
Clinic visit	X	X			X	X	X		
Telephone contact		evening	morning					X	
Study drug count		X			X		X		
Demographics	X								
Medical history	X								
CFTR genotype[b]	X								
[redacted] weight[c]	X	X				X	X		
Physical examination[d]	X	X				X	X		

[a] Informed consent may be obtained before the Screening Visit and must be obtained before any screening assessment is performed.

[b] The *CFTR* 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 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.

[c] [redacted] weight must be measured with the subject in a dry diaper or dry underclothes only. [redacted] weight measurements will be made before the morning dose on Day 1. [redacted].

[d] Full physical examinations will occur at the Screening Visit and the Early Termination of Treatment (ETT) Visit; abbreviated physical examinations will occur at the Day 1 and Day 5 Visits.

Table 11-1 Study VX15-770-124: Part A (Screening, Treatment, Early Termination of Treatment, and Follow-up Periods)

	Screening Period	Treatment Period					Early Termination of Treatment Visit	Follow-up Telephone Call	Follow-up Ophthalmologic Examination
Event/Assessment	Day -28 to Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Within 5 Days After Last Dose of Study Drug	Day 14 (± 2 Days)	8 Weeks (± 14 Days) After Last Dose of Study Drug
Vital signs[e]	X	X				X	X		
12-lead ECGs[f]	X					X	X		
Ophthalmologic examination[g]	X								X
Serum chemistry and hematology[h]	X					X	X		
PK blood collection					X[i]	X[j]	X		
Sweat chloride test[k]	X								

[e] Vital signs include blood pressure (systolic and diastolic), temperature, heart rate, respiration rate, and pulse oximetry. The subject should rest for at least 5 minutes, if possible, before having vital signs measured. Day 1 vital signs measurements will be collected before the morning dose. Temperature must be obtained by the same method throughout the study.

[f] All 12-lead ECGs will be performed before the morning dose. The subject should rest for at least 5 minutes, if possible, before having the ECG performed. The ECG will be performed before any other procedures that may affect heart rate, such as blood draws.

[g] The screening OE may be performed predose on Day 1. For subjects who have the Part A Follow-up OE within 6 months of enrolling in Part B, the screening OE for Part B is not required.

[h] To minimize blood draws, the Screening Visit and Day 1 clinical laboratory assessments will be combined into a single blood draw taken up to 9 days before Day 1 dosing. The results must be received and reviewed before the first dose of study drug. All blood samples will be collected while subjects are in a seated or supine position.

[i] PK samples will be collected before the morning dose and between 2 and 4 hours and between 6 and 8 hours after dosing on Day 4.

[j] A PK sample will be collected between 24 and 60 hours after Day 4 morning dose (Day 5+1 day).

[k] 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.

Table 11-1 Study VX15-770-124: Part A (Screening, Treatment, Early Termination of Treatment, and Follow-up Periods)

	Screening Period	Treatment Period					Early Termination of Treatment Visit	Follow-up Telephone Call	Follow-up Ophthalmologic Examination
Event/Assessment	Day -28 to Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Within 5 Days After Last Dose of Study Drug	Day 14 (± 2 Days)	8 Weeks (± 14 Days) After Last Dose of Study Drug
Study drug administration[1]		X	X	X	X				
In-clinic observation for 4 hours after administration of the first dose of study drug		X							
Study drug dispensing		X							
Adverse events	Continuous from signing of ICF through the Follow-up Telephone Call (Day 14 ± 2 days; see Section 14.1.1.3 of the Clinical Study Protocol)								Ocular adverse events only
Medications and procedures review	Continuous from 28 days before the Screening Visit through the Follow-up Telephone Call (Day 14 ± 2 days)								

CF: cystic fibrosis; *CFTR*: CF transmembrane conductance regulator gene; ECG: electrocardiogram; ETT: Early Termination of Treatment; ICF: informed consent form; OE: ophthalmologic examination; PK: pharmacokinetic; q12h: every 12 hours.

[1] Study drug will be administered q12h for 3 days and the last dose of study drug in Part A will be the morning dose on Day 4. The Day 1 and Day 4 morning doses will be administered in the clinic. Doses administered from the evening dose on Day 1 through the evening dose on Day 3 will be administered q12h at home. Each dose of granules will be mixed with approximately 1 teaspoon (5 mL) of appropriate liquid or soft food (as listed in the study manual). Details of dose preparation and dose administration will be provided in the study manual. The administration dates and times and whether doses were administered with food during the 3 days should be recorded in each subject's dosing diary.

