1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

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

Vertex Study Number: VX15-770-126

IND Number: 74,633

EudraCT Number: 2017-001379-21

Date of Protocol: 05 October 2017 (Version 2.0)

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Summary of Changes to the Protocol

The previous version of this protocol (Version 1.0, 13 April 2017) was amended to create the current version (Version 2.0, 05 October 2017). The protocol history is provided below.

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.0, 13 April 2017	Original version
Version 2.0, 05 October 2017	Current version

Key changes in the current version of the protocol are summarized below.

Change and Rationale	**Affected Sections**
Major revisions	
For subjects not from Study 124 Part B, revised inclusion criterion #5 to change lower weight bound at screening to comply with request from Regulatory Health Authority. Revised text to inform that future changes to study drug dose, age strata, or weight bounds will be communicated to site personnel through a memorandum entitled "Justification for Dose Selection" to ensure clarity and consistency in study conduct.	Sections 8.2.1, 9.2.2
For subjects not from Study 124 Part B, revised study population and inclusion criteria #3 to include subjects with CF <24 months of age who have an ivacaftor-responsive *CFTR* mutation on at least 1 allele. Subjects will be eligible in countries/regions where ivacaftor is approved for use in subjects 2 years of age and older to align with newly approved indication.	Sections 1, 2, 6.1.1, 6.1.2, 6.1.3, 6.2.1, 8, 8.2.1, 11.6.2, 15.1, and 15.2
Added text to alert investigators that the study manual **and** the approved ivacaftor label in their country/region should be consulted to confirm the approved mutations for subject eligibility.	Sections 2, 8, and 11.6.2
Added paragraph to introduce ivacaftor-responsive mutations.	Section 5.1
Added paragraph to indicate that a list of approved ivacaftor-responsive CFTR mutations is included in the study manual, and that any updates to approved mutations will be communicated to investigative sites through a memorandum.	Section 8
Added text to indicate that dosing, age or weight strata may be modified based on available PK data and how this information will be communicated to investigational sites.	Section 9.2.2
Removed Study Visit at Week 104, as the 2-year treatment period concludes at Week 96.	Table 3-1, Table 3-2, Table 3-3, Table 3-4, Figure 2-1, Figure 9-1 and Sections 2, 7.1.2, 7.1.3, 9.1, 9.1.1.2, 9.1.4.1, 9.2.1, 9.4,
Other revisions affecting study implementation	
Revised footnotes and appropriate sections to allow subjects, after their Week 24 Visit, to receive their morning dose at home prior to that day's clinic visit, to allow assessments to be done postdose, and to allow sweat chloride to be assessed outside the ± 2 hour window to allow for flexibility in scheduling the time of a subject's visit. Clarified that time of dose administration need not be recorded after Week 24. The 24-week Follow-up OE window changed to (+ 14 Days) rather than (± 14 Days) to ensure adequate follow-up period.	Table 3-1, Table 3-2, and Table 3-3; Sections 2, 9.1.1.4, 9.4, 11.2, 11.4.1, and 11.6.4

Change and Rationale	Affected Sections
Deleted 'Demographics', and footnote 'c' because neither were needed. Added collection of medical history for Gap Transition subjects who have new conditions that start after the Study 124 Safety Follow-up Visit and prior to the Study 126 Screening Visit.	Table 3-2
Added a 1 day window around the Day 3 Visit. Added footnote "a" and text in appropriate sections to clarify when enrollment in Study 126 will be open for a particular age group. Added footnote "d" to ensure historical CF data are collected at screening or at Day 1. Deleted footnote "j" (OE performed at Week 12 and Week 24) because it is already explained in the table. Added 4-hour observation period after administration of first dose. Deleted study drug count on Day 1. Clarified in footnote "l" and in appropriate section, that if an OE was conducted in Study 124 Part A within 12 weeks of the Day 1 Visit, the Day 1 Visit OE does not need to be repeated. Added to footnote "r" that an additional MBW will be performed on the Week 72 Visit.	Table 3-3; Sections 8.2 and 9.1.1.1
Added a 7-day window around the telephone contacts at Weeks 48 and 96 for subjects in the Observational Arm to allow flexibility in contacting subjects.	Table 3-4; Sections 2 and 9.1.4.1
Revisions to clarify text	
Clarified in footnote 'p' that baseline sweat chloride test is not required at Day 1 if it was completed at screening.	Table 3-2 and Table 3-3; Section 11.4.1
Clarified that enrollment of subjects in Study 126 age cohorts is closely linked to Study 124 and will be based on available PK data.	Section 9.1
Clarified when screening serum chemistry and hematology assessments need to be performed with respect to first dose.	Sections 9.1.1.1, 9.1.1.1.3, and 9.1.1.2.1
Clarified when rescreening OE needs to be repeated.	Section 9.1.1.1.2
Revised text to indicate the IDMC charter will be finalized before the 1st subject is screened.	Sections 2 and 9.1.5
Text was changed to clarify how blood samples from local laboratories should be handled.	Section 11.6.2
Added that subjects who did not participate in Study 124 Part B should have an additional OE exam at Week 12. Simplified text requiring that study drug be discontinued if a new lens opacity or cataract is identified at any OE in the ivacaftor arm.	Section 11.6.5
Removed reference to presentation of various analyses by treatment (dose levels), as these will be addressed in the statistical analysis plan (SAP).	Section 12.3
Removed reference to diary cards as they will not be used in the study.	Section 13.2.1
Deleted Appendices A and B since they were not needed.	Sections 15 and 16

Typographical and administrative changes were also made to improve the clarity of the document.

2 PROTOCOL SYNOPSIS

Title

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

Brief Title

A Study to Evaluate the Safety of Long-term Ivacaftor Treatment in Subjects with Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have an Approved Ivacaftor-Responsive Mutation

Clinical Phase and Clinical Study Type

Phase 3, safety, pharmacodynamics (PD), and efficacy

Ivacaftor Arm Objectives

Primary

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

Secondary

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

Tertiary

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

Observational Arm Objective

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

Ivacaftor Arm Endpoints

Primary

Safety, as determined by:

- Adverse events
- Laboratory values (serum chemistry and hematology)
- 12-lead ECGs and vital signs
- Ophthalmologic examinations (OEs)

Secondary

Absolute change from baseline in sweat chloride through Week 96

Tertiary

- Absolute change from baseline through Week 96 for the following endpoints:
  - Weight
  - Length (assessed as height, as age appropriate)
  - Weight-for-length
  - Weight-for-age z-score
  - Length-for-age z-score
  - Weight-for-length-for-age z-score
  - Body mass index (BMI)
  - BMI-for-age z-score
  - Lung clearance index (LCI) at qualified study sites
  - Fecal elastase-1

- Markers of intestinal inflammation
- Qualitative microbiology cultures
- Annualized rate of pulmonary exacerbations
- Rate of CF-related hospitalizations

Observational Arm Endpoint

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

Number of Subjects

Approximately 75 subjects will be enrolled.

Study Population

Subjects with CF <24 months of age at treatment initiation who have an ivacaftor-responsive *CFTR* mutation on at least 1 allele.

- Subjects will be eligible in countries/regions where ivacaftor is approved for use in subjects 2 years of age and older.
- Investigators should consult the approved ivacaftor label in their country/region to confirm approved mutations for subject eligibility.

