1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

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

Vertex Study Number: VX15-770-124

[redacted]

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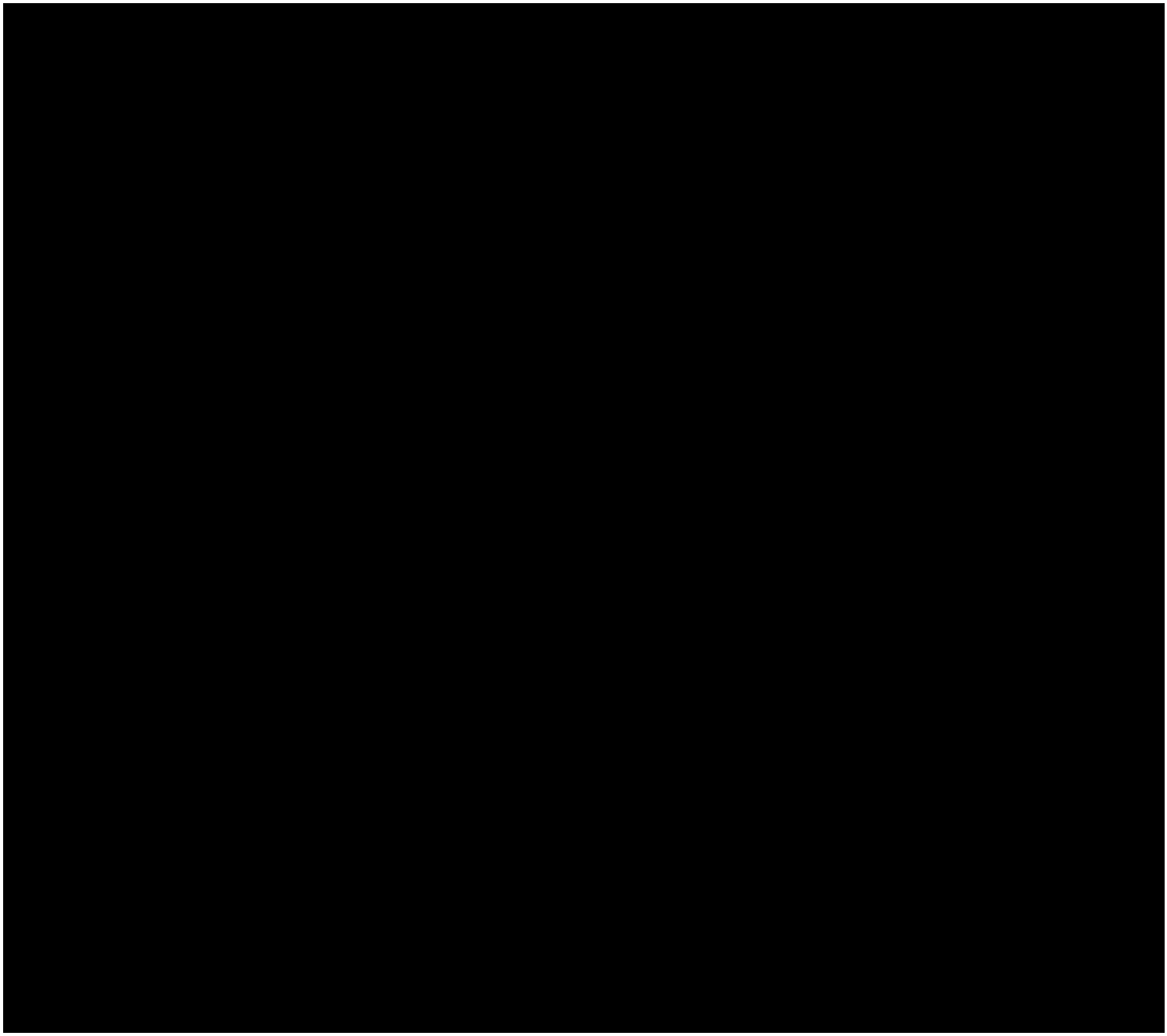

2 PROTOCOL SYNOPSIS

Title

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

Clinical Phase and Clinical Study Type

Phase 3, safety, pharmacokinetics, and efficacy

Part A Objectives

Primary:

- 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 Objectives

Primary:

- 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

Secondary:

- 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 Objectives Cohort 8

Primary:

- 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)

Secondary:

- 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)

[redacted]

Part A Endpoints

Primary:

- Safety, as determined by adverse events, clinical laboratory values (serum chemistry and hematology), standard 12-lead electrocardiograms (ECGs), vital signs, and ophthalmologic examinations (OEs)
- PK parameter estimates of ivacaftor and metabolites M1 and M6 after 4 days of ivacaftor treatment

Part B Endpoints

Primary:

- Safety, as determined by adverse events, clinical laboratory values (serum chemistry and hematology), ECGs, vital signs, and OEs

Secondary:

- PK parameter estimates of ivacaftor and metabolites M1 and M6
- Absolute change from baseline in sweat chloride

[redacted]

Part A/B Endpoints Cohort 8

Primary:

- Safety, as determined by adverse events, clinical laboratory values (serum chemistry and hematology), standard 12-lead ECGs, vital signs, and OEs
- PK parameter estimates of ivacaftor and metabolites M1 and M6

Secondary:

- Absolute change from baseline in sweat chloride

Number of Subjects in 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

Number of Subjects in 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

Number of Subjects in Part A/B Cohort 8

- A minimum of 6 and up to approximately 10 subjects, aged 1 to <4 months, with at least 4 subjects evenly distributed in the age range 1 to <3 months

Study Population

Male and female subjects with CF who are <24 months of age at Day 1 (ivacaftor treatment initiation) and have a *CFTR* gating mutation (as listed below) on at least 1 allele.

Subjects who have 1 of the following 9 *CFTR* mutations on at least 1 allele will be considered eligible for enrollment in this study: *G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P,* or *G1349D.* Subjects who have an *R117H-CFTR* mutation will be eligible in regions where ivacaftor is approved for use in subjects with an *R117H-CFTR* mutation.

Subjects who have an ivacaftor-responsive *CFTR* mutation on at least 1 allele will be considered eligible for enrollment in Part A/B Cohort 8 (consistent with the approved mutations in the region).

Investigational Drug

Active substance: ivacaftor

Activity: CFTR potentiator

Strengths and route of administration: 5.7 mg, 25 mg, 50 mg, and 75 mg; granules in sachet for oral administration

Doses of 25, 50, and 75 mg every 12 hours (q12h) for study in Cohorts 1 through 7.

Doses of 5.7, 11.4, 17.1, 22.8, 25, 50, and 75 mg, q12h, for study in Cohort 8; multiple sachets of 5.7 mg will be used to achieve doses of 11.4, 17.1, and 22.8 mg.

Dosing in all cohorts will be based on safety, PK, age, and weight.

Study Duration for Part A

Excluding the Screening Period, Part A subjects will participate in the study for approximately 10 weeks (from Day 1 through the Part A Follow-up OE).

Study Duration for Part B

Excluding the Screening Period, subjects will participate in Part B for approximately 24 weeks (from Day 1 through Week 24).

Study Duration for Part A/B Cohort 8

Excluding the Screening Period, subjects will participate in Part A/B Cohort 8 for approximately 24 weeks (from Day 1 through Week 24).

Study Design

This is a Phase 3, 2-part, open-label study 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) and they will continue that dose 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 administered.

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 an assessment of safety and PK data for subjects from Cohort 1. Enrollment for subjects in Cohort 3 will begin after an assessment 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), or 75-mg (for subjects 14 to <25 kg on Day 1) ivacaftor will be administered 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 and 3 who will 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, those 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), or 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 follows:
    - Subjects 5 to <7 kg will be dosed with 25 mg q12h
    - Subjects 7 to <14 kg will be dosed with 50 mg q12h
    - Subjects 14 to <25 kg will be dosed with 75 mg q12h
- 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
    - 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. 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 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 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).

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. 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.
- 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 Early Termination of Treatment (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).

Safety Assessments for Parts A, B, and A/B Cohort 8

Adverse events, clinical laboratory values (serum chemistry and hematology), ECGs, vital signs, physical examinations, and OEs

Pharmacodynamic Assessment for Parts B and A/B Cohort 8

Sweat chloride test

[redacted]

Statistical Analyses

Details will be provided in the statistical analysis plan (SAP) for the final analysis, which will be finalized and approved before the clinical database lock. A detailed analysis plan for PK and PK/PD parameter estimations will be presented in a clinical pharmacology analysis plan (CPAP), which will be finalized and approved before database lock.

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 determined to be appropriate based on PK considerations and feasibility assessments for CF subjects meeting the age and enrollment criteria. The study is not powered to detect a significant treatment effect. Relatively rich PK samples (4 samples at steady state) will be collected in Part A, in addition to PK samples collected 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 subjects ≥24 months of age. Based on a review of model-based pediatric simulations, the variability estimate of ivacaftor from Study VX11-770-108, 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. For Part A/B Cohort 8, relatively rich PK samples will be collected at Day 4 of the Treatment Period, followed by additional sparse PK samples through 24 weeks.

Safety analyses for Parts A, B, and A/B Cohort 8 will be conducted separately. Efficacy and PD analyses are applicable to Part B and Part A/B Cohort 8 only, and Part A/B Cohort 8 will be analyzed separately from other cohorts. Parts B and A/B Cohort 8 may also be pooled for analyses of safety, PD, and efficacy endpoints common to both parts. The Safety Set (defined as subjects who receive a dose of study drug) will be used for all safety analyses. The Full Analysis Set (FAS) (defined as subjects who are enrolled and dosed) will be used for all efficacy analyses in Part B and Part A/B Cohort 8. Data from all safety, efficacy, and PD endpoints will be analyzed using descriptive statistics, and presented by study visit and dose level for Parts A and B, and by study visit without separation by dose level for Part A/B Cohort 8.

Nonlinear mixed effects modeling will be applied for the PK analysis of ivacaftor for comparison of ivacaftor disposition to that of adults. The primary exposure estimates of interest are ivacaftor area under the concentration versus time curve (AUC) and minimum observed concentration (C_{min}). Exposure of metabolites M1 and M6 will be described by descriptive statistics.

As noted above, preliminary analyses will be performed on the PK data obtained from each cohort in Part A. The PK analysis, along with safety data from Part A, will be used to appropriately confirm the dose selection for Part B (or adjust the doses if necessary) based on criteria that take into account both the C_{min} and AUC relative to historical results in adult CF subjects. PK parameters other than C_{min} and AUC may be considered if deemed appropriate.

For Part A/B Cohort 8, preliminary analyses of individual PK data collected on Day 4 will be used to inform subsequent dosing for that subject.

IDMC Reviews

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, which will be finalized before the first IDMC review meeting.

3 SCHEDULE OF ASSESSMENTS

Table 3-1 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		
Vital signs[e]	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 (see Section 12.5.1 for details). [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.

[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.

Table 3-1 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
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								
Study drug administration[l]		X	X	X	X				

[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.

[l] 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

Table 3-1 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**
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)								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.

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 3-2 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 (see Section 12.5.1 for details). [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 MBW.

[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 3-2 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	14.1.1.3								
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] LFT: liver function test; PK: pharmacokinetic; q12h: every 12 hours

[redacted]

[q] 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 3-3 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]

[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 final scheduled treatment visit 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 (see Section 12.5.1 for details).

[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 3-3 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**
Adverse events	Continuous from signing ICF through the ETT (if required) and Follow-up Visit (see Section 14.1.1.3)		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; see Section 10.3.1)		

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

Table 3-4 Study VX15-770-124: Part A/B Cohort 8 (Screening, Treatment, Early Termination of Treatment, and Follow-up Periods)

Event/Assessment	Screening Period	Treatment Period (Day 1 to Week 24)							Early Termination of Treatment Visit[a]	Follow-up Visit[b]	Follow-up Ophthalmologic Examination[c]
	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]											
Study drug administration[q]		X	X	X		X	X	X			

[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 (see Section 12.5.1 for details). [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 3-4 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**
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)										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; see Section 10.3.1)										

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.

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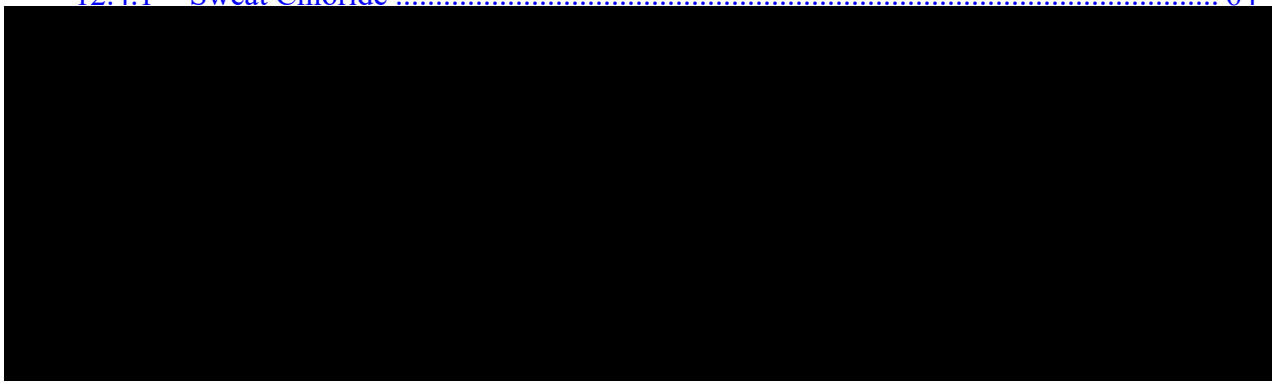

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List of Abbreviations

Abbreviation	Term
ALT	alanine transaminase or alanine aminotransferase
AST	aspartate transaminase or aspartate aminotransferase
AUC	area under the concentration versus time curve
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CF	cystic fibrosis
CFF	Cystic Fibrosis Foundation
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator
CI	confidence intervals
CL	clearance
C_{min}	minimum observed concentration
CPAP	clinical pharmacology analysis plan
CRF	case report form
CSR	clinical study report
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
ECGs	electrocardiograms
EDC	electronic data capture
EENT	eyes/ears/nose/throat
ETT	Early Termination of Treatment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
[redacted]	
G551D	CFTR missense gene mutation that results in the replacement of a glycine residue at position 551 of CFTR with an aspartic acid residue
GCP	Good Clinical Practice
GPS	Global Patient Safety
HIPAA	Health Insurance Portability and Accountability Act and associated regulations
IA	interim analysis
ICF	informed consent form
ICH	International Council for Harmonization
IDMC	independent data monitoring committee
IECs	independent ethics committees
[redacted]	
IQR	interquartile range
IRB	institutional review board

Abbreviation	Term
[redacted]	
IV	intravenous
[redacted]	
LFT	liver function test
[redacted]	
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum value
NCHS	National Center for Health Statistics
OEs	ophthalmologic examinations
PBPK	physiologically-based pharmacokinetic
PD	pharmacodynamics
PK	pharmacokinetics
popPK	population PK
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
R117H	CFTR missense gene mutation that results in the replacement of an arginine residue at position 117 of CFTR with a histidine residue
RVRTC	raised volume rapid thoracoabdominal compression
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SI	SI units (International System of Units)
TEAEs	treatment-emergent adverse events
UK	United Kingdom
ULN	upper limit of normal
US	United States
USA	United States of America

Definition of Terms:

Part A of this study includes Cohorts 1, 2, and 3 and Part B includes Cohorts 5, 6, and 7. Part A/B of the amended protocol includes Cohort 8. Cohort 4 has been dropped from the amended protocol as the age group within that cohort will be studied in Part A/B Cohort 8.

5 INTRODUCTION

5.1 Overview of Cystic Fibrosis

Cystic fibrosis (CF) is a chronically debilitating autosomal, recessive disease with high morbidity and premature mortality that affects approximately 30,000 individuals in the United States[1] and 36,000 in the European Union.[2] The disease affects predominately Whites[3] and is caused by mutations in the CF transmembrane conductance regulator gene (*CFTR*), which results in absent or deficient function of the CFTR protein at the cell surface.[4] CFTR is an epithelial chloride channel responsible for aiding in the regulation of salt and water absorption and secretion in various tissues. The failure to regulate chloride transport in these tissues results in the multisystem pathology associated with CF.[5] In the lungs, obstruction of airways with thick mucus, establishment of a chronic bacterial infection in the airways, and damaging inflammatory responses are all thought to play a role in causing irreversible structural changes in the lungs and respiratory failure. Progressive loss of lung function is the leading cause of mortality.[1, 3] Currently, there is no cure for CF, and, despite adjunctive treatments with nutritional supplements, antibiotics, and mucolytics,[6] the median predicted age of survival of individuals born today with CF is approximately 40 years of age.[1, 7-9]

More than 1900 mutations in the *CFTR* gene have been identified.[10] *CFTR* mutations result in reduced quantity of CFTR at the cell surface or reduced CFTR function, leading to a decrease in epithelial chloride transport.[11, 12] Reduced CFTR function can be due to defects in channel gating (opening and closing of CFTR channel) or channel conductance (rate of chloride travel through the open channel).