Table 11-2 Study VX15-770-124: Part B (Screening and Treatment Periods)

Event/Assessment	Screening Period	Treatment Period (Day 1 to Week 24)							
	Day -28 to Day -1	Day 1	Day 3	Week 2 (± 1 Day)	Week 4 (± 5 Days)	Week 8 (± 5 Days)	Week 12 (± 5 Days)	Week 18 (± 5 Days)	Week 24[a] (± 5 Days)
Informed consent[b]	X								
Inclusion/exclusion criteria review	X	X							
Clinic visit	X	X		X	X	X	X	X	X
Telephone contact			X						
Demographics	X								
Medical history	X								
CFTR genotype[c]	X								
[redacted] weight[d]	X	X		X	X	X	X	X	X
Physical examination[e]	X	X		X	X	X	X	X	X
Vital signs[f]	X	X		X	X	X	X	X	X
12-lead ECGs[g]	X				X		X		X
Ophthalmologic examinations[h]	X						X		X
Serum chemistry and hematology[i]	X			chemistry only	LFTs and hematology only	X	X	X	X
PK blood collection[j]				X		X			X[k]
Sweat chloride test[l]	X	X		X			X		X
[redacted]									
Study drug administration[q]		X		X	X	X	X	X	X

[a] Subjects who complete 24 weeks of study drug treatment in Part B will be eligible to enroll in the open-label treatment arm of the Extension Study. For subjects who enroll, the Week 24 visit can be the same visit as Day 1 in the treatment arm of the Extension Study, and these subjects do not need to complete the Follow-up Visit. All other subjects must complete the ETT and/or Follow-up Visits (as applicable) and will be eligible to enroll in an observational arm of the Extension Study.

[b] Informed consent may be obtained before the Screening Visit and must be obtained before any screening assessment is performed.

[c] Subjects who had *CFTR* genotyping completed in Part A of the study will not require repeat testing upon entry into Part B. 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 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.

[d] [redacted] weight must be measured with the subject in a dry diaper or dry underclothes only. [redacted] weight measurements will be made before the morning dose on Day 1.

[e] Full physical examinations will occur at the Screening and Week 24 Visits; abbreviated physical examinations will occur at all other study visits.

[f] Vital signs include blood pressure (systolic and diastolic), temperature, heart rate, respiration rate, and pulse oximetry. The subject should rest for at least 5 minutes, if possible, before having vital signs measured. Day 1 vital signs measurements will be collected before dosing. Temperature must be obtained by the same method throughout the study.

[g] All 12-lead ECGs will be performed before the morning dose. The subject should rest for at least 5 minutes, if possible, before having the ECG performed. The ECG will be performed before any other procedures that may affect heart rate, such as blood draws.

[h] The screening OE may be performed predose on Day 1. If an adequate slit-lamp examination cannot be conducted at the Part B screening, subjects will not be enrolled in Part B until an adequate repeat slit-lamp examination is completed (within 4 weeks of the Screening Period) and eligibility criteria regarding the ophthalmologic findings are met. If an adequate slit-lamp examination cannot be conducted at any visit where it is required, the subject will continue to receive study drug until an adequate repeat examination is completed (within 4 weeks of the study visit); if an adequate slit-lamp examination cannot be conducted at the second examination or a lens opacity or cataract is identified, study drug dosing will be discontinued. A screening OE will not need to be conducted for subjects who have the Part A Follow-up OE within 6 months of enrolling in Part B.

[i] To minimize blood draws, the Screening Visit and Day 1 clinical laboratory assessments will be combined into a single blood draw taken up to 9 days before Day 1 dosing. The results must be received and reviewed before the first dose of study drug. All blood samples will be collected while subjects are in a seated or supine position.

[j] PK samples will be collected before the morning dose and between 2 and 4 hours and between 6 and 8 hours after the morning dose on Week 2. PK samples will be collected before the morning dose and 1 hour and 4 hours after the morning dose on Week 8. PK samples will be collected before the morning dose and between 2 and 4 hours after the morning dose on Week 24.