Source of Subjects Enrolled in the Ivacaftor Arm

- Subjects who completed ivacaftor treatment in Study 124 Part B
- Subjects who did not participate in Study 124 Part B (e.g., subjects who participated in Study 124 Part A only and subjects who did not participate in Study 124 Part A or B) and are <24 months of age at Day 1 of Study VX15-770-126 (Study 126)

Source of Subjects Enrolled in the Observational Arm

- Subjects who completed ivacaftor treatment in Study 124 Part B and elected not to enroll in the ivacaftor arm of Study 126
- Subjects who received at least 1 dose of ivacaftor and prematurely discontinued ivacaftor treatment in Study 124 Part B

Investigational Drug

Active substance: ivacaftor

Activity: CFTR potentiator

Strength and route of administration: 25 mg, 50 mg, 75 mg, and others (to be determined based on safety and PK data from Study 124, age, and weight); granules for oral administration

Study Duration

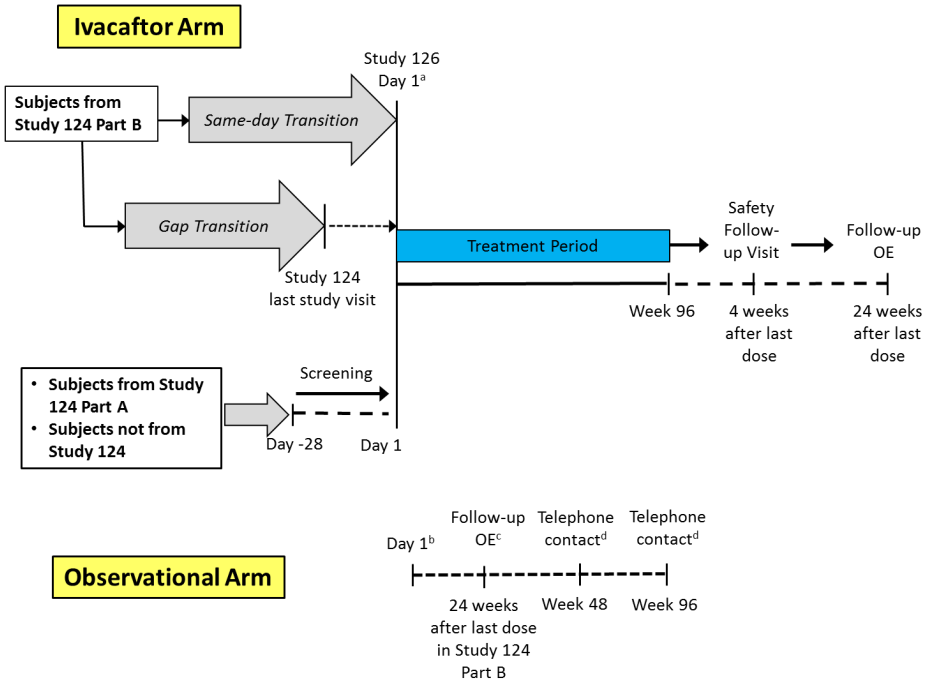
Ivacaftor Arm: Subjects will participate for approximately 128 weeks (from Day 1 through the Follow-up OE).

Observational Arm: Subjects will participate for approximately 96 weeks (from Day 1 through the Week 96 Follow-up Telephone Contact).

Study Design

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

Figure 2-1 VX15-770-126 Study Design



[a] For subjects who have a Same-day Transition, the Week 24 Visit of Study 124 Part B will be the same day as the Day 1 Visit of Study 126. For subjects who have a Gap Transition, the last study visit of Study 124 Part B will not be the same day as the Day 1 Visit of Study 126 (see Section 9.1.1.2.1).

[b] Day 1 for subjects in the observational arm can be the last study visit of Study 124 Part B (see Section 9.1.3).

[c] The Follow-up OE in the observational arm can be performed in Study 124.

[d] Only for subjects who received at least 4 weeks of study drug in Study 124 Part B.

Study Overview for Subjects in the Ivacaftor Arm

This arm will include the following:

- Screening Period (for subjects not from Study 124 Part B only): Day -28 to Day -1
- Treatment Period: Day 1 to Week 96
  - Appropriate doses will be based on Study 124 Parts A and B findings
- Safety Follow-up Visit: 4 weeks (± 7 days) after the last dose of ivacaftor
- Early Termination of Treatment (ETT) Visit (if applicable): as soon as possible after the last dose of ivacaftor
- Follow-up OE: 24 weeks (+ 14 days) after the last dose of ivacaftor

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

Study Overview for Subjects in the Observational Arm

The observational arm will include the following:

- Day 1 Visit
- OE: 24 weeks (+ 14 days) after the last dose of ivacaftor in Study 124

Part B, unless the Follow-up OE was performed in Study 124

- Follow-up Telephone Contacts: Week 48 [± 7 Days] and Week 96 [± 7 Days] (only for subjects who received ≥4 weeks of ivacaftor in Study 124 Part B)

Subjects who receive commercially available ivacaftor will be discontinued from the observational arm after completing the OE.

Assessments

Safety (ivacaftor and observational arms)

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

Pharmacodynamic (ivacaftor arm only)

Sweat chloride

Efficacy (ivacaftor arm only)

Weight, length, weight-for-length, weight-for-age z-score, length-for-age z-score, weight-for-length-for-age z-score, BMI, BMI-for-age z-score, multiple breath washout (MBW), qualitative microbiology cultures, annualized rate of pulmonary exacerbations, rate of CF-related hospitalizations, fecal elastase-1, and markers of intestinal inflammation

Statistical Analyses

The study is not powered to detect a significant treatment effect. The Safety Set (defined as enrolled subjects who receive at least 1 dose of ivacaftor in Study 126) will be used for all safety analyses. The Full Analysis Set (FAS) (defined as enrolled subjects who have at least 1 postbaseline efficacy assessment in Study 126) will be used for all efficacy analyses. Data from all safety and efficacy endpoints will be analyzed using descriptive statistics. For efficacy endpoints, separate tables will be presented for subjects in the ivacaftor arm.

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

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 subject is screened.

3 SCHEDULE OF ASSESSMENTS

Table 3-1 Schedule of Assessments for VX15-770-126 (Ivacaftor Arm: Same-day Transition Subjects From Study 124 Part B)

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

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

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

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

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

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

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

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

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

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

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

Table 3-1 Schedule of Assessments for VX15-770-126 (Ivacaftor Arm: Same-day Transition Subjects From Study 124 Part B)

		Treatment Period (Day 1 Through Week 96)		ETT Visit[a]	Safety Follow-up Visit[b]	24-Week Follow-up OE
Event/Assessment	**Day 1[c]**	**Weeks 12, 36, 60, and 84 (± 7 Days)**	**Weeks 24, 48, 72, and 96 (± 7 Days)**	**As Soon as Possible After the Last Dose**	**4 Weeks (± 7 Days) After the Last Dose**	**24 Weeks (+ 14 Days) After the Last Dose**
Fecal sample collection[k]	X		X	X		
Sweat chloride test[l]	X		X			
Qualitative microbiology cultures	X		X			
Multiple breath washout (optional)[m]	X		X[n]			
Study drug administration[o]	X	X	X			
Study drug count	X	X	X	X		
Pulmonary exacerbations, CF-related hospitalizations	*Continuous from signing of ICF through the last dose of study drug*					
Adverse events	*Continuous from signing ICF through the Safety Follow-up Visit (see Section 13.1.1.3)*					*Ocular adverse events only*
Medications and procedures review	*Continuous from signing of ICF through the Safety Follow-up Visit*					

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

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

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

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

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

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

Table 3-2 Schedule of Assessments for VX15-770-126 (Ivacaftor Arm: Gap Transition Subjects From Study 124 Part B)

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

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

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

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

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

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

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

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

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

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

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

Table 3-2 Schedule of Assessments for VX15-770-126 (Ivacaftor Arm: Gap Transition Subjects From Study 124 Part B)