Gating refers to the amount of time in which the CFTR channel is open and can transport chloride. Ten *CFTR* mutations that lead to CFTR gating functional defects have been identified: *G551D, G178R, G551S, S549N, S549R, G970R, G1244E, S1251N, S1255P,* and *G1349D*. The *G551D* mutation is the most common mutation that causes CFTR gating defects worldwide and results in a severe CF clinical phenotype.[13-15] While reports of individual cases and small cohorts of patients show variable phenotypes in patients carrying the *G551D* mutation[16-18] the 3 largest genotype-phenotype association studies that evaluated patients from different geographical regions have classified the *G551D* mutation as being associated with a severe phenotype,[14, 19-21] with rates of lung disease progression[15] and mortality[13, 14] that are similar to other severe phenotypes. There are few published reports on the clinical features of patients with other non-*G551D* mutations that cause CFTR gating defects; however, an analysis of the US CF Foundation Patient Registry data revealed that the rates of lung disease progression in patients with these mutations are similar to that of patients with the *G551D* mutation.[15]

Mutations that cause CFTR gating defects are present in about 5% of the CF patient population worldwide. Approximately 4% of patients (1032 patients with CF in the US, 1083 in the European Union (EU), and 2374 worldwide) have the *G551D* mutation and the remaining 1% (140 patients in the US, 205 in the EU, and 370 worldwide) have other mutations that cause a CFTR gating defect.[15, 22] The *R117H* mutation causes defects in channel gating, but also in channel conductance.[23] This mutation is present in about 700 people with CF in the US, including about 500 people age 6 years and older.[1, 24] The *R117H* mutation is often associated with delayed onset of clinical symptoms, although CF patients with this mutation have progressive disease, with premature mortality and considerable morbidity.[25-27]

In May 2017, the FDA approved an additional 23 ivacaftor-responsive mutations based on clinical or in-vitro data focused on ivacaftor's mechanism of action as a CFTR modulator. In the US, these 23 residual function mutations are present in over 1800 patients (US Cystic Fibrosis Foundation [CFF] Registry data 2012[24] and 2013[1]; Vertex data on file). In August 2017, the FDA approved an additional 5 residual function mutations, present in over 600 patients in the US,[1] that result in a splicing defect in the *CFTR* gene. The US CFF registry data show a clear progression of lung disease with age in these patients. Intervening early in the disease process can ameliorate this progression. The potential risks of providing ivacaftor to patients with these 28 specific mutations are considered low.

5.2 Overview of Cystic Fibrosis in Infants and Young Children

The diagnosis of CF is suggested by the presence of 1 or more characteristic clinical features, a history of CF in a sibling, or a positive newborn screening test result, and is confirmed by laboratory evidence of abnormal CFTR protein function (a positive sweat test) or by genotyping analysis.[28] Since the introduction and continued advances of newborn screening, many patients with CF are identified through a positive screen test and subsequently diagnosed within the first neonatal year.[28] In the US and the EU, more than 61% of people with CF who were diagnosed in 2012 were found because of an abnormal newborn screen.[1, 29] In the UK, 57% of people with CF who were diagnosed in 2012 were found because of an abnormal newborn screen.[30] In the US, more than 80% of patients with CF are diagnosed by age 2; however, approximately 10% of newly diagnosed cases are 16 years of age or older.[1] In the EU, approximately 60% of patients with CF are diagnosed by 1 year of age,[29] and in the UK, approximately 83% of patients with CF are diagnosed by 1 year of age.[31] Genotyping for mutations in the *CFTR* gene is now routine practice in many countries.

In infants with CF, pancreatic insufficiency[32] and poor nutritional status[33-35] are the most significant clinical manifestations of the disease. These factors often lead to poor growth with subsequent growth delay,[36, 37] poorer cognitive development,[38] and other clinical comorbidities such as decreased lung function and survival.[39, 40] Studies of subjects 1 month through 6 years of age also show the presence of lung disease[41-44] and liver disease.[45] High-resolution computed tomography studies including infants with CF that were diagnosed by newborn screening, but were considered clinically healthy, indicates that structural lung damage is common even very early in disease progression.[44, 46, 47] In a cohort of 81 well-treated CF patients in Australia, by the age of 3 years, 10% had *Pseudomonas aeruginosa* infection and 84% had evidence of bronchiectasis.[48] This is consistent with the results of inflammatory marker studies that have found that airway inflammation begins in infancy.[42, 49, 50] The presence of airway inflammation in infancy signals the beginning of the destructive cycles of chronic inflammation, infection, and irreversible lung damage that are characteristic of CF lung disease.[51] A study of the longitudinal development of *P. aeruginosa* infection in children with CF found that 29% of the infants followed developed nonmucoid infection in the first 6 months of life; overall, the median age for nonmucoid *P. aeruginosa* infection was 1.0 years and for the transition from nonmucoid to mucoid *P. aeruginosa* infection was 13.0 years.[52] Mucoid *P. aeruginosa* infection is considered the major limiting factor in survival for patients with CF.[53]

Poor somatic growth and poor nutritional status are common in patients with CF owing to a number of factors, including exocrine pancreatic insufficiency, increased energy expenditure and appetite suppression due to lung disease, as well as diabetes.[54] Notably, 18% of children with CF fall below the US Centers for Disease Control and Prevention's (CDC) fifth percentile for weight

and 16% of children fall below the CDC fifth percentile for height.[55] Malnourishment is associated with worsening lung function in children with CF and is also an independent predictor of mortality in this population.[56]

Compounds such as CFTR modulators may have the potential to preserve normal lung and pancreatic exocrine function. Data in the literature suggest that early therapeutic intervention is beneficial to young children with CF; studies have demonstrated benefits such as improved measures of growth, nutrition, and lung disease through early intervention in children diagnosed by newborn screening.[57, 58] Moreover, treatments that target the underlying mechanisms of disease at a young age could postpone or even prevent the onset of clinical manifestation of CF such as CF lung disease.[59]

5.3 Overview of Ivacaftor

Ivacaftor is the first CFTR modulator to show an improvement in CFTR function and clinical benefit in patients with CF. Results from Phase 3 studies (VX08-770-102 [Study 102] and VX08-770-103 [Study 103]) showed that ivacaftor is effective in the treatment of subjects with CF 6 years of age and older who have the *G551D-CFTR* mutation, as evidenced by sustained improvements in CFTR channel function (measured by reduction in sweat chloride concentration) and corresponding substantial, durable improvements in lung function, pulmonary exacerbations, respiratory symptoms, and weight gain. Ivacaftor was also well tolerated, as evidenced by the rates and reasons for premature discontinuation and results of safety assessments.[60]

Results from Part 1 (placebo-controlled, double-blind, crossover period) of Study VX12-770-111 (Study 111), a Phase 3 clinical study that assessed efficacy and safety in subjects with CF who have non-*G551D-CFTR* gating mutations, showed that treatment with ivacaftor has systemic benefit, including substantial improvements in both pulmonary and extrapulmonary measures, with corresponding improvements in CFTR function. Ivacaftor produced consistent, clinically meaningful, and highly statistically significant improvements in percent predicted forced expiratory volume in 1 second (FEV_1), body mass index (BMI)/weight, sweat chloride, and the Cystic Fibrosis Questionnaire–Revised (CFQ-R; respiratory domain). These results were comparable to those observed in the Phase 3 studies (Studies 102 and 103) in subjects with the *G551D* mutation in the *CFTR* gene.[60]

Results from Study VX11-770-110 (Study 110), a Phase 3, randomized, double-blind, placebo-controlled, parallel-group study in subjects aged 6 years and older with CF who have an *R117H* mutation, showed that in subjects 18 years of age or older treatment with ivacaftor resulted statistically significant improvements in [redacted], CFTR activity as measured by sweat chloride, and in respiratory symptoms as measured by the CFQ-R respiratory domain score, compared to placebo through 24 weeks of treatment. Although the 6- to 11-years-old subgroup showed a comparable sweat chloride response to the ≥18-years-old subgroup, the younger subgroup did not show any other meaningful response to ivacaftor.[60]

All ivacaftor doses tested in VX06-770-101 (Study 101) showed a very robust improvement in CFTR function as measured by sweat chloride (Study 101 CSR, Figure 11-8). The lowest dose of 25 mg, which is one-sixth the approved adult dose, yielded improvements in sweat chloride in the range of -30 to -40 mmol/L which would be expected to be associated with clinical benefit. This was accompanied by positive trends in relative change in $ppFEV_1$ (Study 101 CSR, Figure 11-6) and nasal potential difference (Study 101 CSR, Figure 11-7).

The starting doses for Part A/B Cohort 8 were selected to maintain exposures within a range that was safe (i.e., not exceeding the range observed with the 150 mg dose in adults) and efficacious (i.e., exposures above those observed with the 25 mg dose in adults as described) (Appendix B).

Results from Study VX11-770-108 (Study 108), a Phase 3, open-label study of orally administered ivacaftor in subjects with CF who are 2 through 5 years of age and have a *CFTR* gating mutation in at least 1 allele, showed that subjects had rapid, substantial, persistent reductions in sweat chloride, improvements in nutritional status, and increases in fecal elastase-1. Additionally, the safety profile of ivacaftor was similar to that identified in the prior Phase 2b/3 analyses for subjects 6 years of age and older with a *CFTR* mutation that causes gating defects.[60]

Ivacaftor is now indicated in the US and the EU for the treatment of CF in patients 6 months of age and older who have at least 1 mutation in the *CFTR* gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data. The approved genotypes vary by country/region.

Based on data from subjects in the 4 to <6 months of age cohort (Study 124, Cohort 7) and the demonstrated safety profile in subjects with a *CFTR* gating defect 6 to <24 months of age (Study 124, Cohorts 5 and 6) and subjects 2 through 5 years of age with a *CFTR* gating defect (Study 108); the demonstrated clinical efficacy in subjects 6 years of age and older with a *G551D-CFTR* mutation (Studies 102 and 103) or a non-*G551D-CFTR* mutation (Study 111); evidence of complications of CF by age 6, and evidence supporting the benefits of early therapeutic intervention, there is great potential for patients less than ~~2~~4 months of age who have an ivacaftor-responsive *CFTR* mutation to benefit from ivacaftor treatment.[60]

6 STUDY OBJECTIVES

6.1 Part A

7 PRIMARY OBJECTIVES

- 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
- 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

7.1 Part B

7.1.1 Primary Objective

- 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

7.1.2 Secondary Objectives

- 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

[redacted]

7.2 Part A/B Cohort 8

For subjects 1 to <4 months of age, Parts A and B will be carried out sequentially in each individual subject, rather than performing a cohort analysis of Part A before starting Part B.

7.2.1 Primary Objectives

- 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)

7.2.2 Secondary Objectives

- 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)

[redacted]

8 STUDY ENDPOINTS

8.1 Part A

8.1.1 Primary Endpoints

- Safety, as determined by adverse events, clinical laboratory values (serum chemistry and hematology), standard 12-lead electrocardiograms (ECGs), vital signs, and ophthalmologic examinations (OEs)
- PK parameter estimates of ivacaftor and metabolites M1 and M6 after 4 days of ivacaftor treatment

8.2 Part B

8.2.1 Primary Endpoint

- Safety, as determined by adverse events, clinical laboratory values (serum chemistry and hematology), ECGs, vital signs, and OEs

8.2.2 Secondary Endpoints

- PK parameter estimates of ivacaftor and metabolites M1 and M6
- Absolute change from baseline in sweat chloride

8.3 Part A/B Cohort 8 Endpoints

8.3.1 Primary Endpoints

- Safety, as determined by adverse events, clinical laboratory values (serum chemistry and hematology), standard 12-lead ECGs, vital signs, and OEs
- PK parameter estimates of ivacaftor and the ivacaftor metabolites M1 and M6

8.3.2 Secondary Endpoints

- Absolute change from baseline in sweat chloride

[redacted]

9 STUDY DESIGN

9.1 Overview of Study Design

This is a Phase 3, 2-part, open-label study as depicted in Figure 9-1. 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 the time of 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 administered.

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 an assessment of safety and PK data for subjects from Cohort 1. Enrollment for subjects in Cohort 3 will begin after an assessment 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), or 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 to 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 ± 14 days after the last dose of study drug, see Section 9.1.3.1).

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 and 3 who age out of the corresponding age cohort (Cohorts 6 or 7) at Part B Day 1 may enroll in an older age cohort in Part B with the Vertex medical monitor's permission. For example, subjects in Cohort 2 who will age out of Cohort 6 may enroll in Cohort 5; and subjects in Cohorts 3 or 4 who will age out of Cohort 7 may enroll in Cohort 6. 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), or 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 follows:
    - Subjects 5 to <7 kg will be dosed with 25 mg q12h
    - Subjects 7 to <14 kg will be dosed with 50 mg q12h
    - Subjects 14 to <25 kg will be dosed with 75 mg q12h
  - 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. The Follow-up Visit will not be required for subjects who enroll in the treatment arm of this study.

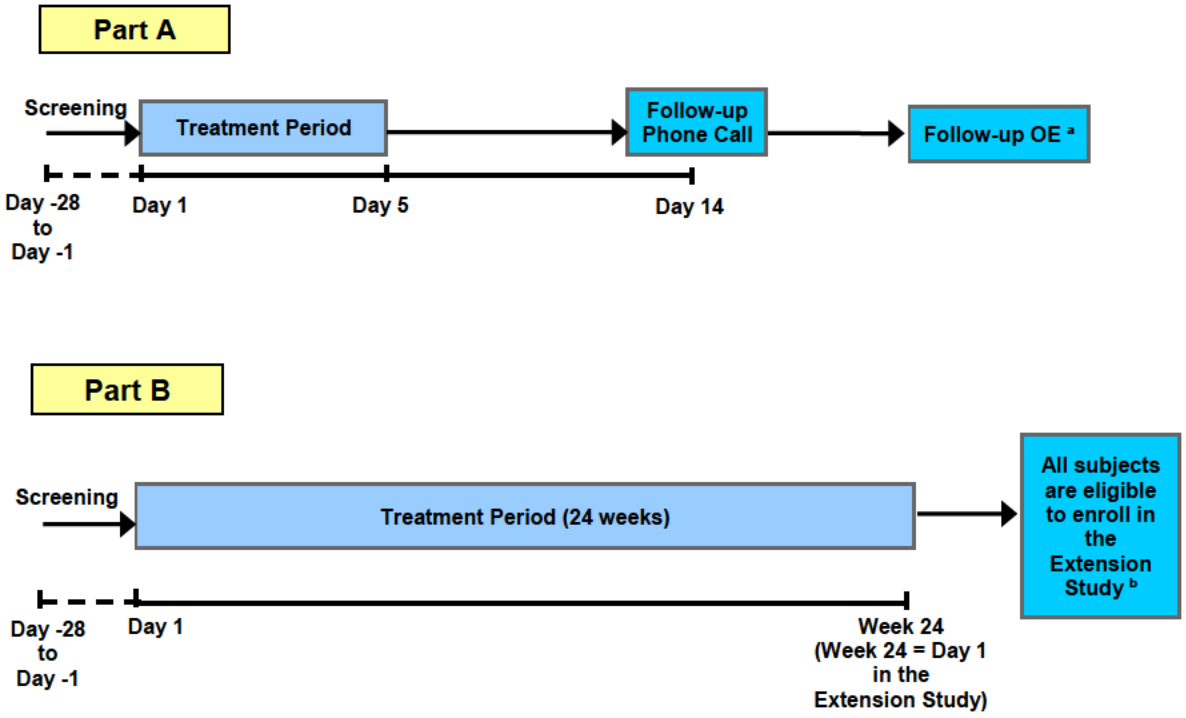
Subjects who complete 24 weeks of study drug treatment who elect not to enroll in the treatment arm of the Extension Study will be required to complete the Follow-up Visit (4 weeks ± 7 days after the last dose of study drug) and will be eligible to enroll in the observational arm of the Extension Study. 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 study drug treatment before their last scheduled dose will be required to complete the ETT Visit, Follow-up Visit, and Follow-up OE (see Section 9.1.3.1). 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 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.

Figure 9-1 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 9-2). 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.

A minimum of 6 and up to approximately 10 subjects will be enrolled, with at least 4 subjects evenly distributed in the age range 1 to <3 months, to have adequate data to assess the PK and safety in this age range.

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.

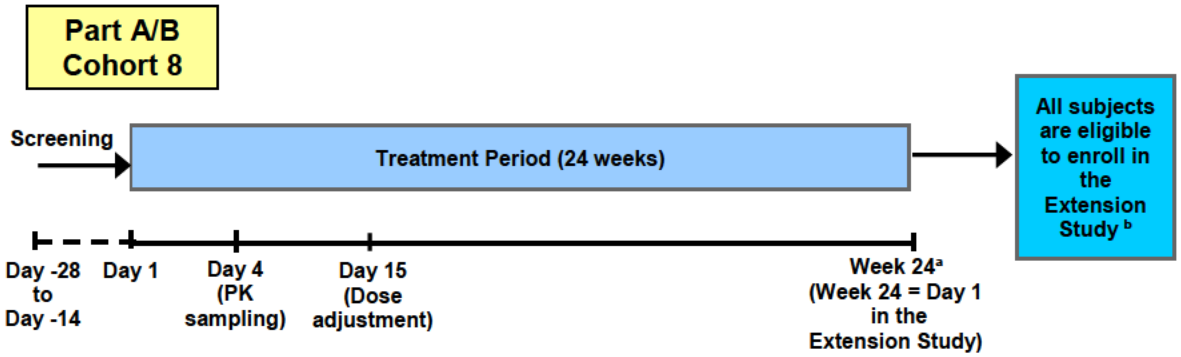
  - Study visits will occur on Days 1, 4, and 15.
  - Follow-up Telephone Call (Day 1 evening)
  - PK samples will be collected before the morning dose on Day 4, and between 2 to 4 hours and between 6 to 8 hours after the Day 4 morning dose.
  - The Day 4 PK data will be reviewed by the study team to determine the dose to be administered on Day 15. 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 to administer to the subject 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.
  - At the Day 15 Visit, a trough PK sample will be collected before the morning dose. The ivacaftor dose will be adjusted (based on the Day 4 PK data) 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.
- 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, (see Section 9.1.3.1).