[k] PK sample collection is optional at Week 24 for subjects who undergo [redacted]

[l] 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. Subjects who had a sweat chloride test during Screening for Part A will not require repeat testing during Screening for Part B. At the Day 1 Visit, the sweat chloride test must be performed before the morning dose. At the Week 2, 12, and 24 Visits, the sweat chloride test must be performed within a window of ± 2 hours relative to the morning dose of the study drug.

[redacted]

Table 11-2 Study VX15-770-124: Part B (Screening and Treatment Periods)

Event/Assessment	Screening Period	Treatment Period (Day 1 to Week 24)							
	Day -28 to Day -1	Day 1	Day 3	Week 2 (± 1 Day)	Week 4 (± 5 Days)	Week 8 (± 5 Days)	Week 12 (± 5 Days)	Week 18 (± 5 Days)	Week 24[a] (± 5 Days)
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
Study drug dispensing		X		X	X	X	X	X	X[r]
[redacted]									
Adverse events	Continuous from signing of ICF through ETT and Follow-up Visit (if required; see Section 14.1.1.3 of the Clinical Study Protocol)								
Medications and procedures review	Continuous from 28 days before the Screening Visit through the ETT and Follow-up Visit (if required)								

CF: cystic fibrosis; *CFTR*: CF transmembrane conductance regulator gene; ECG: electrocardiogram; ICF: informed consent form; [redacted]
IRT: immunoreactive trypsin and/or trypsinogen; [redacted] LFT: liver function test; PK: pharmacokinetic; q12h: every 12 hours

[redacted]

Study drug will be administered q12h. Each dose of granules will be mixed with approximately 1 teaspoon (5 mL) of liquid appropriate liquid or soft food (as listed in the study manual). Details of dose preparation and dose administration will be provided in the study manual. The dose administration dates and times, occurrence and time of regurgitation within 1 hour after dosing, and their timing with respect to food intake, will be recorded for the 2 doses prior to each PK clinic visit in each subject's dosing diary.

[r] Study drug will only be dispensed to subjects enrolling in the open-label treatment arm of the Extension Study.

Table 11-3 Study VX15-770-124: Part B (Early Termination of Treatment Visit and Follow-up Period)

	Early Termination of Treatment Visit[a]	Follow-up Visit[b]	Follow-up Ophthalmologic Examination[c]
Event/Assessment	**As Soon as Possible After the Last Dose of Study Drug**	**4 Weeks (± 7 Days) After the Last Dose of Study Drug**	**24 Weeks (± 14 Days) After the Last Dose of Study Drug**
Clinic visit	X	X	
[redacted] weight[d]	X	X	
Physical examination[e]	X	X	
Vital signs[f]	X	X	
12-lead ECGs[g]	X		
Serum chemistry and hematology[h]	X	X	
Ophthalmologic examination[i]	X		X
PK blood collection	X		
Study drug count	X		
[redacted]			
Adverse events	Continuous from signing ICF through the ETT (if required) and Follow-up Visit		Ocular adverse events only
Medications and procedures review	Continuous from 28 days before the Screening Visit through the ETT and Follow-up Visit (if required)		

ECG: electrocardiogram; ETT: Early Termination of Treatment; ICF: informed consent form; OE: ophthalmologic examination; PK: pharmacokinetic.

[a] Subjects who prematurely discontinue treatment before their last scheduled dose will be required to complete the ETT Visit as soon as possible after the last dose of study drug and the Follow-up Visit. All subjects who prematurely discontinue from study drug treatment in Part B will be eligible to enroll in an observational arm of the Extension Study.

[b] The Follow-up Visit is not required if the subject completes the Part B treatment period and enrolls in the treatment arm of the Extension Study. For all other subjects, the Follow-up Visit is not required if the ETT Visit occurs 3 weeks or later after the last dose of study drug (ivacaftor) or in the event that the subject initiates treatment with commercially available ivacaftor within 3 weeks of the Week 24 or ETT Visit.

[c] Subjects who prematurely discontinue ivacaftor treatment in Part B and received at least 1 dose of ivacaftor treatment in Part B will have a Follow-up OE 24 weeks after the last dose of study drug. Subjects enrolling into the Extension Study within 24 weeks after the last dose of study drug are not required to have the Follow-up OE (the OE will be performed in the Extension Study instead).