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

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

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

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

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

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

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

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

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

Table 3-2 Schedule of Assessments for VX15-770-126 (Ivacaftor Arm: Gap Transition Subjects From Study 124 Part B)

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

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

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

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

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

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

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

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

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

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

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

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

	Screening Period[a]	Treatment Period (Day 1 through Week 96)								ETT Visit[b]	Safety Follow-up Visit[c]	24-Week Follow-up OE
Event/Assessment	**Day -28 to Day -1**	**Day 1**	**Day 3 (± 1 Day)**	**Week 2 (± 1 Day)**	**Week 4 (± 5 Days)**	**Weeks 8 and 18 (± 7 Days)**	**Weeks 12 and 24 (± 7 Days)**	**Weeks 36, 60, and 84 (± 7 Days)**	**Weeks 48, 72, and 96 (± 7 Days)**	**As Soon as Possible After the Last Dose**	**4 Weeks (± 7 Days) After the Last Dose**	**24 Weeks (+ 14 Days) After the Last Dose**
Physical examination[g]	X	X		X	X	X	X	X	X	X	X	
Vital signs[h]	X	X		X	X	X	X	X	X	X	X	
12-lead ECGs[h, i]	X	X			X		X	X	X	X	X	
Serum chemistry and hematology[j]	X			Chem-istry only	LFTs and hema-tology only	X	X	X	X	X	X	
Ophthalmologic examination[k]	X[l]						X		X	X[m]		X
Fecal sample collection [n]	X[o]			X	X	X	X		X	X		

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

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

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

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

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

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

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

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

	Screening Period[a]	Treatment Period (Day 1 through Week 96)								ETT Visit[b]	Safety Follow-up Visit[c]	24-Week Follow-up OE
Event/Assessment	**Day -28 to Day -1**	**Day 1**	**Day 3 (± 1 Day)**	**Week 2 (± 1 Day)**	**Week 4 (± 5 Days)**	**Weeks 8 and 18 (± 7 Days)**	**Weeks 12 and 24 (± 7 Days)**	**Weeks 36, 60, and 84 (± 7 Days)**	**Weeks 48, 72, and 96 (± 7 Days)**	**As Soon as Possible After the Last Dose**	**4 Weeks (± 7 Days) After the Last Dose**	**24 Weeks (+ 14 Days) After the Last Dose**
Sweat chloride test[p]	X	X		X			X		X			
Qualitative microbiology cultures		X					X		X			
Multiple breath washout (optional)[q]		X					X		X[r]			
Study drug administration[s]		X		X	X	X	X	X	X			

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

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

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

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

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

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

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

	Screening Period[a]	Treatment Period (Day 1 through Week 96)								ETT Visit[b]	Safety Follow-up Visit[c]	24-Week Follow-up OE
Event/Assessment	**Day -28 to Day -1**	**Day 1**	**Day 3 (± 1 Day)**	**Week 2 (± 1 Day)**	**Week 4 (± 5 Days)**	**Weeks 8 and 18 (± 7 Days)**	**Weeks 12 and 24 (± 7 Days)**	**Weeks 36, 60, and 84 (± 7 Days)**	**Weeks 48, 72, and 96 (± 7 Days)**	**As Soon as Possible After the Last Dose**	**4 Weeks (± 7 Days) After the Last Dose**	**24 Weeks (+ 14 Days) After the Last Dose**
In-clinic observation for 4 hours after administration of the first dose of study drug		X										
Study drug count				X	X	X	X	X	X	X		
Pulmonary exacerbations, CF-related hospitalizations	*Continuous from signing of ICF through the last dose of study drug*											
Adverse events	*Continuous from signing ICF through the Safety Follow-up Visit (see Section 13.1.1.3)*											*Ocular adverse events only*
Medications and procedures review	*Continuous from signing of ICF through the Safety Follow-up Visit*											

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

Table 3-4 Schedule of Assessments for VX15-770-126 (Observational Arm)

Event/Assessment	Day 1[a]	Ophthalmologic Examination (Week 24 [± 14 Days] After the Last Dose)[b]	Long-term Follow-up Telephone Contact (Week 48 [± 7 Days] and Week 96 [± 7 Days])[c]
Clinic visit	X		
Informed consent	X		
Inclusion/exclusion criteria review	X		
Ophthalmologic examination		X	
Telephone contact			X
Serious adverse events	*Continuous from Day 1 through the Long-term Follow-up Telephone Contact at Week 96*		

OE: ophthalmologic examination

[a] The Day 1 Visit can be the same day as the last study visit of Study 124 Part B. If the Day 1 Visit is not the same day as the last study visit of Study 124 Part B, a clinic visit will be required for signing of the ICF and inclusion/exclusion criteria review.

[b] Subjects in the observational arm will complete the OE approximately 24 weeks after the last dose of ivacaftor. This OE will be performed in Study 126 unless already completed in Study 124 Part B.

[c] Only for subjects who received ≥4 weeks of ivacaftor treatment in Study 124 Part B.

4 TABLE OF CONTENTS

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator gene
CFTR	CF transmembrane conductance regulator protein
CI	confidence interval
CL	clearance
CL/F	apparent clearance
CRF	case report form
EC	ethics committee
ECG	electrocardiogram
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
GCP	Good Clinical Practice
GPS	Global Patient Safety
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous
LCI	lung clearance index
LFT	liver function test
MBW	multiple breath washout
MedDRA	Medical Dictionary for Regulatory Activities
NCHS	Nutrition Examination Survey
OE	ophthalmologic examination
PD	pharmacodynamic, pharmacodynamics
PE	physical examination
PK	pharmacokinetic, pharmacokinetics
PND	postnatal day
q12h	every 12 hours

Abbreviation	Definition
QTc	QT interval corrected
QTcB	QT interval corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected, unexpected, serious adverse reaction
TEAE	treatment-emergent adverse event
UK	United Kingdom
ULN	upper limit of normal
US	United States
Vertex	Vertex Pharmaceuticals Incorporated
WHO-DDE	World Health Organization-Drug Dictionary Enhanced

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 70,000 individuals worldwide, with 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 *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, 6] Currently, there is no cure for CF, and despite adjunctive treatments with nutritional supplements, antibiotics, and mucolytics,[7] the median predicted age of survival of individuals born today with CF is approximately 40 years of age.[1, 8-10]

More than 2000 mutations in the *CFTR* gene have been identified.[11] *CFTR* mutations result in reduced quantity of CFTR at the cell surface or reduced CFTR function, leading to a decrease in epithelial chloride transport.[12, 13] 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).

Mutations that cause CFTR gating defects are present in about 5% of the CF patient population worldwide. Approximately 4% of patients have the *G551D* mutation, and the remaining 1% have other mutations that cause a CFTR gating defect.[14,15] The *R117H* mutation causes defects not only in channel gating but also in channel conductance.[16] 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.[17-19]

Based on clinical and/or in vitro data, 28 additional ivacaftor-responsive mutations were approved in the US in 2017; approval for these additional mutations may be requested in other countries/regions.

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) and/or by genotyping analysis.[20] 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. In the US, more than 80% of patients with CF are diagnosed by age 2.[1] In the EU, approximately 60% of patients with CF are diagnosed by 1 year of age,[21] and in the UK, approximately 83% of patients with CF are diagnosed by 1 year of age.[22] Genotyping for mutations in the *CFTR* gene is now routine practice in many countries.