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).

Figure 9-2 Schematic of Part A/B Cohort 8 Study Design



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.

9.1.1 Screening

Screening Visit assessments are listed in Part A Table 3-1, Part B Table 3-2, and Part A/B Cohort 8 (Table 16-1).

Screening will occur within 28 days before administration of study drug. Screening of subjects 1 to <4 months of age in Part A/B Cohort 8 should be completed at least 14 days prior to Day 1 (treatment initiation) to limit the volume of blood drawn in a 28-day span in this age group. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent from the subject's parent or legal guardian.

To prepare for study participation, the subject's parent or legal guardian will be instructed on the study restrictions (Section 10.3).

9.1.1.1 Repetition of Screening Assessments

Repetition of screening assessment(s) that do not meet eligibility criteria is not permitted, with the following exceptions:

- There is clear evidence of a laboratory error (e.g., hemolyzed sample) or equipment malfunction. In this case, collection of a repeat sample for the appropriate laboratory test may be permitted after discussion with the Vertex medical monitor or authorized designee.
- If a convincing alternative etiology is identified for elevated transaminases, exclusionary liver function test (LFT) levels may be retested within 2 weeks of the original Screening Visit date.
- If an adequate slit-lamp examination could not be conducted (Section 12.6.5).

If repeat values are within the eligibility criteria and completed within the screening window or extended screening window (Section 9.1.1.3), the subject is eligible for the study.

9.1.1.2 Rescreening

Rescreening may be considered only with approval of the Vertex medical monitor. The investigator (or an appropriate authorized designee at the study site) will confirm the assessments (e.g., number/type of blood sample assessments) required for rescreening with the Vertex medical monitor. *CFTR* genotyping and sweat chloride testing do not need to be repeated. If a subject has had an OE including an adequate slit-lamp examination within 12 weeks, the OE does not need to be repeated. If a subject is rescreened, the screening window will begin once the first rescreening assessment has been initiated.

9.1.1.3 Extension of Screening Window

A subject may have the screening window extended by 2 weeks for the following reasons upon approval by the Vertex medical monitor:

- Repetition of screening assessments (Section 9.1.1.1)
- Unexpected operational or logistical delays (e.g., delayed drug shipment)
- To meet the eligibility criteria
- Scheduling of the OE (Section 12.6.5)
- Availability of required equipment

The screening window can be extended by 4 weeks if a slit-lamp examination must be repeated (Sections 9.1.1.1 and 12.6.5).

9.1.2 Treatment Period

Treatment Period assessments are listed in Table 3-1, Table 3-2, Table 3-3, and Table 16-1.

In Part A, subjects will be administered 25 mg, 50 mg, or 75 mg q12h, or other appropriate dose of ivacaftor based on emerging PK data (by weight, see Section 9.3.2), on Days 1 through 3, and 1 morning dose on Day 4. Subjects will be outpatients during the study; visits will occur on Day 1, Day 4, and Day 5. Telephone contact will also occur in the evening of Day 1 and the morning of Day 2.

After preliminary analysis of PK and safety data from Part A is performed and dose selection for Part B is confirmed, subjects in Part B Cohorts 5 and 6 will be administered 25-mg, 50-mg, or 75-mg ivacaftor (by weight, see Section 9.3.2) or other appropriate doses (to be determined based on PK data from Part A) administered q12h for 24 weeks. 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 which time the ivacaftor dose for each subject will be reassessed and adjusted based on body weight (Section 9.3.2). For subjects who participated in Part A, the starting dose in Part B may be different than that of Part A based on body weight on Day 1. Subjects will be outpatients during the study; visits will occur on Day 1 and Weeks 2, 4, 8, 12, 18, and 24; and a telephone contact will occur on Day 3.

In Part A/B Cohort 8, subjects will be administered 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 (see Section 9.3.2). Subjects will be outpatients during the study; visits will occur on Day 1, Day 4, Day 15, Week 4, Week 8, Week 12, Week 18, and Week 24. On Day 4, PK samples will be collected before the morning dose, between 2 to 4 hours and between 6 to 8 hours after the 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 dose or potential dose adjustment will be communicated in writing to the principal investigator to administer 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 based on the Day 4 PK data 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. 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 at which time the recommended age- and weight-appropriate dose(s) will be administered. At the Week 8 Visit, 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. The subject's Week 8 pre- and post-dose PK data will be used to more fully characterize the PK profile. 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.

9.1.3 Follow-up

Follow-up assessments are listed in Part A Table 3-1, Part B Table 3-3, and Part A/B Cohort 8 Table 16-1.

In Part A, there will be a Follow-up Telephone Call (Day 14 ± 2 days) and a Follow-up OE (see Section 9.1.3.1) for all subjects.

In Part B and in Part A/B Cohort 8, there will be a Follow-up Visit 4 weeks ± 7 days after the last dose of study drug.

All subjects who complete 24 weeks of study drug treatment in Part B or Part A/B Cohort 8 will be eligible to enroll in the open-label treatment arm of the Extension Study. The Follow-up Visit will not be required for subjects who enroll in the treatment arm of Extension Study.

Subjects who prematurely discontinue study drug treatment in Part B or in Part A/B Cohort 8, and subjects who complete 24 weeks of study drug treatment in Part B or Part A/B Cohort 8, but

do not enroll in the treatment arm of the Extension Study, will be required to complete the Follow-up Visit. 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 final scheduled treatment visit in Part B or Part A/B Cohort 8, or the ETT Visit.

Subjects who prematurely discontinue study drug treatment and subjects who complete 24 weeks of study drug treatment in Part B or Part A/B Cohort 8, but do not enroll in the treatment arm of the Extension Study, 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.

9.1.3.1 Follow-up Ophthalmologic Examination

In Part A, there will be a Follow-up OE 8 weeks ± 14 days after the last dose of study drug. For subjects who have the Part A Follow-up OE within 6 months of enrolling in Part B, a screening OE for Part B is not required.

In Part B, subjects who prematurely discontinue study drug treatment and received at least 1 dose of ivacaftor treatment in Part B will have a Follow-up OE 24 weeks ± 14 days 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 Part B Follow-up OE (the OE will be performed in the Extension Study instead).

In Part A/B Cohort 8, subjects who prematurely discontinue study drug treatment and received at least 1 dose of ivacaftor treatment in Part A/B Cohort 8 will have a Follow-up OE 12 weeks ± 14 days 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 Part A/B Cohort 8 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 Part B or Part A/B Cohort 8 Follow-up OE.

9.1.4 Early Termination of Treatment

ETT assessments are listed in Part A Table 3-1, Part B Table 3-3, and Part A/B Cohort 8 Table 16-1.

In Part A, subjects who prematurely discontinue treatment before their last scheduled dose will be required to complete the ETT Visit (within 5 days after the last dose of study drug), Follow-up Telephone Call (Day 14).

In Part B, and Part A/B Cohort 8, 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).

9.2 Independent Data Monitoring Committee

Data will be reviewed by an independent data monitoring committee (IDMC) to ensure the safety of the subjects in the study (Section 13.5.6). 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.

9.3 Rationale for Study Design and Study Drug Regimens

Part A of this study is designed to evaluate the safety and characterize the PK of ivacaftor in subjects <24 months of age at the time of treatment initiation. The plasma PK data obtained in Part A will be used for the confirmation (or adjustment if necessary) of planned doses for Part B, as described in Section 13.6.1. The ivacaftor doses identified for the initiation of Part A (25 mg, 50 mg, and 75 mg) are based on modeling and simulation results, as described in Section 9.3.2. Based on emerging data from Part A, these doses may be amended for ongoing cohorts or for future cohorts in Part A and Part B. Subjects may receive higher or lower doses and dosing may be amended to different weight strata as appropriate based on emerging data. If PK data from the initial 5 subjects enrolled in a cohort in Part A are insufficient to determine the appropriate dose for that age group, additional subjects may be enrolled and receive the same or a different dose. Dosing will not proceed in a particular age group in Part B until confirmation of the dose for that age group in Part A.

Part A/B Cohort 8 of this study is designed to evaluate the safety and characterize the PK of ivacaftor in subjects aged 1 to <4 months old who are ≥38 weeks gestation and weigh at least 3 kg at the time of treatment initiation (Day 1). Given the rapid change and uncertainty in CYP maturation in this young age range, an initial lower dose and adjustment of dosing based on a PK evaluation will help ensure appropriate exposures for these patients during the study conduct. Thus, an alternative study design will be used to study the cohort of patients aged 1 month to <4 months. At the end of study, a comprehensive evaluation using all of the data will be used to determine the optimal dose and regimen for this patient population.

9.3.1 Study Design

This open-label study is designed to evaluate the safety, PK, PD, and efficacy of ivacaftor in subjects with CF who are <24 months of age at the time of treatment initiation 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 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 a 24-week treatment period. Subjects who complete 24 weeks of study drug treatment in Part B will be eligible to enroll in an Extension Study and receive open-label ivacaftor treatment. All other subjects will be eligible to enroll in an observational arm of the Extension Study. The Extension Study is designed to evaluate the long-term safety, PD, and efficacy of ivacaftor.

Part A/B Cohort 8 is designed to evaluate the safety, PK, PD, and efficacy of multiple-dose administration of ivacaftor in subjects 1 to <4 months of age starting with an initial relatively low dose of ivacaftor. Subjects will receive this 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. 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. Safety laboratory test results, ECGs, and any adverse events will also be evaluated when determining whether to dose subjects. The ivacaftor dose will be adjusted (based on the Day 4 PK data) 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. The subject is intended to then remain on the same dose of ivacaftor 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.

The entire treatment period of the study will be 24 weeks, after which subjects will be eligible to enroll in an Extension Study and receive open-label ivacaftor treatment. The 24-week treatment period will provide subject data at least through the age of 7 months. Vertex plans to enroll a minimum of 6 and up to approximately 10 subjects to have adequate data to assess the PK and safety in this age range.

Due to the lack of equipoise for a placebo-controlled study based upon the robust efficacy results demonstrated in subjects with CF 6 years of age and older who have a *CFTR* gating mutation (Studies 102, 103, and 111) and supportive results demonstrated in subjects with CF 2 to 5 years of age who have a *CFTR* gating mutation (Study 108), combined with the ethical consequence of withholding a known effective treatment in the study of young children, an open-label design has been selected for this study.

9.3.2 Study Drug Dose and Duration

In Part A, subjects weighing 5 to <7 kg on Day 1 will be administered 25-mg ivacaftor q12h, subjects weighing 7 to <14 kg on Day 1 will be administered 50-mg ivacaftor q12h, and subjects weighing 14 to <25 kg on Day 1 will be administered 75-mg ivacaftor q12h. Doses of ivacaftor will be administered q12h for 3 days with the last dose of study drug administered the morning dose on Day 4 (7 total doses) to obtain steady-state concentrations of ivacaftor. 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. Sites will receive a memorandum entitled "Justification for Dose Selection" as notification of updates to study drug dose, or changes to age strata or weight bounds.

In Part B Cohorts 5 and 6, subjects weighing 5 to <7 kg on Day 1 will be administered 25-mg ivacaftor q12h, subjects weighing 7 to <14 kg on Day 1 will be administered 50-mg ivacaftor q12h, and subjects weighing 14 to <25 kg on Day 1 will be administered 75-mg ivacaftor q12h (or other suitable starting dose based on 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 follows:

- Subjects 5 to <7 kg will be dosed with 25 mg q12h
- Subjects 7 to <14 kg will be dosed with 50 mg q12h
- Subjects 14 to <25 kg will be dosed with 75 mg q12h

The treatment duration will be 24 weeks for Part B. A 24-week treatment duration was utilized in the primary analysis of Study 108, a safety, PK, and PD study conducted in subjects age 2 to <6 years of age. Thus, the 24-week duration of treatment will provide a similar period for evaluation of safety, PK, and PD response in subjects <24 months of age.

In Part A/B Cohort 8, 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.

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. 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 communicated in writing to the principal investigator to administer to the subject on Day 15. The subject should then remain on the same dose of ivacaftor 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.

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.

The entire treatment period of the study will be 24 weeks, after which subjects will be eligible to enroll in an Extension Study and receive open-label ivacaftor treatment. The 24-week treatment period will provide subject data at least through the age of 7 months.

9.3.2.1 Dose Selection

The population PK approach used for selection of doses in subjects 2 to <6 years of age in Study 108 was implemented for dose selection in subjects <24 months of age with the addition of a CYP maturation component to the model. In the population PK model from Study 108, body weight represents changes in ivacaftor PK as a function of body size by incorporation of an allometric model. At the conclusion of Study 108, PK data obtained from subjects 2 to <6 years of age was included in the most recent population PK model.

Dose Selection for Subjects 3 to <24 Months of Age

Using the current model, simulations were performed to predict ivacaftor exposure in 3 weight groups of patients <24 months of age: 4.5 to <7 kg, 7 to <14 kg, and 14 to <25 kg. Target exposure parameters are minimum observed concentration (C_{min}) and area under the concentration versus time curve (AUC) values observed in adult CF patients. The simulations incorporated a maturation function to determine the range of likely exposures given maturational changes in clearance (CL). Since the maturation characteristics of CL for ivacaftor are unknown, a range of values was assumed for simulation purposes. Extent of the change was allowed to vary between 0 to 80% from adult values for a newborn, and CL reached a mature value between 12 and 18 months. Maximum change in CL (80% difference from adults) and maturation rate are consistent with differences in cytochrome P450 3A4 (CYP3A4) expression in infants.[61-63] Maturation of ivacaftor clearance was described as follows:[64]

$$F_{CL} = 1 - (1 - \beta_{CL}) \cdot exp(- Age \cdot (0.693/T_{CL}))$$

$$CL = \Theta_{CL} \cdot (WT/70kg)0.75 \cdot F_{CL}$$

Where, F_{CL} = fraction of mature CL, β = fractional CL at birth (0.2 - 1), T_{CL} = maturation half-life (2.4 - 3.6 months), Θ_{CL} = population mean CL

The simulations support selection of the following doses for CF subjects <24 months of age: 25 mg for 5 to <7 kg, 50 mg for 7 to <14 kg, and 75 mg for 14 to <25 kg.

Dose Selection for Subjects 1 to <4 Months of Age

To select doses for Part A/B Cohort 8, population PK models were updated to include all available data from pediatric subjects 3 months of age and older to account for potential maturation effects. For a more comprehensive estimate of the range of potential exposures, the updated population PK (popPK) models and a physiologically-based pharmacokinetic (PBPK) model were used to predict potential variability in CYP3A4 maturation for the 1 to <4-month-old age group. While these models adequately described the available data from subjects 3 months to 1 year of age (noting that only 2 subjects were <4 months of age), they yielded a range of exposure predictions (AUC_{0-12}) for the 1 to <4-months of age population due to the different predicted CYP3A4 maturation effects. Initial low doses of ivacaftor (5.7 mg q12h or 11.4 mg q12h based on their Day 1 age and weight) were selected using simulations from these models. These initial doses are predicted to yield exposures within or below the adult exposure range and to provide a degree of clinical benefit.

9.3.3 Rationale for Study Assessments

The safety and PK assessments are standard parameters for clinical studies in drug development. The scope of the assessments is considered appropriate for safety monitoring in the context of this study.

The following assessments are widely accepted and generally recognized as reliable, accurate, and relevant to the study of patients with CF.