[d] [redacted] weight must be measured with the subject in a dry diaper or dry underclothes only.

[e] Full physical examinations will be performed at the ETT Visit and Follow-up Visit.

[f] Vital signs include blood pressure (systolic and diastolic), temperature, heart rate, respiration rate, and pulse oximetry. The subject should rest for at least 5 minutes, if possible, before having vital signs measured. Temperature must be obtained by the same method throughout the study.

[g] The subject should rest for at least 5 minutes, if possible, before having the ECG performed. The ECG will be performed before any other procedures that may affect heart rate, such as blood draws.

[h] All blood samples will be collected while subjects are in a seated or supine position.

[i] The OE for the ETT Visit will be conducted for all subjects who prematurely discontinue study drug dosing. If the ETT Visit occurs within 12 weeks of the subject's last OE, the OE at the ETT Visit will not be required. In addition, these subjects will be eligible to enroll in an observational arm of the Extension Study for long-term follow-up OE.

Table 12-4 Study VX15-770-124: Part A/B Cohort 8 (Screening, Treatment, Early Termination of Treatment, and Follow-up Periods)

	Screening Period	Treatment Period (Day 1 to Week 24)							Early Termination of Treatment Visit[a]	Follow-up Visit[b]	Follow-up Ophthalmologic Examination[c]
Event/Assessment	Day -28 to Day -14	Day 1	Day 4	Day 15 (± 1 Day)	Day 17 (± 1 Day)	Week 4 (± 5 Days)	Week 8 (± 5 Days)	Weeks 12, 18, and 24 (± 5 Days)	As Soon as Possible After the Last Dose of Study Drug	4 Weeks (± 7 Days) After Last Dose of Study Drug	12 Weeks (± 14 Days) After Last Dose of Study Drug
Informed consent[d]	X										
Inclusion/exclusion criteria review	X	X									
Clinic visit/ Assessment contact	X	X	X	X		X	X	X	X	X	
Telephone contact		pm			X						
Demographics	X										
Medical history	X										
[redacted] weight[e]	X	X	X	X		X	X	X	X	X	
Physical examination[f]	X	X	X	X		X	X	X	X	X	
Vital signs[g]	X	X	X	X		X	X	X	X	X	
12-lead ECGs[h]	X		X			X		X	X		
Ophthalmologic examinations[i]	X							X[j]	X		X
Serum chemistry[k]	X	X	X	X		X	X	X	X	X	
Hematology[k]	X			X		X		X	X	X	
PK blood collection[l]			X[m]	X		X	X[l]	X	X[n]		
Sweat chloride test[o]	X	X		X		X	X	X	X		
[redacted]											

[a] Subjects who prematurely discontinue treatment before their last scheduled dose will be required to complete the ETT Visit as soon as possible after the last dose of study drug and the Follow-up Visit. All subjects who prematurely discontinue from study drug treatment in Part A/B Cohort 8 will be eligible to enroll in an observational arm of the Extension Study.

[b] The Follow-up Visit is not required if the subject completes the Part A/B Cohort 8 treatment period and enrolls in the treatment arm of the Extension Study. For all other subjects, the Follow-up Visit is not required if the ETT Visit occurs 3 weeks or later after the last dose of study drug (ivacaftor) or in the event that the subject initiates treatment with commercially available ivacaftor within 3 weeks of the final scheduled treatment visit or ETT Visit.

[c] Subjects who prematurely discontinue ivacaftor treatment in Part A/B Cohort 8 and received at least 1 dose of ivacaftor treatment in Part A/B Cohort 8 will have a Follow-up OE 12 weeks after the last dose of study drug. Subjects enrolling into the Extension Study within 12 weeks after the last dose of study drug are not required to have the Follow-up OE (the OE will be performed in the Extension Study instead). Subjects who initiate treatment with commercially available ivacaftor within 3 weeks of the ETT Visit will not have the Follow-up OE.

[d] Informed consent may be obtained before the Screening Visit and must be obtained before any screening assessment is performed.

[e] [redacted] weight must be measured with the subject in a dry diaper or dry underclothes only. [redacted] weight measurements will be made before the morning dose on Day 1.

[f] Full physical examinations will occur at the Screening, Week 24, and Early Termination of Treatment (ETT) Visits; abbreviated physical examinations will occur at all other study visits.