In infants with CF, pancreatic insufficiency[23] and poor nutritional status[24-26] are the most significant clinical manifestations of the disease. These factors often lead to poor growth with

subsequent growth delay,[27, 28] poorer cognitive development,[29] and other clinical comorbidities such as decreased lung function and survival.[30, 31] Studies of subjects 1 month through 6 years of age also show the presence of lung disease[21, 32-34] and liver disease[35]. High-resolution computed tomography studies including infants with CF that were diagnosed by newborn screening, but were considered clinically healthy, indicate that structural lung damage is common even very early in disease progression.[21, 36, 37] In a cohort of 81 well-treated CF patients in Australia, by 3 years, 10% had *Pseudomonas aeruginosa* infection and 84% had evidence of bronchiectasis.[38] This is consistent with the results of inflammatory marker studies that have found that airway inflammation begins in infancy.[33, 39, 40] 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.[41] 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.[42] Mucoid *P. aeruginosa* infection is considered the major limiting factor in survival for patients with CF.[43]

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.[44] 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.[45] Malnourishment is associated with worsening lung function in children with CF and is also an independent predictor of mortality in this population.[46]

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.[47, 48] 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.[49]

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 showed that ivacaftor is effective in the treatment of subjects with CF 6 years of age and older who have gating mutations. Ivacaftor treatment produced improvements in CFTR function, as evidenced by improvements in lung function, sweat chloride, body mass index (BMI)/weight, pulmonary exacerbations, respiratory symptoms, and the Cystic Fibrosis Questionnaire-Revised (CFQ-R; respiratory domain) in subjects who have a *G551D* gating mutations (Studies VX08-770-102 [Study 102] and VX08-770-103 [Study 103]) and in subjects who have non-*G551D* gating mutations (Study VX12-770-111 [Study 111]).[50] Results from Study VX11-770-110 (Study 110) showed that ivacaftor treatment in subjects aged 6 years and older with CF who have an *R117H* mutation resulted in statistically significant improvements in sweat chloride response, but these subjects did not show any other meaningful

response. The safety profiles of ivacaftor from Studies 102, 103, 111, and 110 were all similar and demonstrated that ivacaftor was well tolerated.[50]

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.[50] Results from Study VX11-770-109 (Study 109), a Phase 3, open-label rollover study to evaluate the safety and pharmacodynamics (PD) of long-term ivacaftor in subjects from Study 108, showed that the overall safety profile was durable and remained favorable over an additional 84 weeks of treatment.[51]

Based on the demonstrated safety profile in subjects 2 through 5 years of age with a *CFTR* gating defect (Studies 108 and 109), 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),[50] evidence of complications of CF by age 6, and evidence supporting the benefits of early therapeutic intervention, there is great potential for patients <24 months of age who have an ivacaftor-responsive *CFTR* mutation to benefit from ivacaftor treatment.

6 STUDY OBJECTIVES

6.1 Ivacaftor Arm

6.1.1 Primary Objective

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

6.1.2 Secondary Objective

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

6.1.3 Tertiary Objective

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

6.2 Observational Arm

6.2.1 Primary Objective

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

7 STUDY ENDPOINTS

7.1 Ivacaftor Arm

7.1.1 Primary Endpoint

Safety, as determined by:

- Adverse events
- Laboratory values (serum chemistry and hematology)
- 12-Lead ECGs and vital signs
- Ophthalmologic examinations (OEs)

7.1.2 Secondary Endpoint

Absolute change from baseline in sweat chloride through Week 96

7.1.3 Tertiary Endpoints

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

7.2 Observational Arm Endpoint

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

8 STUDY POPULATION

Subjects with CF <24 months of age at treatment initiation who have an ivacaftor-responsive *CFTR* mutation on at least 1 allele.

- Subjects will be eligible in countries/regions where ivacaftor is approved for use in subjects 2 years of age and older. A list of approved ivacaftor-responsive CFTR mutations is included in the study manual. If ivacaftor is approved for additional mutations in any country/region, a memorandum will be sent to investigative sites in that country/region and subjects with the newly approved mutations will also be eligible.
- Investigators should consult the approved ivacaftor label in their country/region to confirm approved mutations for subject eligibility.

The study is open to subjects who meet all inclusion and exclusion criteria. Subjects will be drawn from 2 sources:

- Subjects who completed Study 124 Part B and elect to enroll in Study VX15-770-126 (Study 126)
- Subjects who did not participate in Study 124 Part B, which includes
  - subjects who participated in Study 124 Part A only
  - subjects who did not participate in Study 124 Part A or B

Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects are enrolled.

8.1 Ivacaftor Arm: Subjects From Study 124 Part B

8.1.1 Inclusion Criteria

1. Subjects transitioning from Study 124 Part B must have completed the last study visit of Study 124 Part B

Added guidance:

- Subjects who had a study drug interruption at the last scheduled visit of Study 124 Part B, subjects who required study drug interruption that was to be continued or initiated at Day 1 in Study 126, or subjects who resumed study drug in Study 124 Part B after a study drug interruption due to elevated transaminases but who did not complete at least 4 weeks of rechallenge with study drug (due to the timing of the rechallenge versus the time remaining in Study 124 Part B) must meet eligibility criteria and have received approval from the Vertex medical monitor.

2. For Gap Transition subjects: hematology and serum chemistry results at baseline with no clinically significant abnormalities that would confound the study assessments or pose an additional risk to administering ivacaftor to the study subject, as judged by the investigator.
3. As judged by the investigator, parent or legal guardian must be able to understand protocol requirements, restrictions, and instructions; and must sign the informed consent form (ICF).

8.1.2 Exclusion Criteria

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 ivacaftor to the subject. Examples of subjects who may not be eligible include
   - subjects with a history of allergy or hypersensitivity to the study drug; and
   - subjects with severe or life-threatening reactions to the study drug in Study 124.
2. Subjects receiving commercially available ivacaftor treatment

8.2 Ivacaftor Arm: Subjects Not From Study 124 Part B

Subjects not from Study 124 Part B will only be allowed to enroll in Study 126 after an adequate number of subjects have completed the corresponding age cohort in Study 124, in conjunction with feedback from regulatory authorities.

8.2.1 Inclusion Criteria

1. Age <24 months at the Day 1 Visit
2. Confirmed diagnosis of CF, defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis or 2 CF-causing mutations
   - If the results of the sweat chloride and/or the genotype test are documented in the subject's medical record, and the historic genotype result is approved by the Vertex medical monitor, the tests do not need to be performed 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.
3. An ivacaftor-responsive *CFTR* mutation on at least 1 allele. Subjects will be eligible in countries/regions where ivacaftor is approved for use in subjects 2 years of age and older.
   - 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, the subject will undergo *CFTR* genotype 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.
4. Hematology, serum chemistry, and vital signs results have no clinically significant abnormalities that would confound the study assessments, as judged by the investigator.
5. Weight at screening must be within the weight limits as defined for the study drug dose levels (Section 9.2.2) or according to the dosing guidelines identified in the "Justification for Dose Selection" memorandum effective at the time a subject is screened.
6. For subjects <3 months of age only, gestational age ≥38 weeks.
7. As judged by the investigator, parent or legal guardian must be able to understand protocol requirements, restrictions, and instructions; and must sign the ICF.