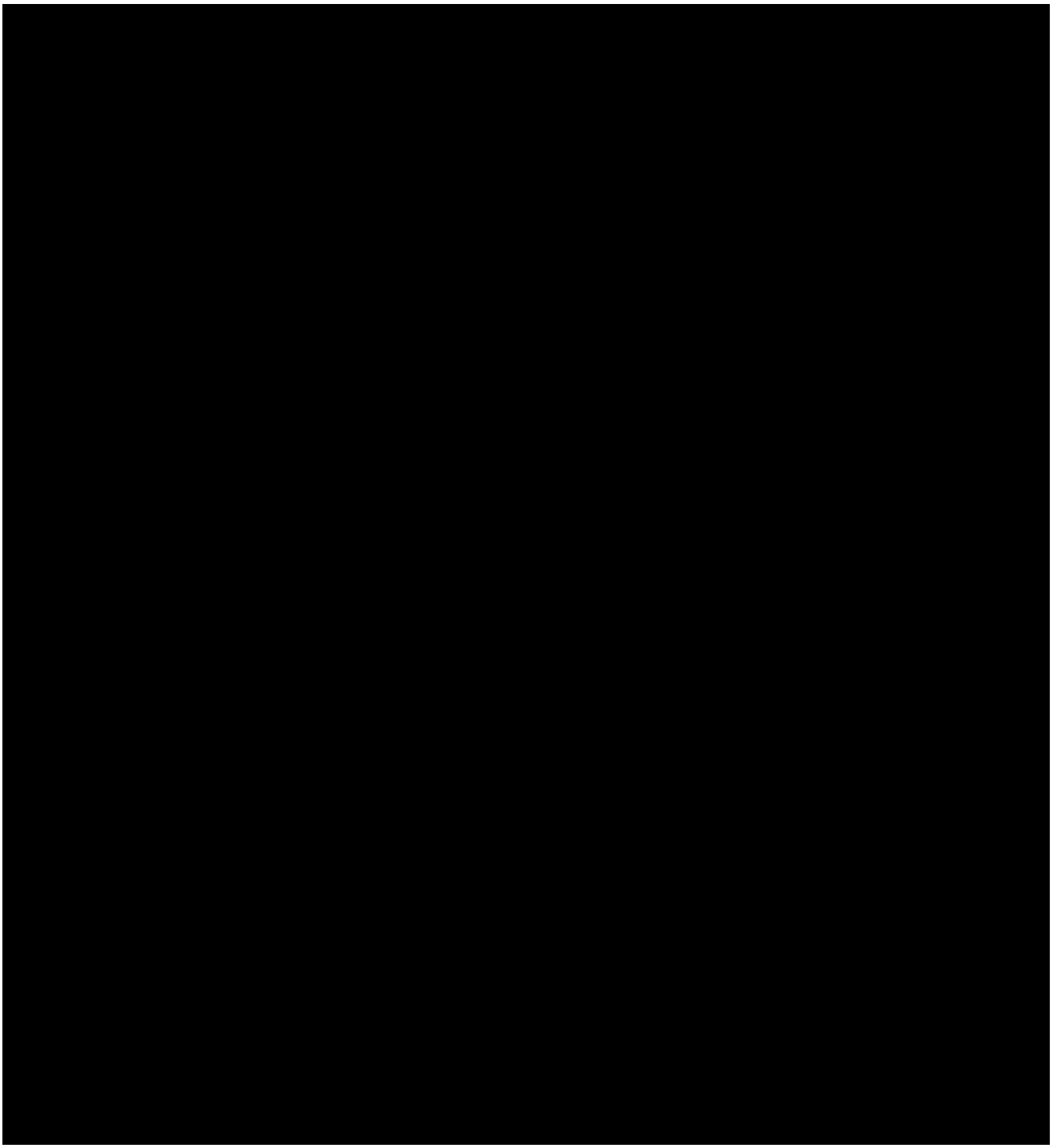
Sweat chloride test: The sweat chloride test (quantitative pilocarpine iontophoresis) is a direct measure of CFTR activity in vivo and is the most commonly used diagnostic tool for CF. Sweat in normal individuals is hypotonic with respect to plasma chloride and sodium due to the absorption of chloride by CFTR and sodium by the epithelial sodium channel from sweat prior to the sweat reaching the surface of the skin. Because patients with CF have diminished CFTR activity, chloride ions are poorly reabsorbed, leading to elevated sweat chloride concentration.[65, 66] Sweat chloride can be measured in patients with CF of all ages, although levels do increase throughout the first 6 months of life.[67] For infants up to and including 6 months of age, interpretation of sweat chloride levels is as follows:

- <30 mmol/L indicates that diagnosis of CF is very unlikely;
- 30 to 59 mmol/L indicates that that CF is possible; and
- ≥60 mmol/L indicates that CF is likely to be diagnosed.[68,69]

In the Phase 3 trials of ivacaftor in subjects 6 years of age and older with CF and the *G551D-CFTR* mutation (Studies 102 and 103) or a non-*G551D-CFTR* mutation (Study 111), treatment with ivacaftor led to a substantial and statistically significant improvement in CFTR function compared with placebo as measured by sweat chloride concentration. In these trials, treatment with ivacaftor resulted in substantial, durable, and statistically significant improvements in FEV_1, respiratory symptoms, weight, and time-to-first pulmonary

exacerbation.[60] In another Phase 3 study of ivacaftor in subjects 2 through 5 years of age with a mutation that causes CFTR gating defects (Study 108), results showed that treatment with ivacaftor for 24 weeks improved CFTR function, as evidenced by improvements in sweat chloride levels. These improvements were also consistent with improvements in subjects greater than 6 years of age with a mutation that causes CFTR gating defects.[60]

Based on the mechanism of action of ivacaftor, and the results of the previous Phase 3 studies of ivacaftor, the sweat chloride test is included in this study as a PD measure of the effect of ivacaftor on CFTR activity.



[redacted]

10 STUDY POPULATION

Eligibility should be reviewed and documented by an appropriately qualified member of the investigator's team before subjects are enrolled in Part A, Part B, and Part A/B Cohort 8.

10.1 Inclusion Criteria

Subjects who meet all of the following inclusion criteria will be eligible.

1. Male or female with confirmed diagnosis of CF, defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis OR 2 CF-causing mutations.

- 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 optional.

2. Have 1 of the following 9 *CFTR* mutations on at least 1 allele: *G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P,* or *G1349D*. Subjects who have an *R117H-CFTR* mutation will be eligible in regions where ivacaftor is approved for use in subjects with an *R117H-CFTR* mutation. Subjects eligible for Part A/B Cohort 8 may also have other ivacaftor-responsive mutations (see Appendix A).

- 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 (see Section 12.6.2). If a historic genotype result is not available at screening or if the historic genotype result is not approved by the Vertex medical monitor, the subject will be tested for *CFTR* genotype at screening and the results must be reviewed before the first dose of ivacaftor. Subjects who have been enrolled and whose screening genotype does not confirm study eligibility will not receive study drug.
- Subjects who have an ivacaftor-responsive mutation on at least 1 allele will be eligible to enroll in Part A/B Cohort 8 in regions where ivacaftor is approved (consistent with the approved mutations in the region; see Appendix A).
    - Subjects must be ≥1 to <4 months of age, ≥38 weeks gestation, and weigh ≥3 kg at Day 1 (treatment initiation); subjects 3 months of age must weigh ≥5 kg on Day 1 (Section 9.3.2)
    - Subjects must have a documented genotype test (performed to applicable national standards). Genotype testing is expected to be initiated prior to screening. Results of the genotype test are to be reviewed and approved by the Vertex medical monitor prior to Day 1.
        - Subjects with the *R117H* genotype should have the 5T variant or a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis.

3. Aged 0 to <24 months at Day 1; subjects who completed Part A who are ≥24 months of age on Day 1 in Part B are not eligible to enroll in Part B.
4. For Cohorts 7 and 8 only, gestational age ≥38 weeks.
5. Hematology, serum chemistry, and vital signs results at screening with no clinically significant abnormalities that would interfere with the study assessments, as judged by the investigator.
6. Weight at screening must be within the weight limits as defined for the study drug dose levels (Section 9.3.2).

7. As judged by the investigator, the individual (i.e., parent or legal guardian) signing the informed consent on behalf of the subject must be able to understand the protocol requirements, restrictions, and instructions and should be able to ensure the subject's compliance with study requirements and the subject's likelihood for completing the study as planned.
8. Parent or legal guardian must sign the informed consent form (ICF).

10.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will not be eligible.

1. History of any illness or condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject.
2. An acute upper or lower respiratory infection, or pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before Day 1
3. *This exclusion criterion is waived for subjects enrolling in Part A/B Cohort 8.* Colonization with organisms associated with a more rapid decline in pulmonary status (e.g., *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*) at screening. The investigator could be guided by the following suggested criteria for a subject to be considered free of colonization:

- The subject should have had 2 respiratory tract cultures negative for these organisms within the past 12 months, with no subsequent positive cultures.
- These 2 respiratory tract cultures should have been separated by at least 3 months.
- One of these 2 respiratory tract cultures should have been obtained within the past 6 months.

4. Abnormal liver function at screening or any prior history of clinically relevant elevated (>2 × upper limit of normal [ULN]) serum aspartate transaminase (AST), serum alanine transaminase (ALT), or bilirubin (excluding newborn hyperbilirubinemia)
5. History of solid organ or hematological transplantation
6. Any clinically significant "non-CF-related" illness within 2 weeks before Day 1. "Illness" is defined as an acute (serious or nonserious) condition (e.g., gastroenteritis)
7. Use of any moderate or strong inducers or inhibitors of cytochrome P450 (CYP) 3A within 2 weeks before Day 1
8. Participation in a clinical study involving administration of either an investigational or a marketed drug within 30 days or 5 terminal half-lives (whichever is longer or as determined by the local requirements) before screening
9. Hemoglobin <9.5 g/dL at screening
10. Chronic kidney disease of Stage 3 or above
11. An adequate slit-lamp examination could not be conducted at the screening OE
12. Presence of a lens opacity or cataract identified at the screening OE (excluding those considered congenital and nonprogressive, such as a suture cataract)

10.3 Study Restrictions

10.3.1 Prior and Concomitant Medications and Other Study Restrictions

Information regarding all prior and concomitant medications, including the subject's CF medications, other medications, and herbal and naturopathic remedies (including drug name, dose, and dose regimen) administered during the following periods will be collected:

- For subjects who are enrolled in Part A: from 28 days before the Part A Screening Visit through the Follow-up Telephone Call (Day 14 ± 2 days) in Part A
- For subjects who are enrolled in Part B: from 28 days before the Part B Screening Visit through:
  - the Week 24 Visit for subjects who complete the study and enter the treatment arm of the Extension Study,
  - the Follow-up Visit (if required) for subjects who complete the study and do not enter the treatment arm of the Extension Study, and
  - the ETT or Follow-up Visit (if required) for subjects who prematurely discontinue from treatment.
- For subjects who are enrolled in Part A/B Cohort 8: from 28 days before (or from birth, as relevant) the Part A/B Cohort 8 Screening Visit through:
  - the Week 24 Visit for subjects who complete the study and enter the treatment arm of the Extension Study,
  - the Follow-up Visit (if required) for subjects who complete the study and do not enter the treatment arm of the Extension Study, and
  - the ETT or Follow-up Visit (if required) for subjects who prematurely discontinue from treatment.

For any subjects in Part A, Part B, or Part A/B Cohort 8 who are screened but are not subsequently enrolled in the study, details of prior and concomitant medications will only be documented in the subject's source documents.

For all subjects enrolled in the study, it is recommended that subjects remain on current medication regimens for their CF from 28 days before Day 1 through the end of study participation.

10.3.2 Prohibited Medications

Subjects must have ended use of moderate and strong inducers and inhibitors of CYP3A, including certain herbal medications and food containing grapefruit or Seville oranges at least 14 days before Day 1 in Part A, Part B, or Part A/B Cohort 8 as applicable.

In Part A, subjects may not consume these items until the end of the Day 5 Visit or, if applicable, the ETT Visit.

In Part B and Part A/B Cohort 8, subjects may not consume these items while on study drug. If a subject discontinues from study drug prematurely, the subject may consume these items after the ETT Visit.

A more comprehensive list of restricted medications will be provided in the study manual. Noncompliance with these restrictions will be addressed on a case-by-case basis with the Vertex medical monitor.

10.4 Removal of Subjects

Subjects may withdraw from the study at any time at the request of the parent or legal guardian. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. If a subject has been withdrawn from study drug treatment, the subject should continue to be followed through the ETT, Follow-up Visit, Follow-up Call, and Follow-up OEs, as indicated in Sections 9.1.3, 9.1.3.1, and 9.1.4, provided the subject's parent or legal guardian has not withdrawn consent.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject's parent or legal guardian. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject's parent or legal guardian return all unused investigational product(s), request that the subject return for a Follow-up Visit, if applicable (see Section 9.1.3), and follow up with the subject's parent or legal guardian regarding any unresolved adverse events.

If the subject's parent or legal guardian withdraws consent, no further evaluations will be performed and no additional data will be collected. Vertex may retain and continue to use any data collected before such withdrawal of consent.

A subject **will be** discontinued from study treatment for any of the following reasons:

- Vertex, regulatory authorities, or the site's institutional review board (IRB) or ethics committee (EC) closes the study.
- A subject is noncompliant with study protocol requirements, restrictions, and instructions.
- A subject participates in another therapeutic clinical study.
- A subject develops a new lens opacity or cataract (see Section 12.6.5).
- The assessment of benefit-risk is no longer favorable.

A subject **may be** discontinued from the study treatment, after discussion between the investigator and the Vertex medical monitor, for any of the following reasons:

- A subject develops a medical condition that requires prolonged concomitant therapy with a prohibited medication or prolonged interruption of ivacaftor.
- A subject develops a life-threatening adverse event, or a serious adverse event (SAE) that places them at immediate risk.
- A subject experiences an increase in liver function test levels (LFTs; e.g., AST or ALT levels) as described in Section 12.6.2.
- An adequate repeat slit-lamp examination cannot be performed (see Section 12.6.5).

10.5 Replacement of Subjects

Subjects who withdraw or are withdrawn for nonsafety reasons during the study drug treatment periods may be replaced at Vertex's discretion.

11 STUDY DRUG ADMINISTRATION AND MANAGEMENT

11.1 Preparation and Dispensing

Study drug may be dispensed only under the supervision of the investigator or an authorized designee and only for administration to the study subjects.

11.2 Administration

On Day 1 of Part A, subjects who meet all inclusion and exclusion criteria will receive a single dose of 25-mg, 50-mg, or 75-mg ivacaftor (or other dose, based on emerging PK data; dose by weight, see Section 9.3.2) in the clinic. 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) and administered with an age-appropriate fat-containing meal or snack. All subjects will be observed for 4 hours after administration of the first dose of study drug.

In Part A, doses administered from the evening dose on Day 1 through the evening dose on Day 3 will be administered q12h at home, and the Day 1 and Day 4 morning dose will be administered in the clinic. Parents will be instructed on how to empty the packet and administer ivacaftor with food or liquid. Details of dose preparation and dose administration will be provided in the study manual. A diary of the dose administration dates and times, occurrence and time of regurgitation within 1 hour after dosing, and whether doses were administered with food during the 3 days will be kept by the subject's parents/caregivers.

On Day 1 of Part B, subjects who meet all inclusion and exclusion criteria will receive a single dose of 25-mg, 50-mg, or 75-mg ivacaftor, or other suitable starting dose based on PK data from Part A (by weight, see Section 9.3.2) in the clinic; all subjects will be observed for 4 hours after administration of the first dose of study drug. 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) and administered orally q12h with an age-appropriate fat-containing meal or snack from Day 1 through Week 24. Details of dose preparation and dose administration will be provided in the study manual.

At the Part B Week 2, Week 8, and Week 24 Visits, the administration dates and timing with respect to food intake and occurrence and time of regurgitation within 1 hour after dosing for the 2 doses of study drug administered immediately prior to the study visit should be recorded 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.

On Day 1 of Part A/B Cohort 8, subjects who meet all inclusion and no exclusion criteria will receive a single dose of 5.7 mg or 11.4 mg ivacaftor based on Day 1 age and weight (see Section 9.3.2) in the clinic. 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) and administered with an age-appropriate fat-containing meal or snack. All subjects will be observed for 4 hours after administration of the first dose of study drug.

In Part A/B Cohort 8, doses from the evening dose on Day 1 through the evening dose on Day 14 will be administered q12h at home, except for the Day 4 morning dose, which will be administered in the clinic. Parents will be instructed on how to empty the packet and administer ivacaftor with food or liquid. Details of dose preparation and dose administration will be

provided in the study manual. A diary of the dose administration dates and times, occurrence and time of regurgitation within 1 hour after dosing, and whether doses were administered with food/liquid during the 3 days prior to the Day 4 Visit, will be kept by the subject's parents/caregivers. If regurgitation of a dose should occur, the subject should not be re-dosed

At the Day 15 Visit of Part A/B Cohort 8, the ivacaftor dose will be adjusted, if necessary, to 5.7, 11.4, 17.1, 22.8, or 25 mg based on PK data from Day 4 (see Section 9.3.2), and the adjusted dose will be administered starting with the evening dose on Day 15. The subject should then 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.

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) and administered orally q12h with an age-appropriate fat-containing meal or snack from the evening dose on Day 15 through Week 24. Aside from doses administered during scheduled clinic visits, doses from the evening dose on Day 15 through Week 24 will be administered q12h at home. Details of dose preparation and dose administration will be provided in the study manual.

At the Part A/B Cohort 8 Week 4, 8, 12, 18, and 24 Visits, the dose administration dates and times, occurrence and time of regurgitation within 1 hour after dosing, and whether doses were administered with food/liquid will be recorded for the 2 doses of study drug administered immediately 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.

When possible, subjects should take the dose of ivacaftor at the same time each day. If the caregiver of the subject forgets to administer a dose and remembers within 0 to 6 hours (before the halfway point of the dosing interval), the subject should be given the dose at that time and resume their normal schedule for the following dose. If caregiver of the subject forgets to give a dose and remembers within 6 to 12 hours after the missed dose, they should skip that dose and resume their normal schedule for the following dose.

11.3 Method of Assigning Subjects to Treatment Groups

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

11.4 Dose Modification for Toxicity

The investigator may interrupt study drug dosing if medically necessary. If study drug dosing must be interrupted for more than 72 hours, the Vertex medical monitor must be notified. In these instances, study drug dosing may only resume after approval by the Vertex medical monitor. Specific instructions for interruption for elevated LFT levels are provided in Section 12.6.2.

11.5 Packaging and Labeling

Ivacaftor granules in a foil-laminated sachet/packet will be supplied by Vertex in kits. Study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing for ivacaftor will be included in the pharmacy manual.

11.6 Study Drug Supply, Storage, and Handling

The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for as described in Section 11.7. Study drug must be stored at temperatures of ≤25°C (77°F) with excursions to 30°C (86°F). Additional storage and handling conditions will be provided in the pharmacy manual.