[g] Vital signs include blood pressure (systolic and diastolic), temperature, heart rate, respiration rate, and pulse oximetry. The subject should rest for at least 5 minutes, if possible, before having vital signs measured. Day 1 vital sign measurements will be collected before the morning dose. Temperature must be obtained by the same method throughout the study.

[h] All 12-lead ECGs will be performed before the morning dose. The subject should rest for at least 5 minutes, if possible, before having the ECG performed. The ECG will be performed before any other procedures that may affect heart rate, such as blood draws.

[i] The screening OE may be performed at any time from screening until before the first dose on Day 1. If an adequate slit-lamp examination cannot be conducted at screening, subjects will not be enrolled until an adequate repeat slit-lamp examination is completed (within 4 weeks of the Screening Period). Eligibility criteria regarding the ophthalmologic findings must be met prior to dosing.

[j] OE to be performed at the Week 12 and Week 24 Visits.

[k] To minimize the volume of blood drawn on Day 1, clinical laboratory assessments will be determined from a single blood draw taken during the Screening Period Day -28 to Day -14. The results must be received and reviewed before the first dose of study drug. All blood samples will be collected while subjects are in a seated or supine position.

[l] PK samples will be collected before the morning dose and between 2 to 4 hours and between 6 to 8 hours after the morning dose on Day 4 and the Week 8 Visit. PK samples will be collected before the morning dose on Day 15, and on the Week 4, 12, 18, and 24 Visits.

[m] If all PK samples collected on Day 4 are missing or cannot be analyzed, PK samples collected on Day 15 will be used to assess whether the initial dose should be adjusted at the Week 4 Visit.

[n] Assessment will be performed only if within 3 days of last dose of study drug.

[o] 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. At the Day 1 Visit, the sweat chloride test must be performed before the morning dose. At the Day 15 and Week 4, 8, 12, 18 and 24 Visits, the sweat chloride test must be performed within a window of ± 2 hours relative to the morning dose of the study drug.

[redacted]

Table 12-4 Study VX15-770-124: Part A/B Cohort 8 (Screening, Treatment, Early Termination of Treatment, and Follow-up Periods)

	Screening Period	Treatment Period (Day 1 to Week 24)							Early Termination of Treatment Visit[a]	Follow-up Visit[b]	Follow-up Ophthalmologic Examination[c]
Event/Assessment	**Day -28 to Day -14**	**Day 1**	**Day 4**	**Day 15 (± 1 Day)**	**Day 17 (± 1 Day)**	**Week 4 (± 5 Days)**	**Week 8 (± 5 Days)**	**Weeks 12, 18, and 24 (± 5 Days)**	**As Soon as Possible After the Last Dose of Study Drug**	**4 Weeks (± 7 Days) After Last Dose of Study Drug**	**12 Weeks (± 14 Days) After Last Dose of Study Drug**
Study drug administration[q]		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		
Study drug dispensing		X		X		X	X	X[r]			
[redacted]											
Adverse events	Continuous from signing of ICF through ETT and Follow-up Visit (if required; see Section 14.1.1.3 of the Clinical Study Protocol)										Ocular adverse events only
Medications and procedures review	Continuous from 28 days before the Screening Visit (or from birth, as relevant) through the ETT and Follow-up Visit (if required)										

CF: cystic fibrosis; ECG: electrocardiogram; ETT: early termination of treatment; ICF: informed consent form; [redacted] OE: ophthalmologic examination; PK: pharmacokinetic; q12h: every 12 hours

[q] Study drug will be administered q12h. Each dose of granules will be mixed with approximately 1 teaspoon (5 mL) of appropriate liquid or soft food (as listed in the study manual). Details of dose preparation and dose administration will be provided in the study manual. The dose administration dates and times, occurrence and time of regurgitation within 1 hour after dosing, and their timing with respect to food intake, will be recorded for the 2 doses prior to each PK clinic visit in each subject's dosing diary. In addition, the time of administration of study drug and occurrence and time of regurgitation within 1 hour after dosing in clinic on the day of the visit will be recorded.

[r] Week 12 and Week 18 Visits only. Study drug will only be dispensed at Week 24 to subjects enrolling in the open-label treatment arm of the Extension Study.