8.2.2 Exclusion Criteria

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 ivacaftor 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 of Day 1
3. Known colonization with organisms associated with a more rapid decline in pulmonary status (e.g., *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*). A subject is excluded if they have a positive culture of one of these organisms.
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, e.g., physiologic jaundice or breastmilk jaundice of the newborn)
5. Hemoglobin <9.5 g/dL at screening
6. History of solid organ or hematological transplantation
7. Any clinically significant "non-CF-related" illness within 2 weeks of Day 1. "Illness" is defined as an acute (serious or nonserious) condition (e.g., gastroenteritis)
8. Use of any moderate or strong inducers or inhibitors of cCYP3A within 2 weeks of Day 1
9. 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. Note: Participation in a noninterventional study (including observational studies, registry studies, and studies requiring blood collections without administration of study drug) is permitted.
10. Chronic kidney disease of Stage 3 or above
11. Unable to undergo an adequate slit-lamp examination at screening
12. Presence of a lens opacity or cataract identified at the screening OE (excluding those considered congenital and nonprogressive, such as a suture cataract)

8.3 Observational Arm

8.3.1 Inclusion Criterion

1. Completed ivacaftor treatment in Study 124 Part B and elected not to enroll in the ivacaftor arm of Study 126, or received at least 1 dose of ivacaftor and prematurely discontinued ivacaftor treatment in Study 124 Part B and received at least 1 dose of ivacaftor treatment in Study 124 Part B

8.3.2 Exclusion Criterion

1. Receiving ivacaftor treatment

9 STUDY IMPLEMENTATION

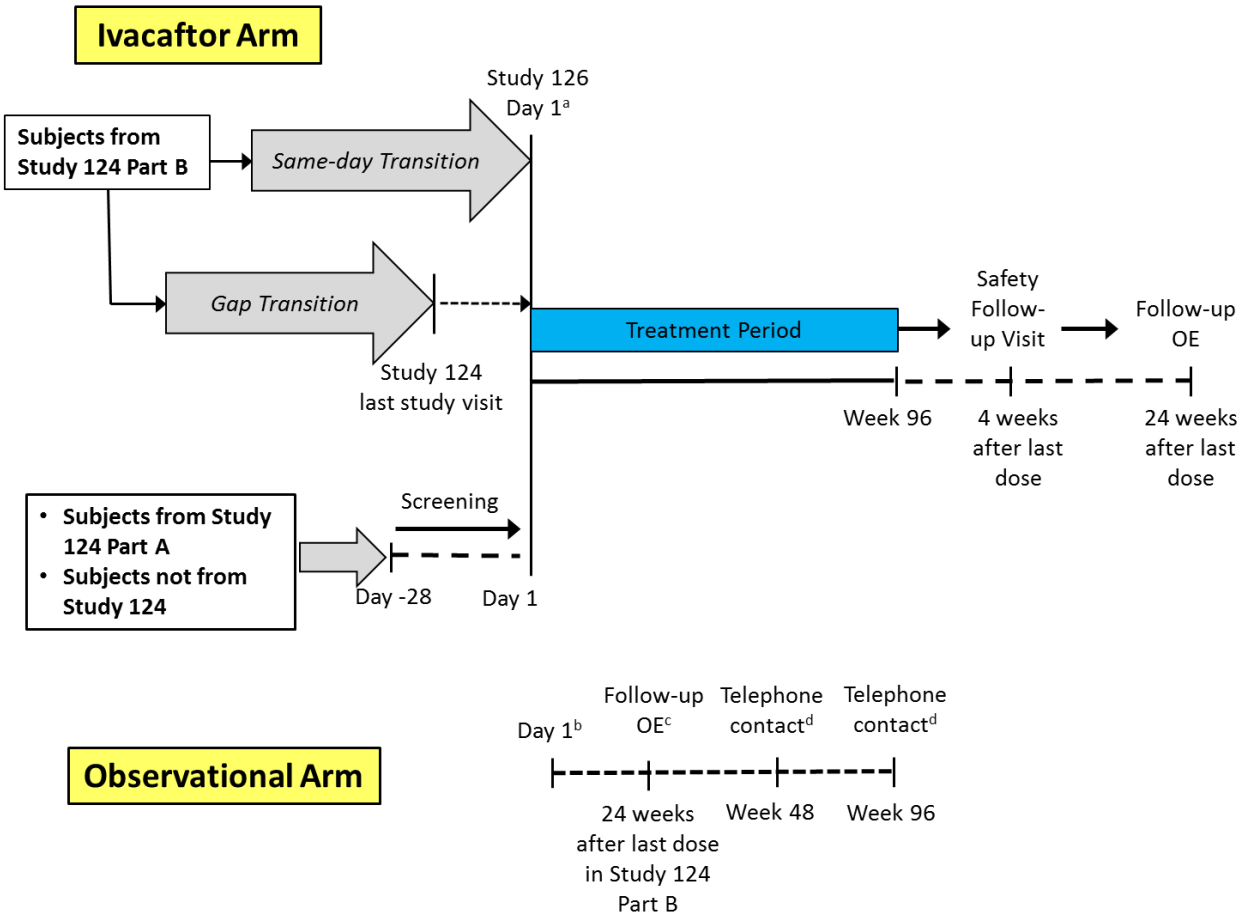
9.1 Overview of Study Design

This is a Phase 3, 2-arm, multicenter study.

Enrollment in Study 126 is closely linked to Study 124 which will enroll subjects according to defined age cohorts, starting with ages 12 to <24 months, followed sequentially by appropriately grouped descending age cohorts based on available PK data.

This study includes an ivacaftor arm (open-label, 96-week treatment period) and an observational arm. The study design is shown in Figure 9-1.

Figure 9-1 VX15-770-126 Study Design



[a] For subjects who have a Same-day Transition, the Week 24 visit of Study 124 Part B will be the same day as the Day 1 Visit of Study 126. For subjects who have a Gap Transition, the last study visit of Study 124 Part B will not be the same day as the Day 1 Visit of Study 126 (see Section 9.1.1.2.1).

[b] Day 1 for subjects in the observational arm can be the last study visit of Study 124 Part B (see Section 9.1.3).

[c] The Follow-up OE in the observational arm can be performed in Study 124.

[d] Only for subjects who received at least 4 weeks of study drug in Study 124 Part B.

9.1.1 Ivacaftor Arm

9.1.1.1 Ivacaftor Arm: Screening (Subjects Not From Study 124 Part B)

Subjects not from Study 124 Part B will only be allowed to enroll in Study 126 after an adequate number of subjects have completed the corresponding age cohort in Study 124, in conjunction with feedback from regulatory authorities.

Subjects who participated only in Study 124 Part A and subjects who did not participate in Study 124 will have a Screening Period. *CFTR* genotyping does not need to be repeated for subjects from Study 124 Part A or for subjects whose genotype is adequately documented in their medical record and who receives approval from the Vertex medical monitor (Section 11.6.2).

The investigator (or an appropriate authorized designee at the study site) will obtain informed consent from the subject's parent or legal guardian before any study specific procedures are performed. Screening will occur within 28 days before administration of study drug.

- If serum chemistry and hematology assessments are performed >9 days before Day 1, they must be repeated on Day 1, and the results must be reviewed and eligibility confirmed before the first dose of study drug.
- If an OE was conducted in Study 124 Part A within 12 weeks of the Day 1 Visit, the Day 1 Visit OE does not need to be repeated.

Screening Visit assessments are listed in Table 3-4.

To prepare for study participation, the subject's parent or legal guardian will be instructed on the study restrictions (Section 9.3).

9.1.1.1.1 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 with approval of the Vertex medical monitor.
- An adequate slit-lamp examination could not be conducted (Section 11.6.5).

If repeat values are within the eligibility criteria and completed within the screening window or extended screening window (Section 9.1.1.1.3), the subject is eligible for the study.

9.1.1.1.2 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 and the OE only needs to be repeated if it has been >12 weeks since the last adequate slit-lamp examination.

If a subject is rescreened, the rescreening window (28 days) will begin once the first rescreening assessment has been initiated.

9.1.1.1.3 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 9.1.1.1.1)
- Unexpected operational or logistical delays (e.g., delayed drug shipment)
- Scheduling of the OE (Section 11.6.5)
- Availability of required equipment

A subject may have the screening window extended by 4 weeks upon approval by the Vertex medical monitor for a repeat slit-lamp examination (Sections 9.1.1.1.1 and 11.6.5).