11.7 Drug Accountability

The pharmacist or designated study site staff will maintain information regarding the dates and amounts of (1) study drug received, (2) study drug dispensed to the subjects, and (3) study drug returned by the subjects' parent or legal guardian. Subjects' parent or legal guardian will be instructed to return all used and unused materials associated with the study drug to the site. These materials will be retained at the site according to instructions provided by Vertex or its designee until inventoried by the study monitor. The study monitor will review study drug records and inventory throughout the study.

11.8 Disposal, Return, or Retention of Unused Drug

The study site staff or pharmacy personnel will retain all materials returned by the subjects' parent or legal guardian until the study monitor has performed drug accountability. At the end of the study, the study monitor will provide instructions as to the disposition of any unused investigational product. If the study monitor authorizes destruction at the study site, the investigator will ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Vertex. Destruction will be adequately documented.

11.9 Compliance

Study drug accountability should be assessed at each visit by counting returned dosage units (sachets/packets).

If there is continued non-compliance with study requirements, restrictions, instructions, and study drug dosing despite educational efforts, the investigator should contact the Vertex medical monitor to discuss noncompliance and discontinuation of the subject from the study.

11.10 Blinding and Unblinding

This will be an open-label study.

12 ASSESSMENTS

12.1 Timing of Assessments

The timing of assessments is shown in:

- Table 3-1 for Part A (Screening, Treatment, ETT, and Follow-up Periods)
- Table 3-2 for Part B (Screening and Treatment Periods)
- Table 3-3 for Part B (ETT Visit and Follow-up Periods)
- Table 16-1 for Part A/B Cohort 8 (Screening, Treatment, ETT, and Follow-up Periods)

12.2 Subject and Disease Characteristics

Subject and disease characteristics include demographics and medical history. In addition, the following historical data will be collected for each Part B and Part A/B Cohort 8 subject from birth to screening: age at CF diagnosis, [redacted] pulmonary exacerbations, LFTs, and CF-related medications-of-interest. The following historical data from birth to screening will also be collected:

- Maternal/pregnancy history: complications in pregnancy, gestational age at delivery, method of delivery
- Quarterly (approximately every 12 weeks) [redacted]
- The dates and reasons for all [redacted]
- Any use (yes or no) of the following medications will be assessed: inhaled tobramycin, inhaled aztreonam, inhaled colimycin, inhaled hypertonic saline, dornase alfa, ibuprofen, azithromycin, and pancreatic enzyme replacement therapy.
- Historical pancreatic status measurements

12.3 Pharmacokinetics

12.3.1 Blood Sampling

At visits indicated in Part A Table 3-1, Part B Table 3-2 and Table 3-3, and Part A/B Cohort 8 Table 16-1, blood samples will be collected for the determination of the concentrations of ivacaftor and metabolites M1 and M6 in plasma. Approximately 0.25 mL of blood will be collected at each PK time point.

PK blood sampling time points are relative to the morning dose of study drug. The sampling schedule is as follows:

Part A

- Day 4: before the morning dose; between 2 and 4 hours and between 6 and 8 hours after the Day 4 morning dose
- Day 5: between 24 and 60 hours after the Day 4 morning dose.
- For subjects who prematurely discontinue treatment, a PK blood sample will be collected at the ETT Visit.
- The administration dates and times and their timing with respect to food intake of all study drug doses administered outside the clinic should be recorded in each subject's dosing diary.

Part B

- 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.
- The dose administration dates and times, 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.

Part A/B Cohort 8

- Day 4: before the morning dose; between 2 to 4 hours and between 6 to 8 hours after the Day 4 morning dose
- Day 15: before the morning dose
- Weeks 4, 12, 18 and 24: before the morning dose
- Week 8: before the morning dose; between 2 to 4 hours and between 6 to 8 hours after the Week 8 morning dose
- For subjects who prematurely discontinue treatment, a PK blood sample will be collected at the ETT Visit only if within 3 days of last dose of study drug.
- The dose administration dates and times, occurrence and time of regurgitation within 1 hour after dosing, and whether doses were administered with food/liquid will be recorded for the 2 doses of study drug administered immediately prior to each PK clinic visit in each subject's dosing diary.

The total anticipated blood volume collected at each study visit is presented in Table 12-1. Cumulatively, each subject is expected to have 27.0 mL of blood collected over the course of the study (from Screening to Week 24), excluding the ETT. The total blood volume collected at any single study visit is not expected to exceed about 1% of a subject's estimated total blood volume (based on body weight) and the total blood volume collected over the course of any 4 weeks is not expected to exceed about 3% of a subject's estimated blood volume. Total blood volume was estimated based on the expectation of total volume being at least 80 mL blood/kg body weight (240 mL at Day 1 for a subject weighing 3 kg).[93]

Table 12-1 Expected Blood Volumes to be Collected at Each Study Visit

Study Visit	Assessments Requiring Blood Collection	Total Blood Volume (mL)
Screening (Day -28 to -14)	Serum chemistry, Hematology	2.3
Day 1	Serum chemistry, IRT	2.2
Day 4	Serum chemistry, PK[a]	2.6
Day 15	Serum chemistry, Hematology, PK[a]	2.8
Week 4	Serum chemistry, Hematology, PK[a]	2.8
Week 8	Serum chemistry, PK[a]	2.6
Weeks 12, 18, and 24	Serum chemistry, Hematology, PK[a], IRT	3 × 3.9 = 11.7
ETT	Serum chemistry, Hematology, PK[b]	2.8

ETT: Early Termination of Treatment; IRT: immunoreactive trypsin and/or trypsinogen; PK: pharmacokinetic

[a] 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 Week 8. PK samples will be collected before the morning dose on Day 15, and on Weeks 4, 12, 18, and 24.

[b] PK sample will be collected only if within 3 days of last dose of study drug.

The acceptable windows for the PK sampling time points are listed in Table 12-2. Samples collected outside these acceptable windows will be considered protocol deviations. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing.

Table 12-2 Acceptable Pharmacokinetic Sampling Windows

Study Part	Nominal Sampling Times	Acceptable Window
Part A	ETT Visit	at the time of the ETT Visit
	Day 4: 0 (before morning dose)	within 60 minutes before dosing
	Day 4: between 2 and 4 hours after the Day 4 morning dose	within the time window of 2 to 4 hours after the Day 4 morning dose
	Day 4: between 6 and 8 hours after the Day 4 morning dose	within the time window of 6 to 8 hours after the Day 4 morning dose
	Day 5: 24 and 60 hours after the Day 4 morning dose	within the time window of 24 to 60 hours after the Day 4 morning dose
Part B	ETT Visit	at the time of the ETT Visit
	Week 2: 0 (before morning dose)	within 60 minutes before dosing
	Week 2: between 2 and 4 hours after the morning dose	within the time window of 2 and 4 hours after the morning dose
	Week 2: between 6 and 8 hours after the morning dose	within the time window of 6 and 8 hours after the morning dose
	Week 8: 0 (before morning dose)	within 60 minutes before dosing
	Week 8: 1 and 4 hours after the morning dose	± 15 minutes
	Week 24: 0 (before morning dose)	within 60 minutes before dosing
	Week 24: between 2 and 4 hours after the morning dose	within the time window of 2 to 4 hours after the morning dose
Part A/B Cohort 8	ETT Visit[a]	at the time of the ETT Visit
	Day 4: 0 (before morning dose)	within 60 minutes before dosing
	Day 4: between 2 and 4 hours after the Day 4 morning dose	within the time window of 2 to 4 hours after the Day 4 morning dose
	Day 4: between 6 and 8 hours after the Day 4 morning dose	within the time window of 6 to 8 hours after the Day 4 morning dose
	Day 15, Weeks 4, 12, 18, and 24: 0 (before morning dose)	within 60 minutes before dosing
	Week 8: 0 (before morning dose)	within 60 minutes before dosing
	Week 8: between 2 and 4 hours after the Week 8 morning dose	within the time window of 2 to 4 hours after the Week 8 morning dose
	Week 8: between 6 and 8 hours after the Week 8 morning dose	within the time window of 6 to 8 hours after the Week 8 morning dose

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

12.3.2 Processing and Handling of Pharmacokinetic Samples

Detailed procedures for the collection of blood samples and further procedures for processing and handling of samples for PK analysis will be provided in the Sample Handling Guideline. The shipment address and assay laboratory contact information will be provided to the investigational site before initiation of the study.

12.3.3 Bioanalysis

Samples will be analyzed using a validated analytical method in compliance with Vertex or designee standard operating procedures. A description of the assay and validation data will be provided in separate reports.

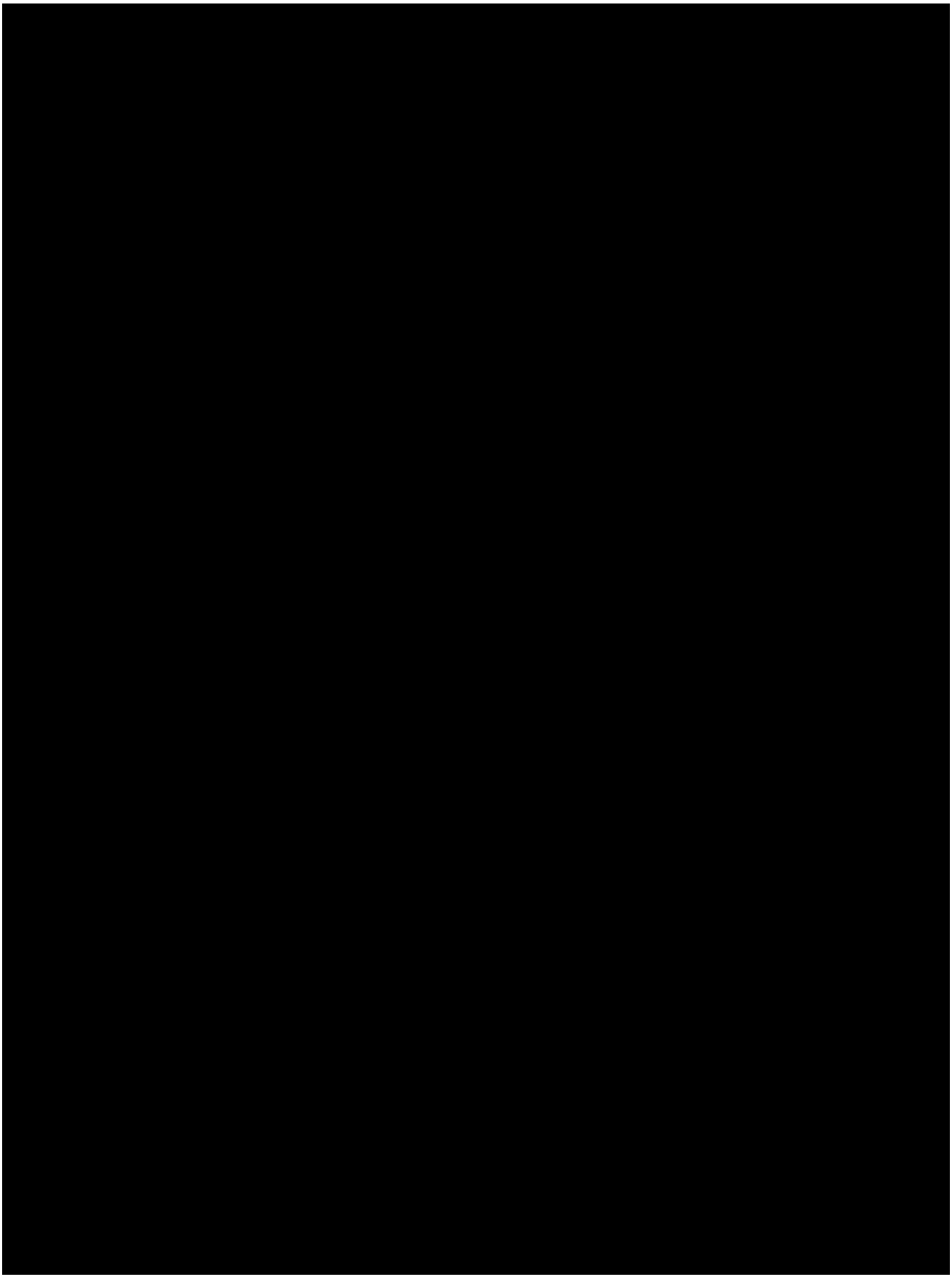
12.4 Pharmacodynamics

12.4.1 Sweat Chloride

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 collection will be completed at visits as indicated in Part A Table 3-1, Part B Table 3-2, and Part A/B Cohort 8 Table 16-1. In Part B and in Part A/B Cohort 8, the sweat chloride test at the Day 1 Visit must be performed before the morning dose. At subsequent visits, the sweat chloride test must be performed within a window of ± 2 hours relative to the morning dose of the study drug. Change from baseline in sweat chloride will be analyzed as a secondary endpoint of Part B and Part A/B Cohort 8 in this study.

[redacted]



12.6 Safety

Safety evaluations will include adverse events, clinical laboratory assessments (serum chemistry and hematology), vital signs, ECGs, physical examinations (with clinically significant abnormalities recorded as medical history or adverse events), and OEs.

12.6.1 Adverse Events

All adverse events will be assessed, documented, and reported in accordance with ICH GCP guidelines. Section 14.1 outlines the definitions, collection periods, criteria, and procedures for documenting, grading, and reporting adverse events. A separate document that details adverse event case report form (CRF) completion guidelines for investigators as well as training will be provided.

12.6.2 Clinical Laboratory Assessments

Blood samples will be collected at times specified in Part A Table 3-1, Part B Table 3-2 and Table 3-3, and Part A/B Cohort 8 Table 16-1. If, under exceptional circumstances, these blood samples must be drawn and/or analyzed at a local laboratory, approval must be first obtained

from the Vertex medical monitor. All blood samples will be collected while subjects are in a seated or supine position. Specific instructions for the collection, processing, and shipment of samples will be provided in a separate Laboratory Manual. Laboratory test results that are abnormal and considered clinically significant must be reported as adverse events (see Section 14.1).

The safety laboratory test panels are shown in Table 12-3:

Table 12-3 Safety Laboratory Test Panels

Serum Chemistry	Hematology
Glucose	Hemoglobin
Blood urea nitrogen	Hematocrit
Creatinine	Red blood cell count
Sodium	Platelet count
Potassium	White blood cell count
Calcium	Differential (absolute and percent):
Phosphate	Eosinophils
Bilirubin, direct bilirubin	Basophils
Alkaline phosphatase	Neutrophils
Aspartate transaminase (=SGOT)	Lymphocytes
Alanine transaminase (=SGPT)	Monocytes
Lactate dehydrogenase	
Gamma-glutamyl transferase	
Protein	
Albumin	
Amylase	
Lipase	

***CFTR* Genotype**:

Subjects must have a *CFTR* ivacaftor-responsive mutation on at least 1 allele to meet inclusion criteria (see Appendix A: CFTR Mutations Included in the Study). For all Parts, the genotype results must be available before the first dose of study drug. Subjects who had *CFTR* genotyping completed in Part A of the study will not require repeat testing upon entry into Part B.

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, including an assessment whether the genotyping meets applicable standards.

For Parts A and B, 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 at screening and the results must be reviewed before the first dose of study drug.

Subjects will not receive the study drug if *CFTR* genotype is not confirmed by either an approved historic genotype and approval of Vertex medical monitor result OR by genotype testing at screening.

For Part A/B Cohort 8, subjects must have documented genotype test results reviewed and approved by the Vertex medical monitor prior to Day 1. Genotype testing is expected to be initiated prior to screening and results must be available prior to Day 1.

Instruction for collecting a sample for *CFTR* genotyping will be included in the Laboratory Manual.

Elevation of LFT Parameters:

Subjects with new treatment-emergent ALT or AST elevations of >3 × ULN must be followed closely, including repeat confirmatory testing performed by the central laboratory within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT and AST levels, as clinically indicated. In addition, if ALT or AST are >5 × ULN, repeat follow-up levels must be obtained within 7 ± 2 days and followed up 7 days later. All reasonable efforts should be made to repeat confirmatory analysis by the central laboratory. If, under exceptional circumstances, these blood samples must be drawn and/or analyzed at a local laboratory, approval must be first obtained from the Vertex medical monitor. Elevations in LFTs measured by the local laboratory must be reported immediately to the Vertex medical monitor, and the subject must have the tests repeated and sent to the central laboratory as soon as possible (ideally within 48 to 72 hours).

LFT Elevations Leading to Study Drug Interruption:

Study drug administration must be interrupted immediately, and the Vertex medical monitor must be notified if any of the following criteria is met:

- ALT or AST >8 × ULN, or
- ALT or AST >5 × ULN for 2 weeks or more, or
- ALT or AST >3 × ULN in association with elevation of bilirubin >2 × ULN and/or clinical jaundice

Repeat testing should be performed within 48 to 72 hours to confirm the initial elevation.

A thorough investigation of potential causes should be conducted, and the subject should be followed closely for clinical progression.

If no convincing alternative etiology (e.g., concurrent infections) for the elevated transaminases is identified, regardless of whether ALT or AST levels have improved, the subject must be discontinued from the study in consultation with the Vertex medical monitor (Section 10.4). Subjects in whom treatment is discontinued for elevated transaminases should have their transaminases monitored closely until levels normalize or return to baseline.