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

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

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use a date before the first dose date.
2. Missing or partial medication stop date:
    a. If only DAY is missing, use the last day of the month.
    b. If DAY and Month are both missing, use the last day of the year.
    c. If DAY, Month and year are all missing, assign 'continuing' status to stop date.

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

Table 11-4 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 C: Imputation Rules for Missing AE dates

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

If only Day of AE start date is missing:

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

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

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

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

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

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

If Year of AE start date is missing:

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

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

Table 11-4 Analysis Visit Windows for Safety Assessments for Part B

Safety Assessment	Visit[a]	Target Study Day	Analysis Visit Window (in study days)
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, Date of Week 24 Visit]
	Follow-up Visit	NA	Use nominal visit
LFTs	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, Date of Week 24 Visit]
	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, Date of Week 24 Visit]
	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, Date of Week 24 Visit]
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, Date of Week 24 Visit]
	Follow-up Visit	NA	Use nominal visit
Ophthalmologic Exam	Baseline	1	≤1
	Week 12	84	[2,126]
	Week 24	168	[127, Date of Week 24 Visit]
	Follow-up OE visit	NA	Use nominal visit

When a subject is lost to follow up and last dose date is unknown, impute last dose date of all study drugs as last on-treatment visit date.
[a]Visit name is used to report data in tables, listings and figures.

Table 11-5 Analysis Visit Windows for Efficacy Assessments for Part B

Safety Assessment	Visit[a]	Target Study Day	Analysis Visit Window (in study days)
[redacted]			
	Follow-up Visit	NA	Use nominal visit
Sweat Chloride	Baseline	1	≤1
	Week 2	14	[2,49]
	Week 12	84	[50,126]
	Week 24	168	[127, Date of Week 24 Visit]
[redacted]			

[redacted]

When a subject is lost to follow up and last dose date is unknown, impute last dose date of all study drugs as last on-treatment visit date.

[a]Visit name is used to report data in tables, listings and figures.

Table 11-6 Analysis Visit Windows for Safety Assessments for Part A/B Cohort 8

Safety Assessment	Visit[a]	Target Study Day	Analysis Visit Window (in study days)
Serum Chemistry	Baseline	1	≤1
	Day 4	4	[2,9]
	Day 15	15	[10,21]
	Week 4	28	[22,42]
	Week 8	56	[43,70]
	Week 12	84	[71,105]
	Week 18	126	[106,147]
	Week 24	168	[148, Date of Week 24 Visit]
	Follow-up Visit	NA	Use nominal visit
Hematology	Baseline	1	≤1
	Day 15	15	[2,21]
	Week 4	28	[22,56]
	Week 12	84	[57,105]
	Week 18	126	[106,147]
	Week 24	168	[148, Date of Week 24 Visit]
	Follow-up Visit	NA	Use nominal visit
Standard 12-Lead ECG	Baseline	1	≤1
	Day4	4	[2,16]
	Week 4	28	[17,56]
	Week 12	84	[57,105]
	Week 18	126	[106,147]
	Week 24	168	[148, Date of Week 24 Visit]
Vital Signs	Baseline	1	≤1
	Day 4	4	[2,9]
	Day 15	15	[10,21]
	Week 4	28	[22,42]
	Week 8	56	[43,70]
	Week 12	84	[71,105]
	Week 18	126	[106,147]

	Week 24	168	[148, Date of Week 24 Visit]
	Follow-up Visit	NA	Use nominal visit
Ophthalmologic Exam	Baseline	1	≤1
	Week 12	84	[2,126]
	Week 24	168	[127, Date of Week 24 Visit]
	Follow-up OE visit	NA	Use nominal visit

When a subject is lost to follow up and last dose date is unknown, impute last dose date of all study drugs as last on-treatment visit date.
[a] Visit name is used to report data in tables, listings and figures.

Table 12-7 Analysis Visit Windows for Efficacy Assessments for Part A/B Cohort 8

Safety Assessment	Visit[a]	Target Study Day	Analysis Visit Window (in study days)
[redacted]			
Sweat Chloride	Baseline	1	≤1
	Day 15	15	[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, Date of Week 24 Visit]

[redacted]

When a subject is lost to follow up and last dose date is unknown, impute last dose date of all study drugs as last on-treatment visit date.

[a] Visit name is used to report data in tables, listings and figures.