Regardless of approved extensions in the screening window, all subjects to be enrolled in the ivacaftor arm must have Day 1 serum chemistry and hematology assessments performed and reviewed for eligibility within 9 days before dosing on Day 1.

9.1.1.2 Ivacaftor Arm Treatment Period (All Subjects)

Ivacaftor will be administered every 12 hours (q12h) from Day 1 through the morning dose of the Week 96 Visit. At each visit, except the final treatment period visit, the ivacaftor dose for each subject will be reassessed and adjusted if necessary. See Section 9.2.2 for information about ivacaftor doses.

Subjects will be outpatients; study visits will occur as follows:

- For subjects from Study 124 Part B: Day 1 and Weeks 12, 24, 36, 48, 60, 72, 84, and 96.
- For subjects not from Study 124 Part B: Day 1 and Weeks 2, 4, 8, 12, 18, 24, 36, 48, 60, 72, 84, and 96; a telephone contact will occur at Day 3.

Treatment Period assessments are listed in Table 3-1 and Table 3-2 for subjects from Study 124 Part B and in Table 3-3 for subjects not from Study 124 Part B.

9.1.1.2.1 Transition from Study 124 Part B to Day 1 of Study 126

All subjects must sign the ICF before any Study 126-related assessments. Subjects from Study 124 Part B can transition into Study 126 as follows:

- **Same-day Transition:** If the Day 1 Visit is the same day as the Week 24 Visit of Study 124 Part B, the subject will not have to perform any Day 1 assessments that were performed at the Week 24 Visit of Study 124 Part B (Table 3-1).
- **Gap Transition:** If the Day 1 Visit is NOT the same day as the last study visit of Study 124 Part B, all Day 1 assessments will need to be performed (Table 3-2), with the possible exception of the following:
    - Clinical laboratory assessments: Results must be reviewed and eligibility confirmed before dosing on Day 1.
        - If the Day 1 Visit is conducted ≤9 days after the last study visit of Study 124 Part B, the serum chemistry and hematology assessments performed at the last study visit of Study 124 Part B will not need to be repeated.

- If the Day 1 Visit is conducted >9 days after the last study visit of Study 124 Part B, the serum chemistry and hematology assessments must be repeated on Day 1, and the results must be reviewed and eligibility confirmed before the first dose of study drug.

- OE: If an OE was conducted in Study 124 Part B within 24 weeks of the Day 1 Visit, the Day 1 Visit OE does not need to be repeated. Otherwise, an OE must be conducted within 14 days of the Day 1 Visit. Throughout this study, these subjects should have OEs approximately every 24 weeks (± 14 days) from the last OE in Study 124.

9.1.1.3 Ivacaftor Arm Safety Follow-up Visit (All Subjects)

There will be a Safety Follow-up Visit 4 weeks ± 7 days after the last dose of ivacaftor. The Safety Follow-up Visit is not required if the Early Termination of Treatment (ETT) Visit occurs 3 weeks or later after the last dose of ivacaftor or if the subject begins treatment with commercially available ivacaftor.

Safety Follow-up assessments are listed in Table 3-1 and Table 3-2 for subjects from Study 124 Part B and Table 3-3 for subjects not from Study 124 Part B.

9.1.1.4 Ivacaftor Arm Follow-up Ophthalmologic Examination (All Subjects)

There will be a Follow-up OE 24 weeks + 14 days after the last dose of ivacaftor for all subjects.

9.1.1.5 Ivacaftor Arm Early Termination of Treatment (All Subjects)

Subjects who prematurely discontinue treatment before their last scheduled dose will be required to complete the ETT Visit, Safety Follow-up Visit, and Follow-up OE. The ETT Visit must be completed as soon as possible after the last dose of ivacaftor. If the ETT Visit occurs 3 weeks or later after the last dose of ivacaftor, the Safety Follow-up Visit will not be required.

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

If the subject withdraws consent for the study, no further evaluations should be performed and no additional data should be collected. Vertex may retain and continue to use any data collected before such withdrawal of consent.

ETT assessments are listed in Table 3-1 and Table 3-2 for subjects from Study 124 Part B and Table 3-3 for subjects not from Study 124 Part B.

9.1.2 Observational Arm

9.1.3 Observational Arm Day 1 Visit

The Day 1 Visit can be on the same day as the last study visit of Study 124 Part B (see Table 3-4). Demographics and baseline characteristics will be taken from the most recent Study 124 Part B visit from which these data are available.

9.1.4 Observational Arm Ophthalmologic Examination

An OE will be conducted approximately 24 weeks after the last dose of ivacaftor in Study 124 Part B, unless an OE was already conducted approximately 24 weeks after the last dose of ivacaftor in Study 124 Part B.

9.1.4.1 Observational Arm Long-term Follow-up

Subjects who received at least 4 weeks of study drug in Study 124 Part B will be followed for 96 weeks; telephone contact will be made at Week 48 (± **7** Days) and Week 96 (± **7** Days).

9.1.4.2 Observational Arm Early Discontinuation

Subjects who receive commercially available ivacaftor will be discontinued from the observational arm after completing the observational arm OE (Section 9.1.4).

9.1.5 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 12.3.5). 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 subject is screened.

9.2 Rationale for Study Design and Study Drug Regimens

9.2.1 Study Design

Based on the mechanism of action of ivacaftor and available data indicating that the CFTR-potentiating effects of ivacaftor stop when ivacaftor treatment is discontinued, it is likely that ivacaftor will be a chronic treatment for patients with CF. Given the study objectives of generating data about long-term safety and providing data to complement existing efficacy studies in subjects having *CFTR* gating mutations, an open-label study of extended duration provides the best way to provide as many patients as possible potentially beneficial therapy while providing necessary monitoring to ensure safety. The 96-week duration of the ivacaftor arm of this study allows for the evaluation of the long-term safety and PD of ivacaftor treatment, as well as an exploration of the efficacy of long-term ivacaftor treatment in subjects <24 months of age at treatment initiation.

Subjects who completed Study 124 Part B will be eligible for enrollment. To increase the study sample size, subjects who did not participate in Study 124 Part B (subjects who participated in Study 124 Part A only, or subjects who did not participate in Study 124) and are <24 months of age at the Day 1 Visit in Study 126 are also eligible for enrollment.

The Observational Arm will evaluate the ocular safety following ivacaftor treatment and the potential for long-term, off-treatment effects in subjects who received ≥4 weeks of ivacaftor in Study 124 Part B.

9.2.2 Study Drug Dose and Duration

The same population pharmacokinetic (PK) approach used for selection of doses in subjects 2 to <6 years of age in Study VX11-770-108 (Study 108) was used for dose selection in subjects <24 months of age. In the population PK model, body weight represents changes in ivacaftor PK as a function of body size by incorporation of an allometric model. Simulations performed using the population PK model supported a dose of 50 mg q12h for subjects with a body weight <14 kg and 75 mg q12h for subjects with a body weight ≥14 kg in Study 108. At the conclusion of Study 108, PK data obtained from subjects 2 to <6 years of age were included in the most recent population PK model. Body weight is the most important predictor of ivacaftor disposition, with an ivacaftor apparent clearance (CL/F) of 39% and 131% of the reference 70-kg subject for the typical 20-kg and 100-kg subjects, respectively.[52]

Using the current model, simulations were performed to provide different weight strata for doses of ivacaftor. The simulations incorporated a maturation function to determine the range of likely exposures given the maturational changes in clearance (CL). Because 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% and 80% from adult values for a newborn, and CL reached a mature value between 12 and 18 months. The maximum changes in CL and maturation rate are consistent with the differences in CYP3A4 expression in infants.[53, 54]

The simulations support selection of the following doses for CF subjects <24 months of age: 25 mg for ≥5.0 to <7 kg, 50 mg for ≥7 to <14 kg, and 75 mg for ≥14 to <25 kg. These doses may be modified in the future based on available PK data and may result in additional doses or different age and/or weight strata.