If a convincing alternative cause of transaminase elevation has been identified, study drug may be resumed once transaminases return to ≤2 × ULN. Approval of the Vertex medical monitor is required before resumption of study drug. Upon resumption of study drug, transaminases should be assessed weekly for 4 weeks. If a protocol-defined transaminase elevation occurs within 4 weeks of rechallenge with the study drug (with confirmation of the initial elevation by repeat testing within 48 to 72 hours), then the study drug must be permanently discontinued, regardless of the presumed etiology.

Additional Evaluations:

Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required. Any changes to the scheduled times of clinical laboratory determination will be agreed between the investigator and Vertex and documented in the study master files.

12.6.3 Physical Examinations and Vital Signs

A physical examination of all body systems and vital signs assessment will be performed at screening and select study visits as shown in Part A Table 3-1, Part B Table 3-2 and Table 3-3, and Part A/B Cohort 8 Table 16-1. At other visits, symptom-directed physical examinations and symptom-directed vital signs assessments can be performed at the discretion of the investigator or healthcare provider.

A physical examination includes a review of the following systems: head/neck/thyroid; eyes/ears/nose/throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. After screening, any clinically significant abnormal findings in physical examinations will be reported as adverse events.

The abbreviated physical examination will include an assessment of the following body systems: head/neck/thyroid, EENT, cardiovascular system, respiratory system, skin, and abdomen.

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.

12.6.4 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout at the time points listed in Part A Table 3-1, Part B Table 3-2 and Table 3-3, and Part A/B Cohort 8 Table 16-1. Additional standard 12-lead ECGs will be performed at any other time if clinically indicated. The performance of all ECGs will adhere to the following guidelines:

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

The ECG traces will be manually read at the study site at the Screening and Follow-up Visits. A printout of the ECG traces will be made for safety review by the investigator and maintained with source documentation. All traces will be centrally evaluated by a qualified pediatric cardiologist. Clinically significant ECG abnormalities occurring during the study through the Follow-up Visit will be recorded as adverse events.

To ensure safety of the subjects, the investigator will make comparisons of the ECG findings to baseline measurements. Repeat ECGs will be performed as deemed appropriate. Subject eligibility to continue in the study will be evaluated.

12.6.5 Ophthalmologic Examinations

Subjects will undergo an OE at the time points in Part A Table 3-1, Part B Table 3-2 and Table 3-3, and Part A/B Cohort 8 Table 16-1. The OE must be conducted by a licensed ophthalmologist, preferably a pediatric ophthalmologist. The OE will include:

- examination of the lens with a slit-lamp (portable or otherwise; pharmacologically-dilated examination). Details of the slit-lamp examination will be documented.
- assessment of the red reflex (pharmacologically-dilated examination)
- Screening OEs only: examination of the fundus (retina, optic nerve, and vessels), pupils, and eye movements

In addition, at screening, relevant medical history will be obtained for all subjects, including the following:

- history of steroid use
- history of trauma to the eye
- any family history of glaucoma, congenital cataracts, or cataracts arising later in life

At screening for all Parts, the subject is not eligible for enrollment if:

- an adequate slit-lamp examination cannot be conducted
- a lens opacity/cataract is identified (excluding those considered congenital and nonprogressive, such as a suture cataract)

During the screening period, if an adequate slit-lamp examination cannot be conducted, the slit-lamp examination may be repeated until an adequate repeat slit-lamp examination is completed (Sections 9.1.1.1 and 9.1.1.3) and eligibility criteria regarding the ophthalmologic findings are met.

For Part A, the Follow-up OE will be performed 8 weeks after the last dose of study drug (Section 9.1.3.1).

During the Part B and Part A/B Cohort 8 treatment periods, if a new lens opacity or cataract is identified at any OE, the Vertex medical monitor must be notified and study drug dosing must be discontinued. If an adequate slit-lamp examination cannot be conducted at any visit where it is required in Part B (Table 3-2) or Part A/B Cohort 8 (Table 16-1), the subject will continue receiving 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 within 4 weeks of the study visit, study drug dosing may be discontinued.

For Part B (Table 3-3) and Part A/B Cohort 8 (Table 16-1), the OE for the ETT Visit will be conducted for all subjects who prematurely discontinue study drug dosing, 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. A Follow-up OE will also be performed (Section 9.1.3.1).

Lastly, all Part B and Part A/B Cohort 8 subjects who do not continue ivacaftor in the open-label treatment arm of the Extension Study will be eligible to enroll in the observational arm of the Extension Study for long-term follow-up OEs.

12.6.6 Contraception and Pregnancy

Not applicable.

13 STATISTICAL AND ANALYTICAL PLANS

Analysis of all data, including safety, efficacy, PK, PD, and exploratory data, will be performed by Vertex (or designee). The results of the study will be reported in the clinical study report (CSR).

Details will be provided in the statistical analysis plan (SAP) for the final analysis, which will be finalized and approved before the clinical database lock. A detailed analysis plan for PK and

PK/PD parameter estimations will be presented in a clinical pharmacology analysis plan (CPAP), which will be finalized and approved before the database lock. As the study design is open-label, a draft SAP for the final analysis will be available before the first subject is dosed.

13.1 Sample Size and Power

The sample size of a minimum of 15 subjects in Part A, 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) (see Section 9.3.2)
- Subjects who have an ivacaftor-responsive mutation on at least 1 allele (see Appendix A) 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[29, 30, 95]. If it is assumed that 61% of these cases are detected by newborn screening [29, 30, 95] and 5% carry a gating mutation[22, 95] 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 × 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 4 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.[96, 97] The inclusion of data from pediatric patients ≥24 months of age with the population PK approach is expected to reduce the required sample size.[97]

Given the above feasibility assessment and PK considerations, a minimum of 15 subjects in Part A, 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.

13.2 Part A Analyses

A preliminary PK analysis will take place after all samples have been collected and bioanalysis is complete for each cohort in Part A. The available data will be used to confirm dose(s) for use in Part B.

13.2.1 Analysis Set

Safety Set: The Safety Set for Part A includes all subjects who received at least 1 dose of study drug (i.e., ivacaftor). The dose assignment for the Safety Set will be as treated.

13.3 Part B Analyses

The analyses of safety and efficacy will be based on the 24-week data.

13.3.1 Analysis Sets

The Safety Set for Part B is defined as subjects who received at least 1 dose of study drug (i.e., ivacaftor). The Safety Set is to be used for all safety summaries. The dose assignment for the Safety Set will be as treated.

Full Analysis Set (FAS): The FAS for Part B includes all subjects who are enrolled and receive at least 1 dose of study drug (i.e., ivacaftor).

13.4 Part A/B Cohort 8 Analyses

The analyses of safety and efficacy will be based on the 24-week data.

13.4.1 Analysis Sets

The Safety Set for Part A/B Cohort 8 is defined as subjects who received at least 1 dose of study drug (i.e., ivacaftor). The Safety Set is to be used for all safety summaries. The dose assignment for the Safety Set will be as treated.

The FAS for Part A/B Cohort 8 includes all subjects who are enrolled and receive at least 1 dose of study drug (i.e., ivacaftor).

13.5 Statistical Analysis

Safety analyses for Part A, Part B, and Part A/B Cohort 8 will be conducted separately. Efficacy and PD analyses are applicable to Parts B and Part A/B Cohort 8 only~~,~~ and Part A/B Cohort 8 will be analyzed separately from other cohorts. Parts B and A/B Cohort 8 may also be pooled for analyses of safety, PD, and efficacy endpoints common to both parts.

13.5.1 General Considerations

All individual subject data, including derived variables, will be presented in the data listings, which will include data for all subjects included in the study from all of the analysis sets. All analyses will be performed using SAS® (SAS Institute, Cary, North Carolina, USA).

Continuous data will be summarized by means of descriptive statistics (number of subjects [n], mean, standard deviation [SD], standard error [SE], median, minimum value [min], maximum value [max], and 95% confidence intervals [CI], as appropriate).

Categorical data will be summarized by contingency tables (n, percentage, and 95% CI).

Additionally, all subject data, including derived variables, will be presented in subject data listings; listings will display all subjects who were enrolled or dosed.

For safety analyses, only descriptive analyses will be carried out (i.e., no statistical hypothesis testing will be performed).

Annualized event rates will be normalized to annualized event rates for the final analysis; however, in the event of data being used for a regulatory submission, event rates will be normalized to a 24-week period.

Definition of the baseline value: The baseline value will be defined separately for Parts A, B, and A/B Cohort 8 as the most recent non-missing measurement collected before the initial administration of study drug in the respective study part. Note that this definition applies to both scheduled and unscheduled measurements; if an unscheduled value is the most recent non-missing measurement, it will be taken as baseline. The absolute change from baseline value will be defined as postbaseline value minus baseline value. The definitions will apply to all analysis variables: demographics, background, baseline characteristics, safety, and efficacy (Part B and Part A/B Cohort 8), unless otherwise specified.

13.5.2 Background Characteristics

13.5.2.1 Subject Disposition

Number and percentage of subjects in the following categories will be summarized as appropriate:

- Enrolled
- Enrolled and dosed (Safety Set)
- Last Treatment Period Visit Completed (Day 1, Day 2, Day 3, Day 4, and Day 5 in Part A; Day 1, Week 2, Week 4, Week 8, Week 12, Week 18, and Week 24 in Part B; and Day 1, Day 4, Day 15, Week 4, Week 8, Week 12, Week 18, and Week 24 in Part A/B Cohort 8).

- Prematurely discontinued the study drug treatment during the Treatment Period and the reasons for discontinuation

The disposition summary will be based on all subjects and will be provided for the interim and final analysis.

13.5.2.2 Demographics and Baseline Characteristics

Demographic, background (e.g., medical history), and baseline characteristics will be summarized. Protocol deviations/violations will be provided as a subject data listing only. No statistical tests will be carried out to evaluate any baseline imbalance between dose groups.

13.5.2.3 Prior and Concomitant Medications

All 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 summarized by preferred name in frequency tables in 2 parts:

- **Prior medication**: any medication that started before the first dose of study drug, regardless of when it ended.
- **Concomitant medication**: medication received at or after dosing of study drug, or medication that was received before dosing with study drug and continued after dosing of study drug.

If medication start date is at or after date of first dosing of study drug, then 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 first dosing of study drug, then the medication will be summarized as prior medication regardless of whether the medication start date is missing or not. Note that medication that started before first dosing of study drug and continued after dosing will be summarized as prior medication and separately as concomitant medication.

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

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 Part B and Part A/B Cohort 8.

If the data contain missing or partial medication start and stop dates which do not allow definitive classification as either prior medication, concomitant medication, or both, a conservative rule will be implemented and will be provided in the SAP.

13.5.2.4 Study Drug Exposure and Compliance

Exposure to study drug (i.e., duration of treatment) will be summarized for the Safety Set in terms of duration of treatment a subject received (in days).

Dosing compliance will be summarized for the Safety Set, and is calculated as the actual number of dosing occasions at which study drug was administered, as a percentage of the planned number of dosing occasions.

Duration of treatment and dosing compliance will be summarized by means of descriptive summary statistics.

13.5.3 Efficacy Analysis (Part B)

Statistical methodology will be restricted to descriptive statistics only. All efficacy analyses will be based on the FAS.

13.5.3.1 Analysis of Primary Variables

Not applicable.

13.5.3.2 Analysis of Secondary Efficacy Variables

13.5.3.2.1 Change from Baseline in Sweat Chloride

Sweat chloride results (including changes from baseline) will be analyzed as a continuous variable using descriptive summary statistics and presented by visit and treatment (dose level). In addition, data summaries excluding subjects who have an *R117H-CFTR* mutation will be carried out separately.

[redacted]

13.5.4 Efficacy Analysis (Part A/B Cohort 8)

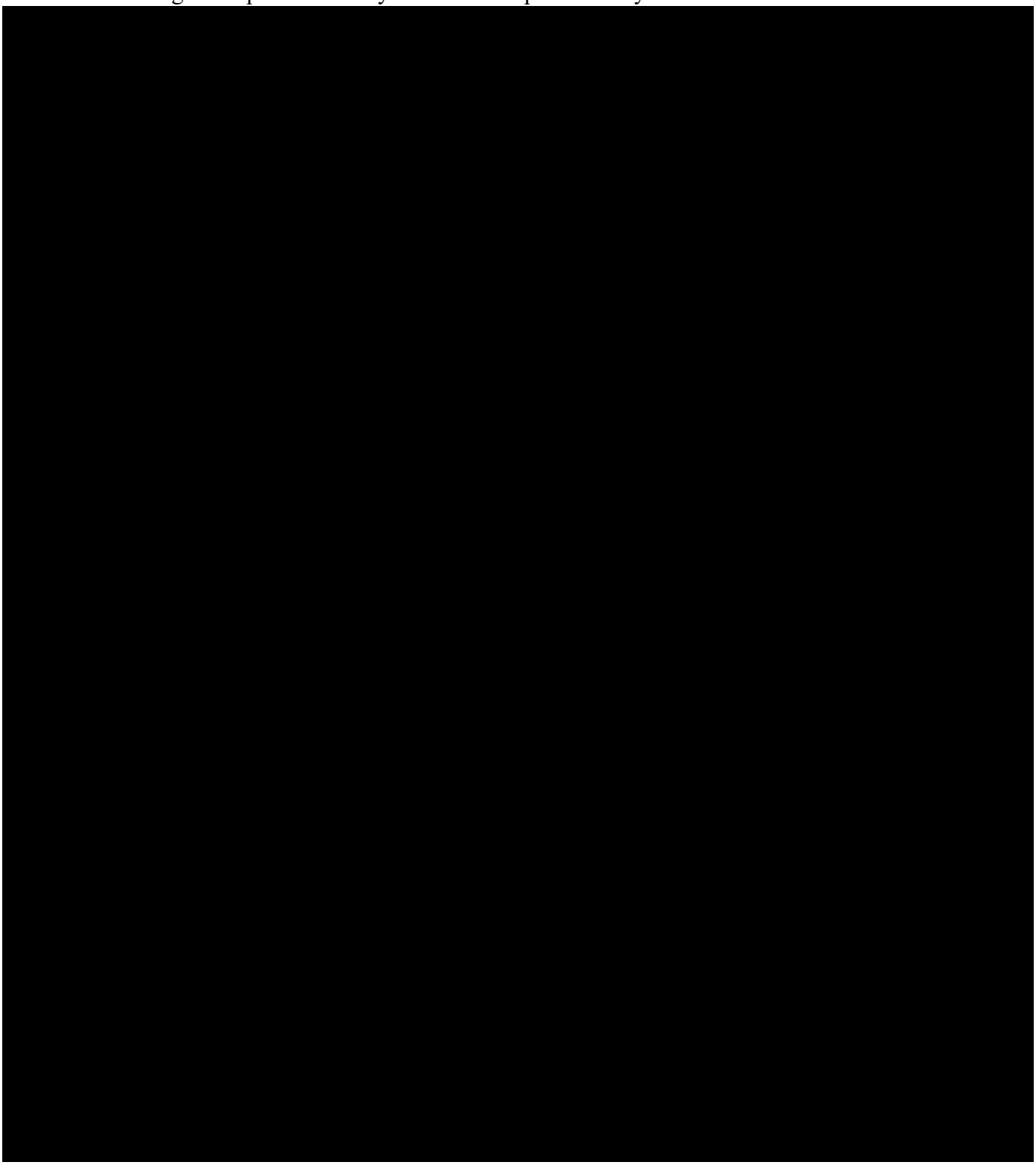
13.5.4.1 Analysis of Primary Variables

Not applicable.

13.5.4.2 Analysis of Secondary Efficacy Variables

13.5.4.2.1 Change from Baseline in Sweat Chloride

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



[redacted]

13.5.5 Safety Analysis

Evaluating safety is the primary objective of this study. The overall safety profile of ivacaftor will be assessed in terms of the following:

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory results (serum chemistry and hematology)
- Standard 12-lead ECG outcomes
- Vital signs
- Physical examinations
- OEs

TEAEs are the key safety assessment. Descriptive analysis of safety will be performed; raw values, changes from baseline, shifts-from-baseline, and clinical abnormalities will be summarized, where applicable.

All safety analyses will be based on the Safety Set.

13.5.5.1 Adverse Events

TEAEs, defined as adverse events with start date or increased severity on or after the first dose of study drug through the end of participation (as applicable), will be summarized by treatment (dose level). TEAEs will hereafter be referred to as adverse events. Adverse event summary tables will include the following analyses presented by treatment (dose level):

- All adverse events
- Related (defined as possibly related or related) adverse events
- Adverse events leading to treatment discontinuation
- SAEs
- Adverse events by severity
- Adverse events by relationship

Summaries will be presented by MedDRA system organ class and preferred term using frequency counts and percentages. A subject with multiple occurrences of the same adverse event or a continuing adverse event will be counted only once, with the highest severity or relationship.

For Part A/B safety results will be summarized by visit only and not by treatment (dose level).

In addition, a table containing individual subject adverse event data for all deaths and other serious and significant adverse events will be provided.

13.5.5.2 Clinical Laboratory Assessments

All statistical analyses of laboratory values will be performed using SI units. Continuous serum chemistry and hematology results will be summarized at each visit and presented by treatment (dose level). For Part A/B safety results will be summarized by visit only and not by treatment (dose level). Changes from baseline will also be summarized. The number and percentage of subjects with shift changes from baseline based on the laboratory normal ranges will be tabulated.

In addition, a listing containing individual subject serum chemistry and hematology values outside the reference ranges will be provided. These listings will include data from scheduled and unscheduled time points.

Clinically significant abnormal findings will be reported as adverse events.