Data from Studies 124 and 126 and any updated modeling approaches resulting from such data may result in updated dose recommendations. Changes to study drug dose, age strata or weight bounds will be communicated to site personnel through a memorandum entitled "Justification for Dose Selection" to ensure clarity and consistency in study conduct.

Once a subject reaches 24 months of age, ivacaftor will be dosed at 50 mg q12h for subjects <14 kg and 75 mg q12h for subjects ≥14 kg, in accordance with the approved recommended dosages for commercially available ivacaftor.

9.2.3 Rationale for Study Assessments

The safety 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.

OEs are included in this study because a juvenile toxicity study conducted in albino rats to support clinical studies of ivacaftor in children <2 years of age demonstrated the presence of cataracts (lens opacities) when newborn rats were dosed with ivacaftor beginning at postnatal day (PND) 7 through PND 35, particularly at the highest dose tested. The results of chronic toxicity studies in the rat and dog did not reveal a cataractogenic potential. Although the relevance of this finding to humans is unknown, subjects will undergo an OE at the time points indicated in Table 3-1, Table 3-2, Table 3-3, and Table 3-4 to monitor the potential risk of cataracts (lens opacities).

The efficacy assessments were evaluated in Study 124 and are included in this study to evaluate the long-term effects of ivacaftor treatment. The efficacy assessments are widely accepted and are 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 before the sweat reaches the surface of the skin. Because patients with CF have diminished CFTR activity, chloride ions are poorly reabsorbed, leading to elevated sweat chloride concentration.[55, 56] Sweat chloride can be measured in patients with CF of all ages, although levels do increase throughout the first 6 months of life.[57]

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.

Measures of nutritional status: Poor somatic growth and poor nutritional status are common in patients with CF owing to a number of factors, including increased energy expenditures and appetite suppression due to lung disease as well as diabetes and pancreatic insufficiency-related fat malabsorption.[44] Growth deficiencies in children as young as 2 years of age are associated with worsening lung function and are also independent predictors of mortality in children with CF.[58] Furthermore, growth deficiencies at 4 months of age are most predictive of later growth deficiencies.[29]

While it is unknown if poor weight gain predicts clinical lung disease or whether progressive lung disease leads to poor weight gain, change in weight is a clinically relevant endpoint. Given that ivacaftor is a systemic therapy, it has the potential to improve extrapulmonary manifestations of CF. Modulation of CFTR function in the pancreas and gastrointestinal tract may lead to improvements in digestion and, consequently, weight gain.

In Phase 3 Studies 102 and 103, the improvement in mean weight gain after 24 weeks of ivacaftor versus placebo treatment was substantial, clinically meaningful, and statistically significant in subjects ≥12 years of age (Study 102) and 6 to 11 years of age, inclusive (Study 103). In open-label Phase 3 Study 108, conducted in subjects 2 through 5 years of age, substantial improvements in nutritional status with ivacaftor treatment were observed for weight, weight-for-age z-scores, BMI, and BMI-for-age z-scores; these improvements continued to Week 24.

As children gain weight as part of normal growth, adjustment for age and sex is necessary to assess changes in nutritional status in a population of boys and girls in varying stages of growth. To evaluate the effect of ivacaftor on growth and nutrition adjusted for age and sex, weight-for-age, length-for-age, weight-for-length-for-age, and BMI-for-age z-scores will be determined.

Qualitative microbiology cultures: Microbiological endpoints, such as bacterial colony counts and selection of resistant bacterial strains, are well-established endpoints used to evaluate antimicrobial therapies in CF.[35, 59, 60] Because compounds such as ivacaftor that restore CFTR function may increase hydration of airway secretions and lead to a decrease in acquisition of bacteria in the CF airway, acquisition of bacteria is included as a tertiary endpoint in this study. Because the majority of subjects <24 months of age do not expectorate spontaneously, oropharyngeal swabs will be used to obtain airway cultures in this study.

Pulmonary exacerbations and CF-related hospitalizations: Pulmonary exacerbations are used to assess efficacy in therapies targeting improvement in CF disease.[61, 62] These events have been associated with the severity and rate of progression of lung disease in patients with CF. To date, however, there is no generally accepted objective definition of an exacerbation,[63] and large multicenter CF clinical studies have used many variations of physician-derived definitions[64-68] in patients 6 years of age and older. Despite the lack of a standard definition, reduction in exacerbation rate has served as a key clinical efficacy measure in definitive CF clinical studies, supporting the registration of 2 chronic CF pulmonary therapies.[65, 67] Definitions for pulmonary exacerbation in subjects <24 months of age are being evaluated in ongoing studies of CF therapies,[69] but they have not yet been validated for use in clinical studies involving subjects of

this age. In this study, pulmonary exacerbation has been defined based on modification of criteria used in previous and ongoing trials in young children with CF, and occurrence will be derived based on both primary and alternative definitions. In addition, data on CF-related hospital admissions will be collected to assess the rate of these clinically significant events.

Measures of pancreatic function: Fecal elastase-1 is used clinically to diagnose pancreatic exocrine insufficiency in patients with CF. The increasing use of fecal elastase-1 in the clinic is a result of the relative ease of collecting samples for its assessment and the establishment of diagnostic cut-offs for pancreatic exocrine function.[70-73] Therefore, fecal elastase-1 represents a feasible measure to evaluate exocrine pancreatic function after treatment in this study. In open-label Phase 3 Study 108 conducted in subjects 2 through 5 years of age, substantial increases from baseline in fecal elastase-1 were observed at Week 24.[50] These results suggest an improvement in pancreatic function with ivacaftor treatment.

Markers of intestinal inflammation: Fecal samples will be collected to investigate biomarkers related to intestinal inflammation in CF patients, including but not limited to fecal calprotectin. Fecal calprotectin has been shown to be increased in pediatric patients with CF.[74] These data support the concept that intestinal inflammation is a feature of CF, and that intestinal inflammation can be monitored by measuring noninvasive biomarkers such as fecal calprotectin in clinical studies with CF patients.

Multiple breath washout (MBW) for LCI values: LCI is a measure of ventilation inhomogeneity derived from MBW assessment that is based on tidal breathing techniques that have been evaluated in patients as young as infants.[75, 76] This assessment will explore the value of MBW in the diagnosis of early changes in lung function in infants with CF (see Section 11.5.6).

9.3 Study Restrictions

9.3.1 Prior and Concomitant Medications

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 from Study 124 Part B: from Day 1 through the Safety Follow-up Visit (Section 9.1.1.3)
- For subjects not from Study 124 Part B: from 28 days before the Screening Visit through the Safety Follow-up Visit (Section 9.1.1.3)

For any subjects who are screened but are not enrolled in the study, details of prior and concomitant medications will only be documented in the subject’s source documents.

For subjects in the ivacaftor arm, 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.

9.3.2 Prohibited Medications/Dietary Restrictions

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.

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 or authorized designee.

9.4 Study Drug Dosage and Administration

The starting dose will be 25, 50, or 75 mg ivacaftor granules, or another suitable dose (to be determined based on safety and PK data from Study 124 Parts A and B, age, and weight; see Section 9.2.2). At each clinic visit, the ivacaftor dose for each subject will be reassessed based on body weight and adjusted if necessary.