13.5.5.3 Electrocardiogram

Continuous ECG measurements will be summarized by visit and treatment (dose level). For Part A/B safety results will be summarized by visit only and not by treatment (dose level). Changes from baseline will also be summarized. In addition, the number and percentage of subjects by maximum and minimum on-treatment value and by maximum and minimum on-treatment increase from baseline in QT/QTc intervals will be presented. A shift table for ECG complexes analyzed and a listing of abnormal ECG complexes from the ambulatory recordings will also be presented.

13.5.5.4 Vital Signs

The following vital signs will be summarized by visit and treatment (dose level): systolic and diastolic blood pressure (mmHg), temperature (°C), pulse oximetry (%), heart rate (beats per minute), and respiration rate (breaths per minute). For Part A/B safety results will be summarized by visit only and not by treatment (dose level). Changes from baseline will also be summarized.

Clinically significant findings in vital signs will be reported as adverse events.

13.5.5.5 Physical Examination

Physical examination results will be presented in individual subject data listings only. Clinically relevant results identified after screening will be reported as adverse events.

13.5.5.6 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 treatment (dose level). For Part A/B safety results will be summarized by visit only and not by treatment (dose level).

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

[redacted]

13.5.6 Interim and IDMC Analyses

13.5.6.1 Interim Analysis

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

- a sufficient number of subjects in Cohort 5 have completed their Week 12 Visit
- a sufficient number of subjects in Cohort 5 have completed their Week 24 Visit

Additional interim analyses for regulatory, safety, or operational purposes may also be performed.

13.5.6.2 IDMC Analysis

See Section 9.2.

13.6 Clinical Pharmacology Analysis

13.6.1 Pharmacokinetic Analysis (Part A and Part B)

Nonlinear mixed effects modeling will be applied for the PK analysis of ivacaftor for comparison of ivacaftor disposition to that of adults. The primary exposure estimates of interest are ivacaftor AUC and C_{min}. Exposure of metabolites M1 and M6 will be described by descriptive statistics.

Preliminary analyses will be performed on the PK data obtained from a minimum of 5 subjects from each cohort in Part A. The PK analysis, along with safety data from Part A, will be used to appropriately confirm the dose selection for Part B (or adjust the doses if necessary) based on criteria that take into account both the C_{min} and AUC relative to historical results in adult CF subjects. At least 4 samples per subject are needed. If PK data from a completed cohort in Part A are insufficient to confirm the appropriate dose for that age group, additional subjects may be enrolled in Part A until a dose can be confirmed. PK parameters other than C_{min} and AUC may be considered if deemed appropriate.

A detailed plan of the quantitative methods used to derive PK parameter estimations for Parts A and B will be presented in the CPAP.

13.6.2 Pharmacokinetic Analysis (Part A/B Cohort 8)

The primary exposure estimates of interest are the AUC and C_{min} of ivacaftor and its metabolites (M1 and M6). These exposures will be described by descriptive statistics. Preliminary analyses will be performed on Day 4 PK data obtained from individual subjects in Part A/B Cohort 8 to assist in the Day 15 dose adjustment. Details of this dose adjustment are further described in Report P292.

A detailed plan of the noncompartmental analyses used to derive PK parameter estimations of ivacaftor and its M1 and M6 metabolites for Part A/B Cohort 8 will be presented in the CPAP.

PK analysis of ivacaftor may be performed using nonlinear mixed effects modeling, as data allow.

14 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

14.1 Adverse Event and Serious Adverse Event Documentation, Severity Grading, and Reporting

14.1.1 Adverse Events

14.1.1.1 Definition of an Adverse Event

An adverse event is defined as any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or worsening of a pre-existing condition (e.g., increase in its severity or frequency) after the informed consent form (ICF) is signed.

An adverse event is considered serious if it meets the definition in Section 14.1.2.1.

14.1.1.2 Clinically Significant Assessments

Study assessments including laboratory tests, ECGs, physical examinations, vital signs, and ophthalmologic examinations will be assessed and those deemed to have clinically significant worsening from baseline will be documented as an adverse event. When possible, a clinical diagnosis for the study assessment will be provided, rather than the abnormal test result alone (e.g., urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself will be listed as the adverse event (e.g., bacteria in urine or decreased hemoglobin).

An abnormal study assessment is considered clinically significant if the subject has 1 or more of the following:

- Concomitant signs or symptoms related to the abnormal study assessment
- Further diagnostic testing or medical/surgical intervention
- A change in the dose of study drug or discontinuation from the study

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether the study assessment results are clinically significant will be made by the investigator.

A laboratory value that is Grade 4 will not automatically be an SAE. A Grade 4 laboratory value will be an SAE if the clinical status of the subject indicates a life-threatening adverse event.

14.1.1.3 Documentation of Adverse Events

In each study part, all adverse events will be collected from the time ICF is signed until the following time points:

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)

- For subjects enrolled in Part A: through Day 14, with the exception of ocular adverse events noted during the Follow-up OE in Part A
- For subjects enrolled in Part B who complete the study and enter the treatment arm of the Extension Study: through the Week 24 Visit
- For subjects who enrolled in Part B who complete the study and do not enter the treatment arm of the Extension Study: the Follow-up Visit (if required), with the exception of ocular adverse events noted during the Follow-up OE in Part A
- For subjects who enrolled in Part B who prematurely discontinue from treatment: the ETT or Follow-up Visit (if required)
- For subjects enrolled in Part A/B Cohort 8 who complete the study and enter the treatment arm of the Extension Study: through the Week 24 Visit
- For subjects who enrolled in Part A/B Cohort 8 who complete the study and do not enter the treatment arm of the Extension Study: the Follow-up Visit (if required), with the exception of ocular adverse events noted during the Follow-up OE
- For subjects who enrolled in Part A/B Cohort 8 who prematurely discontinue from treatment: the ETT or Follow-up Visit (if required)

Ocular adverse events will continue to be collected as follows:

- In Part A, from the Follow-up Telephone Call (Day 14) through the Follow-up OE (8 weeks after the last dose of study drug)
- In Part B, from the Follow-up Visit (4 weeks after the last dose of study drug) through the Follow-up OE (24 weeks after the last dose of study drug)
- In Part A/B Cohort 8, from the Follow-up Visit (4 weeks after the last dose of study drug) through the Follow-up OE (12 weeks after the last dose of study drug)

All subjects' parents or legal guardians will be queried, using non-leading questions, about the occurrence of adverse events at each study visit. When possible, a constellation of signs and/or symptoms will be identified as 1 overall event or diagnosis. All adverse events for enrolled subjects will be recorded in the CRF and source document. Adverse events for subjects who are screened but not subsequently enrolled in the study will be recorded only in the subject's source documents. The following data will be documented for each adverse event:

- Description of the event
- Classification of “serious” or “nonserious”
- Date of first occurrence and date of resolution (if applicable)
- Severity
- Causal relationship to study drug
- Action taken
- Outcome
- Concomitant medication or other treatment given

For the purposes of study analysis, if the adverse event has not resolved at the end of the study reporting period (the Follow-up Visit), it will be documented as ongoing. For subjects who enroll in the Extension Study, adverse events that are ongoing at the time of the last visit in Study 124 will be monitored in the Extension Study. For purposes of safety monitoring, the investigator is required to follow the adverse event to symptom resolution or until the condition stabilizes.

14.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious adverse events.

The guidance available at the following website will be consulted: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007, Center for Biologics Evaluation and Research, http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775.htm (accessed September 2019). When considering the severity of an AE in a pediatric subject, the investigator will consider that reference ranges for pediatric clinical laboratory parameters may differ from those in the vaccine scale. The severity of an adverse event that does not appear in this scale will be determined according to the definitions in Table 14-1.

Table 14-1 Grading of Adverse Event Severity

Classification	Definition
Grade 1 (Mild)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 (Moderate)	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4 (Life-threatening)	Life-threatening consequences; urgent intervention indicated
Grade 5 (Death)	Death related to adverse event

14.1.1.5 Adverse Event Causality

Every effort will be made by the investigator to assess the relationship of the adverse event, if any, to the study drug. Causality will be classified using the categories presented in Table 14-2.

Table 14-2 Classifications for Adverse Event Causality

Classification	Definition
Related	There is an association between the event and the administration of investigational study drug, a plausible mechanism for the event to be related to the investigational study drug and causes other than the investigational study drug have been ruled out, and/or the event reappeared on re-exposure to the investigational study drug.
Possibly related	There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.

Table 14-2 Classifications for Adverse Event Causality

Classification	Definition
Unlikely related	The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.
Not related	The event is related to an etiology other than the investigational study drug (the alternative etiology will be documented in the study subject's medical record).

14.1.1.6 Study Drug Action Taken

The investigator will classify the study drug action taken with regard to the adverse event. The action taken will be classified according to the categories shown in Table 14-3.

Table 14-3 Classifications for Study Drug Action Taken With Regard to an Adverse Event

Classification	Definition
Dose not changed	Study drug dose not changed in response to an adverse event
Dose reduced	Study drug dose reduced in response to an adverse event
Drug interrupted	Study drug administration interrupted in response to an adverse event
Drug withdrawn	Study drug administration permanently discontinued in response to an adverse event
Not applicable	Action taken regarding study drug administration does not apply. "Not applicable" will be used in circumstances such as when the investigational treatment had been completed before the adverse event began and no opportunity to decide whether to continue, interrupt, or withdraw treatment is possible.

14.1.1.7 Adverse Event Outcome

An adverse event will be followed until the investigator has determined and provided the final outcome. The outcome will be classified according to the categories shown in Table 14-4.

Table 14-4 Classifications for Outcome of an Adverse Event

Classification	Definition
Recovered/Resolved	Resolution of an adverse event with no residual signs or symptoms
Recovered/Resolved With Sequelae	Resolution of an adverse event with residual signs or symptoms
Not Recovered/Not Resolved (Continuing)	Either incomplete improvement or no improvement of an adverse event, such that it remains ongoing
Fatal	Outcome of an adverse event is death. "Fatal" will be used when death is at least possibly related to the adverse event.
Unknown	Outcome of an adverse event is not known (e.g., a subject lost to follow-up)

14.1.1.8 Treatment Given

The investigator ensures adequate medical care is provided to subjects for any adverse event, including clinically significant laboratory values related to study drug. In addition, the

investigator will describe whether any treatment was given for the adverse event. “Yes” is used if any treatment was given in response to an adverse event, and may include treatments such as other medications, hospitalization, surgery, or physical therapy. “No” indicates the absence of any kind of treatment for an adverse event.

14.1.2 Serious Adverse Events

14.1.2.1 Definition of a Serious Adverse Event

An SAE is any adverse event that meets any of the following outcomes:

- Fatal (death, regardless of cause, that occurs during participation in the study or occurs after participation in the study and is suspected of being a delayed toxicity due to administration of the study drug)
- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- Congenital anomaly or birth defect
- Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., an allergic bronchospasm requiring intensive treatment in an emergency room or at home)

If a subject has a hospitalization or procedure (e.g., surgery) for an event or condition that occurred before the subject’s parent or legal guardian signed the ICF, and the hospitalization or procedure was planned before the subject’s parent or legal guardian signed the ICF, the hospitalization or procedure should not be considered to indicate an SAE, unless an adverse event caused the hospitalization or procedure to be rescheduled sooner or to be prolonged relative to what was planned. In addition, hospitalizations clearly not associated with an adverse event (e.g., social hospitalization for purposes of respite care) should not be considered to indicate an SAE.

Clarification will be made between the terms “serious” and "severe," because they are not synonymous. The term “severe” is often used to describe the intensity (severity) of a specific event, as in mild, moderate, or severe myocardial infarction. The event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as “serious,” which is based on subject/event outcome or action described above, and is usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining expedited regulatory reporting obligations.

14.1.2.2 Reporting and Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent through the Follow-up Visit or ETT Visit (if Follow-up Visit is not required; see Section 9.1.3), regardless of causality, will be reported by the investigator to Vertex Global Patient Safety (GPS) **within 24 hours of identification**. In

addition, all SAEs that occur after the study has concluded and are considered related to study drug will be reported to Vertex GPS **within 24 hours of identification**.

For SAEs that occur after obtaining informed consent and assent (where applicable) through the Safety Follow-up Visit, the SAE Form will be completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (preferred choice)

Fax: [redacted]

For technical issues related to submitting the form, contact telephone: [redacted]

SAEs that occur after the Safety Follow-up Visit and are considered related to study drug(s) will be recorded on the Vertex Clinical Trial Safety Information Collection Form (hereafter referred to as the "SAE Form") using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the investigator for relationship to the investigational study drug and possible etiologies. On the SAE Form, relationship to study drug will be assessed only as related (includes possibly related) or not related (includes unlikely related), and severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the event to resolution and report to Vertex the outcome of the event using the SAE Form.

14.1.2.3 Expedited Reporting and Investigator Safety Letters

Vertex, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug to all regulatory authorities and participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable. In addition, Vertex, or authorized designee, will be responsible for the submission of safety letters to central independent ethics committees (IECs).

It is the responsibility of the investigator or designee to promptly notify the local IRB/local IEC of all unexpected serious adverse drug reactions involving risk to human subjects.

14.2 Administrative Requirements

14.2.1 Product Complaints

A product complaint is defined as any verbal or written communication addressed to Vertex, or designee, of inquiry or dissatisfaction with the identity, strength, quality, or purity of a released drug product, IMP, or medical device. In addition, suspected counterfeit/falsified product is considered a product complaint.

Product complaints are to be reported to Vertex.

14.2.2 Ethical Considerations

The study will be conducted in accordance with the current ICH GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and in accordance with local applicable laws and regulations. The IRB/IEC will review all appropriate study

documentation to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, sample ICF, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or Vertex, as allowable by local applicable laws and regulations.

14.2.3 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject's parent or legal guardian before study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with current ICH E6 GCP Guidelines and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

14.2.4 Investigator Compliance

No modifications to the protocol will be made without the approval of both the investigator and Vertex. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (i.e., efficacy assessments) will require IRB/IEC notification before implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. Vertex will submit all protocol modifications to the required regulatory authorities.

When circumstances require an immediate departure from procedures set forth in the protocol, the investigator will contact Vertex to discuss the planned course of action. If possible, contact will be made before the implementation of any changes. Any departures from protocol will be fully documented in the source documentation and in a protocol deviation log.

14.2.5 Access to Records

The investigator will make the office and/or hospital records of subjects enrolled in this study available for inspection by Vertex or its representative at the time of each monitoring visit and for audits. The records will also be available for direct inspection, verification, and copying, as required by applicable laws and regulations, by officials of the regulatory health authorities (FDA and others). The investigator will comply with applicable privacy and security laws for use and disclosure of information related to the research set forth in this protocol.

14.2.6 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all CRFs, study reports, and communications relating to the study will identify subjects by assigned subject numbers and access to subject names linked to such numbers shall be limited to the site and the study physician and shall not be disclosed to Vertex. As required by applicable laws and regulations in the countries in which the study is being conducted, the investigator will allow Vertex and/or its representatives access to all pertinent medical records to allow for the verification of data gathered in the CRFs/SAE Forms and the review of the data collection process. The FDA and regulatory authorities in other jurisdictions, including the IRB/IEC, may also request access to all study records, including source documentation, for inspection.

For sites participating in the study in the US, and in accordance with the Health Insurance Portability and Accountability Act and associated regulations ("HIPAA") an executed HIPAA authorization shall be obtained by the site from each subject (or the legal representative of the subject) before research activities may begin. Each HIPAA authorization shall comply with all HIPAA requirements including authorization allowing the site access to and use of the subject's personally identifiable health information, authorization for the site to disclose such information to Vertex, the FDA, and other parties requiring access under the protocol, and statements as to the purpose for which such information may be used and for how long.

14.2.7 Record Retention

The investigator will maintain all study records according to current ICH E6 GCP Guidelines and/or applicable local regulatory requirement(s), whichever is longest, as described in the Clinical Trial Agreement. If the investigator withdraws from the responsibility of keeping the study records, custody will be transferred to a person willing to accept the responsibility and Vertex will be notified.

14.2.8 Study Termination

At any time, Vertex may terminate this study in its entirety or may terminate this study at any particular site. In addition, for reasonable cause, either the investigators or their IRBs/IECs may terminate the study at their center.

Conditions that may lead to reasonable cause and warrant termination include, but are not limited to:

- Subject or investigator noncompliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by the FDA or other regulatory authority

Written notification that includes the reason for the clinical study termination is required.

14.2.9 End of Study

The end of study is defined as the last scheduled visit (or scheduled contact) of the last subject.

14.3 Data Quality Assurance

Vertex or its designated representative will conduct a study site visit to verify the qualifications of each investigator, inspect clinical study site facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct study documentation per the current ICH E6 GCP Guidelines.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data for each enrolled subject will be entered into a CRF by study site

personnel using a secure, validated, web-based electronic data capture (EDC) application. Vertex will have read-only access to site-entered clinical data in the EDC application.

Instances of missing, discrepant, or uninterpretable data will be queried with the investigator for resolution. Any changes to study data will be made to the CRF and documented in an audit trail, which will be maintained within the clinical database.

14.4 Monitoring

Monitoring and auditing procedures developed or approved by Vertex will be followed to comply with GCP guidelines. On-site checking of the CRFs/SAE Forms for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by Vertex or its designee. Monitoring will be done by personal visits from a representative of Vertex, or designee (study site monitor), who will review the CRFs/SAE Forms and source documents. The study site monitor will ensure that the investigation is conducted according to the protocol design and regulatory requirements.

14.5 Electronic Data Capture

Vertex will provide the study sites with secure access to and training on the EDC application sufficient to permit study site personnel to enter or correct information in the CRFs on the subjects for which they are responsible.

A CRF will be completed for each enrolled study subject. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data will indicate the subject's participation in the study and will document the dates and details of study procedures, adverse events, other observations, and subject status.

The investigator, or designated representative, will complete the CRF as soon as possible after information is collected.

The audit trail entry will show the user's identification information and the date and time of any correction. The investigator will provide formal approval of all the information in the CRFs, including any changes made to the CRFs, to endorse the final submitted data for the subjects for whom the investigator is responsible.

Vertex will retain the CRF data and corresponding audit trails. A copy of the final archival CRF in the form of a CD or other electronic media will be placed in the investigator's study file.

14.6 Confidentiality and Disclosure

Any and all scientific, commercial, and technical information disclosed by Vertex in this protocol or elsewhere will be considered the confidential and proprietary property of Vertex. The investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the investigator’s employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The investigator shall not use such information for any purpose other than determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The investigator understands that the information developed from this clinical study will be used by Vertex in connection with the development of the study drug and other drugs and diagnostics, and therefore may be disclosed as required to other clinical investigators, business partners and associates, the FDA, and other government agencies. The investigator also understands that, to allow for the use of the information derived from the clinical study, the investigator has the obligation to provide Vertex with complete test results and all data developed in the study.

14.7 Publications and Clinical Study Report

14.7.2 Clinical Study Report

A clinical study report, written in accordance with the ICH E3 Guideline, will be submitted in accordance with local regulations.

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16 APPENDIX A: *CFTR* MUTATIONS INCLUDED IN THE STUDY

Subjects who have 1 of the following ivacaftor-responsive *CFTR* mutations on at least 1 allele will be considered eligible for enrollment in this study in regions where ivacaftor is approved for use in subjects 4 months of age and older with an ivacaftor-responsive mutation per Inclusion Criterion 2:

The list below represents acceptable mutations, which are detectable by a genotyping assay or other method (e.g., sequencing) performed to applicable national standards; however, this list may not include every eligible mutation, and investigators should refer to the currently approved regional/local label or contact the medical monitor regarding other mutations that may also meet study eligibility criteria.

Table 16-1 List of *CFTR* Gene Mutations that Produce CFTR Protein and are Responsive to Ivacaftor

711+3A→G	*F311del*	*I148T*	*R75Q*	*S589N*
2789+5G→A	*F311L*	*I175V*	*R117C*	*S737F*
3272-26A→G	*F508C*	*I807M*	*R117G*	*S945L*
3849+10kbC→T	*F508C; S1251N*[a]	*I1027T*	*R117H*	*S977F*
A120T	*F1052V*	*I1139V*	*R117L*	*S1159F*
A234D	*F1074L*	*K1060T*	*R117P*	*S1159P*
A349V	*G178E*	*L206W*	*R170H*	*S1251N*
A455E	*G178R*	*L320V*	*R347H*	*S1255P*
A1067T	*G194R*	*L967S*	*R347L*	*T338I*
D110E	*G314E*	*L997F*	*R352Q*	*T1053I*
D110H	*G551D*	*L1480P*	*R553Q*	*V232D*
D192G	*G551S*	*M152V*	*R668C*	*V562I*
D579G	*G576A*	*M952I*	*R792G*	*V754M*
D924N	*G970D*	*M952T*	*R933G*	*V1293G*
D1152H	*G1069R*	*P67L*	*R1070Q*	*W1282R*
D1270N	*G1244E*	*Q237E*	*R1070W*	*Y1014C*
E56K	*G1249R*	*Q237H*	*R1162L*	*Y1032C*
E193K	*G1349D*	*Q359R*	*R1283M*	
E822K	*H939R*	*Q1291R*	*S549N*	
E831X	*H1375P*	*R74W*	*S549R*	

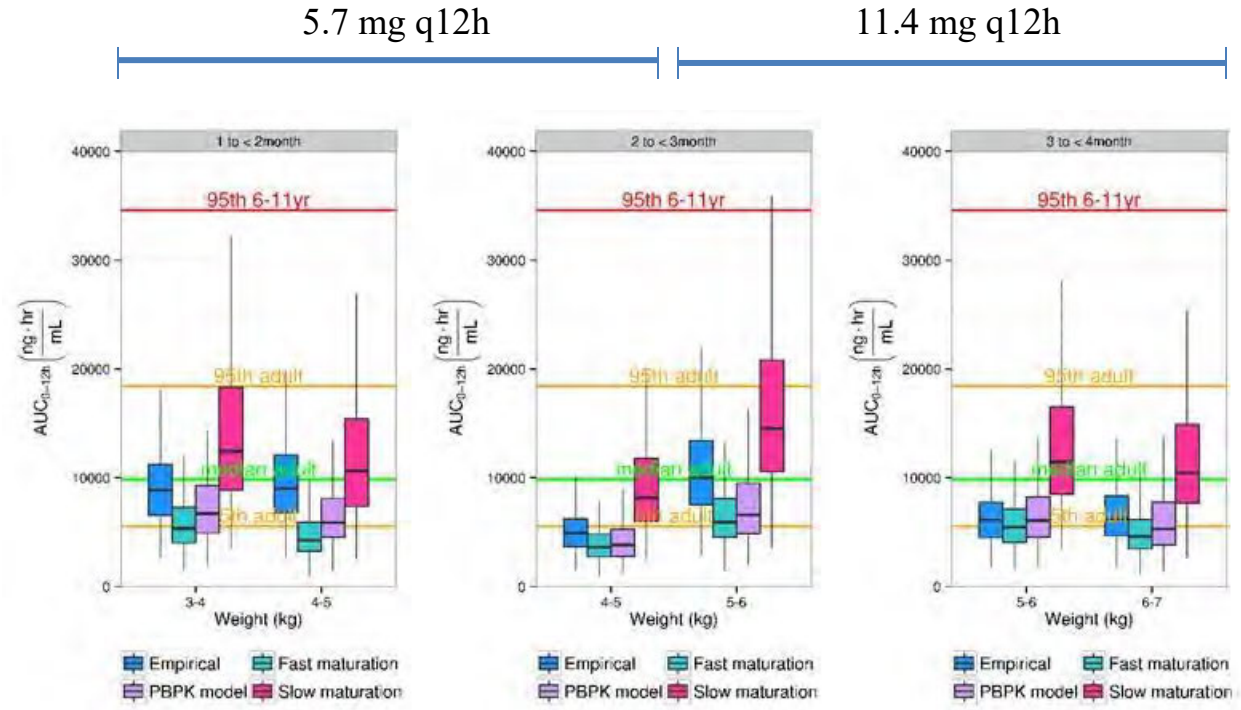
[a] Complex/compound mutation where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

Subjects with the *R117H* genotype should have the 5T variant or a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis.

17 APPENDIX B: SELECTION OF STARTING DOSE FROM DIFFERENT MODELS

Steady-state AUC_{0-12} exposures for different weight and age groups were simulated to select the starting ivacaftor doses from the available ivacaftor doses of 5.7, 11.4, 17.1, 22.8, and 25 mg q12h. These simulations used 4 different models to account for uncertainty in CYP3A maturation possibilities, which impacts the exposures for this age range as shown in Figure 17-1 (Report P292). The ivacaftor starting doses presented in Table 17-1 were selected to ensure that the highest predicted exposures from the 4 models were within the range previously shown to be safe and efficacious in adults. The majority of predicted exposures for all models exceeds the mean AUC_{0-12} exposure for the adult 25 mg dose of 955.6 ng-h/mL (Study 101 CSR, Table 14.4.2.1), which provided efficacy as evidenced by improvement in sweat chloride.

Figure 17-1 Selection of Starting Dose From Different Models



Source: Report P292

AUC_{0-12}: area under the concentration versus time curve from the time of dosing to 12 hours; PBPK: physiologically-based pharmacokinetic; q12h: every 12 hours; yr: year

Note: Marker lines: Green line indicates the median of the adult values. Orange lines indicate 5th and 95th percentiles of the adult values. Red line is the 95th percentile of 6- to 11-year-old values from Study VX08-770-103 (Report K199 2014). Boxplots: the median is represented by a horizontal line, and the interquartile range (IQR) is represented by a box. The whiskers represent the largest and smallest values within 1.5 × IQR.

Table 17-1 Starting Dose Table

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

Source: Report P292

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

18 PROTOCOL SIGNATURE PAGES

18.1 Sponsor Signature Page

Protocol #: VX15-770-124	Version #: 4.0	Version Date: 01 April 2021
Study Title: 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		

[redacted]

18.2 Investigator Signature Page

Protocol #: VX15-770-124	Version #: 4.0	Version Date: 01 April 2021
Study Title: 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		

I have read Protocol VX15-770-124, Version 4.0, and agree to conduct the study according to its terms. I understand that all information concerning ivacaftor and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date

1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol Addendum for Cystic Fibrosis

Cystic Fibrosis Studies for the Following Programs

Ivacaftor (VX-770)

[redacted]

Version and Date of Protocol Addendum: Version 3.0, 29 July 2020
Replaces Version 2.0, dated 15 May 2020

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210-1862, USA

Summary of Changes to Cystic Fibrosis Clinical Study Protocols

Vertex is currently evaluating several CFTR modulators in clinical studies for the treatment of cystic fibrosis (CF), a serious and life-threatening disease. In completed studies, treatment with these CFTR modulators has generally resulted in rapid, robust, clinically meaningful, and statistically significant improvements in clinical measures, and are generally safe and well tolerated. Adverse events (AEs) seen with these treatments are mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects.

During this COVID-19 pandemic, the safety of the subjects, investigators, and site personnel participating in these clinical studies is Vertex's first priority, thus it is important to minimize any unnecessary risk to COVID-19 exposure through travel to study sites. This addendum summarizes the measures taken for ongoing CF clinical studies. These operational adjustments were implemented to align with Health Authority guidance ensuring the protection of subjects, investigators, and site personnel while maintaining compliance with GCP and minimizing impact to the integrity of the studies. Overall, the benefit-risk of these studies remains favorable.

Vertex recommends that subjects and sites refer to local guidance regarding travel restrictions. There are no operational changes to the study protocols for subjects who can travel to the study sites for their visits. However, to ensure continued safety of subjects who ***cannot*** travel to the study sites for their visits (for any reason due to COVID-19), specific alternative measures are being implemented to minimize the risk of exposure to COVID-19 (see table below). As the COVID-19 pandemic evolves, Vertex will continue to assess the need for additional actions to ensure the safety of all involved in these clinical studies.

Addendum Version 3.0 summarizes additional measures taken for these ongoing CF clinical studies (see table below) to ensure continued safety.

Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

Protocol Change	Rationale for Change	Study Number
Addendum Version 3.0, dated 29 July 2020		
Assessments Unscheduled visit(s) will be permissible at the discretion of the investigator(s) or Vertex. The unscheduled visit(s) may be conducted at any time during the study (including after the protocol defined last study visit) in the event assessments specified to be collected at a scheduled visit were not collected due to COVID-19.	To ensure subject safety and/or to facilitate evaluation of safety and/or efficacy if assessments are not performed per the schedule in the protocol due to COVID-19.	VX15-770-124 [redacted]
Implementaion of measures described in addenda versions 1.0 and 2.0, as applicable.	To ensure subject safety and/or to facilitate evaluation of safety and/or efficacy while maintaining study integrity and the safety of subjects and site personnel.	

Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

Protocol Change	Rationale for Change	Study Number
Addendum Version 2.0, dated 15 May 2020		
Assessments Weight and height[redacted]/stature may be assessed by subjects or their caregivers using medical grade scales and stadiometers, as indicated per protocol and per local regulation. Sites and subjects will receive training and guidance as needed on these devices. Subjects or caregivers will provide these measurements to site personnel by telephone or video call. Investigators will review results and contact subjects for follow-up as needed. All data will continue to be retained in the subject's source files.	To allow for collection of key data to assess safety and/or efficacy while maintaining study integrity and the safety of subjects and site personnel. *Addendum 1 allowed for these assessments to be performed by qualified personnel conducting the in-home visits. Addendum 2 allows for these assessments to be performed by subjects or caregivers.*	VX15-770-124 [redacted]

Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

Protocol Change	Protocol Change	Protocol Change
Addendum Version 1.0, dated 24 April 2020		
Consenting of Subjects ICFs may be provided electronically or by post mail to subjects (and/or caregivers, as indicated per protocol). The subjects and/or caregivers will review the ICF with an appropriately qualified member of the investigator's team via telephone contact or video call. After this review, subjects and/or caregivers will consent (or assent, if applicable), and/or reconsent verbally and by signing and dating the ICF and returning it to the site via post mail. The signed and dated ICF will then be signed and dated by the investigator. Subjects participating in select studies may have the opportunity to enroll in longterm extension studies. Informed consent (or assent, if applicable), and/or reconsent for subjects (and/or caregivers, as indicated per protocol) may be obtained per the same process described above, as applicable.	To provide alternative methods of obtaining reconsent or consent, as applicable, while ensuring subject safety.	VX15-770-124 [redacted]
Study Drug Shipping Study drug may be shipped directly from the site to the subject, as applicable, and if permitted by local regulations; subject protected health information will not be released to Vertex. Reconciliation, return, and destruction of study drug will continue to occur at the clinical site as indicated per protocol and in adherence to local regulations.	To ensure subjects can continue treatment with study drug without interruption while ensuring their safety. To clarify that despite these alternative measures, reconciliation, return, and destruction of study drug will remain as indicated per protocol.	[redacted]
In-home Visits and/or Telephone Contact Study visits may be conducted as in-home visits by qualified personnel as requested by participating sites on a per-subject basis. In addition, all subjects may be contacted by site personnel by telephone or video call, irrespective of in-home visits.	To provide subjects the opportunity to continue participation in the clinical studies while ensuring their safety by minimizing the risk to COVID-19 exposure through travel.	[redacted]

Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

Protocol Change	Protocol Change	Protocol Change
Addendum Version 1.0, dated 24 April 2020		
Safety Assessments and Reporting Safety assessments, as indicated per protocol, may be performed by qualified personnel conducting the in-home visits (e.g., personnel from site or qualified health care agency). These assessments may include the following, as indicated per protocol, and per local regulation: • vital signs • pulse oximetry • height/length/stature • weight • physical examination (complete or abbreviated) • pregnancy test (serum or urine) • urinalysis • blood draws for safety test panels (chemistry, LFT panel, lipid panel, hematology, coagulation). Blood and/or urine samples for safety assessments are analyzed as indicated per protocol for subjects who have in-home visits. Blood and/or urine samples for safety assessments may be collected and analyzed at local laboratories for subjects who do not have in-home visits, but do not complete the assessment at the site. In addition, safety assessents will be evaluated by telephone. These assessments may include the review of the following: • AEs • signs and symptoms/systems for CF • medications • planned or unplanned hospitalizations for CF • study drug administration • outcomes related to PEx • outcomes related to antibiotic treatment Investigators will review results (in-home and telephone) and contact subjects for follow-up as needed. All data will continue to be retained in the subject's source files. Any clinically significant finding (e.g., AE, SAE, laboratory abnormalities) will continue to be reported as indicated per protocol.	To assess the safety and tolerability of the CFTR modulator evaluated in the specific clinical study while ensuring subject safety. These safety assessments will continue to provide safety data while minimizing burden to subjects and site personnel. To clarify that despite these alternative measures, all adverse events and serious adverse events should be reported as indicated per protocol.	VX15-770-124 [redacted]

Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

Protocol Change	Protocol Change	Protocol Change
Addendum Version 1.0, dated 24 April 2020		
Efficacy and Other Assessments Efficacy and other assessments, as indicated per protocol, may be performed by qualified personnel conducting the in-home visits. These assessments may include the following, as indicated per protocol, and per local regulation. In-home Spirometry Assessment A spirometry device may be provided to subjects for in-home assessments of lung function as indicated per protocol. Sites and subjects will receive training and guidance as needed. Patient Reported Outcome CFQ-R questionnaires may be provided to subjects (electronically or post mail) to be completed at home as indicated per protocol. Subjects will return these questionnaires to the site via post mail. Other Assessments • ECGs • sweat chloride • blood samples for *CFTR* genotype testing, [redacted], PK, FSH, [redacted]	To be able to assess safety, treatment effectiveness, and quality of life measures of the CFTR modulator evaluated in the specific clinical study while ensuring subject safety.	All Efficacy and Other Assessments [redacted] VX15-770-124 [redacted]

Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

Protocol Change	Protocol Change	Protocol Change
Addendum Version 1.0, dated 24 April 2020		
Remote Monitoring Vertex has implemented remote monitoring visits where applicable, including remote source data verification, as allowed per local regulations. Remote monitoring will focus on collection of safety data, and data supporting primary and key secondary endpoints.	To allow for review of key data to inform on the safety of subjects receiving treatment. To allow for review of other key data to inform on the objectives of the study while maintaining study integrity and the safety of subjects and site personnel.	VX15-770-124 [redacted]

AE: adverse event; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; ECG: electrocardiogram; [redacted]
FSH: follicle-stimulating hormone; GCP: Good Clinical Practice; ICF: informed consent form; [redacted] LFT: liver function test;
PEx: pulmonary exacerbation; PK: pharmacokinetic; SAE: serious adverse event; [redacted]