Once a subject reaches 24 months of age, ivacaftor will be dosed at 50 mg q12h for subjects with a body weight <14 kg and 75 mg q12h for subjects with a body weight ≥14 kg, in accordance with the approved recommended dosages for commercially available ivacaftor.

For subjects not from Study 124 Part B, the first dose of ivacaftor will be administered in the clinic, and subjects will be observed for 4 hours after dose administration.

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 from Day 1 through Week 96. Details of dose preparation and dose administration will be provided in the study manual.

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 the 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.

At the Day 1 and Week 2, 4, 8, 12, 18, and 24 Visits, the time of administration of ivacaftor in the clinic on the day of the visit will be recorded.

9.5 Dose Modification for Toxicity

The investigator must not adjust the study drug dose for toxicity.

9.6 Study Drug Interruptions

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 on interruption for elevated LFT levels are provided in Section 11.6.2.

9.7 Removal of Subjects

Subjects may withdraw from the study at any time at their own request. 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, Safety Follow-up, and OE Follow-up Visits, as indicated in Sections 9.1.1.3 and 9.1.1.5, 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 Safety Follow-up Visit, if applicable (see Section 9.1.1.5), and follow up with the subject's parent or legal guardian regarding any unresolved adverse events (AEs).

If the subject's parent or legal guardian withdraws consent for the study, 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 IRB or ethics committee (EC) closes the study.
- A subject is noncompliant with study protocol requirements, restrictions, and instructions to an extent that is considered unacceptable by the investigator or Vertex medical monitor.
- A subject participates in another interventional clinical study.
- A subject develops a new lens opacity or cataract (see Section 11.6.5).

A subject **may be** discontinued from 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 has an increase in liver function test levels (LFTs; e.g., AST or ALT levels) as described in Section 11.6.2.
- Clinically significant findings are observed in the slit-lamp examination.

During the course of the study, if ivacaftor is approved and available for the treatment of CF in populations enrolled in this study, subjects may be discontinued at the discretion of the sponsor. If a subject is switching to commercially available ivacaftor, the ETT Visit (Section 9.1.1.5) will be completed before dosing with commercial drug begins, and the Safety Follow-up Visit will not be required.

Alternatively, if local health authorities decline to approve ivacaftor, or if ivacaftor cannot be given to patients within a given age cohort (e.g., an appropriate dose cannot be determined), then subjects of the relevant populations may be discontinued after communication to investigators and IRBs/IECs of the benefits/risks for the relevant subject population. If subjects are discontinued from the study, an ETT Visit should occur as soon as possible after the last dose of study drug and a Safety Follow-up Visit should occur within 4 weeks (± 7 days) after the last dose of study drug.

9.8 Replacement of Subjects

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

10 STUDY DRUG INFORMATION AND MANAGEMENT

10.1 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.

10.2 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.

10.3 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 10.4.

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.

10.4 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’ parents or legal guardians 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.

10.5 Disposal, Return, or Retention of Unused Drug

The study site staff or pharmacy personnel will retain all materials returned by the subjects’ parents or legal guardians 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.

10.6 Compliance

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

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

10.7 Blinding and Unblinding

This will be an open-label study.

11 ASSESSMENTS

11.1 Timing of Assessments

The timing of assessments for the ivacaftor arm is shown in:

- Table 3-1: subjects from Study 124 Part B who have a Same-day Transition (Section 9.1.1.2.1)
- Table 3-2: subjects from Study 124 Part B who have a Gap Transition (Section 9.1.1.2.1)
- Table 3-3: subjects from Study 124 Part A or subjects not from Study 124 Parts A or B

The timing of assessments for the observational arm is shown in Table 3-4.

11.2 Subject and Disease Characteristics

For subjects transitioning from Study 124 Part B, demographics, medical history, and historical data will be taken from Study 124. For all other subjects, demographics, medical history, length, weight, and the additional historical data described below will be collected before (e.g., at screening) or at Day 1.

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) length and weight measurements
- The dates and reasons for all CF-related hospitalizations
- Any use (yes or no) of the following medications: inhaled tobramycin, inhaled aztreonam, inhaled colimycin, inhaled hypertonic saline, dornase alfa, ibuprofen, azithromycin, and pancreatic enzyme replacement therapy
- Historical pancreatic status measurements (prior fecal elastase-1 assessments)

11.3 Pharmacokinetics

Not applicable.

11.4 Pharmacodynamics (Ivacaftor Arm Only)

11.4.1 Sweat Chloride

Collection of sweat chloride samples will be performed at qualified study sites using an approved Macroduct® (Wescor, Logan, UT) collection device. Sweat chloride samples will be sent to a central laboratory for testing and interpretation of results. Individual sweat chloride test results will not be disclosed to the study sites. Specific instructions for the collection, handling,

processing, and shipping of sweat chloride samples to the central laboratory will be provided separately.

The sweat chloride test at the Day 1 Visit must be performed before the ivacaftor dose. Baseline sweat chloride test is not required at Day 1 if it was completed at screening. At subsequent visits through Week 24, the sweat chloride test must be performed within a window of ± 2 hours relative to the ivacaftor dose. After the Week 24 Visit, the sweat chloride test may be performed at any time during the visit. Change from baseline in sweat chloride will be analyzed as a secondary endpoint in this study.

11.5 Efficacy and Exploratory Assessments (Ivacaftor Arm Only)

11.5.1 Measures of Nutritional Status

Length and weight must be measured with the subject in a dry diaper or dry underclothes only. Length should be measured throughout the study while the subject is lying supine by measuring from the crown of the head to the bottom of the feet with the hips and legs straightened. Change from baseline in weight, length, weight-for-length, weight-for-age z-score, length-for-age z-score, weight-for-length-for-age z-score, BMI, and BMI-for-age z-score will be analyzed as a tertiary endpoint in this study.

11.5.2 Qualitative Microbiology Cultures

A cotton-tipped swab will be used to collect the microbiology specimen from the posterior oropharyngeal wall and tonsillar pillars. Specific instructions for the collection, processing, and shipment of samples will be provided in a separate Laboratory Manual.

11.5.3 Pulmonary Exacerbations

The incidence of pulmonary exacerbations will be recorded. For this study, given the absence of a consensus definition for pulmonary exacerbation in clinical studies in this population, 2 definitions will be applied to the signs and symptoms shown below for analyses of pulmonary exacerbations:

Definition 1: Treatment with oral, inhaled, or intravenous (IV) antibiotics **AND** fulfillment of 1 or more of the criteria from List A or List B, within 3 days before antibiotic start date through antibiotic stop date.

Definition 2: Treatment with oral, inhaled, or IV antibiotics **AND** fulfillment of 1 criterion from List A or 2 criteria from List B, within the period 3 days before antibiotic start date through antibiotic stop date.[77]

The occurrence of any new or changed antibiotic therapy (IV, inhaled, oral) and the presence of the following signs and symptoms will be collected:

List A:

- Oxygen saturation <90% on room air or ≥5% decrease from baseline
- New lobar infiltrate(s) or atelectasis on chest x-ray
- Hemoptysis (more than streaks on more than 1 occasion in the past week)

List B:

- Increased work of breathing or respiratory rate (duration ≥3 days)

- New or increased adventitial sounds on lung exam (duration ≥3 days)
- Weight loss of ≥5% from the highest value or decrease across 1 major percentile for age in the past 6 months
- Increased cough (duration ≥3 days)
- Worked harder to breathe during physical activity (duration ≥3 days)
- Increased chest congestion or change in sputum (duration ≥3 days)

11.5.4 CF-related Hospitalizations

Subject's parents/caregivers will be queried about CF-related hospitalizations. The dates and reasons for the CF-related hospitalizations will be collected.

11.5.5 Markers of Intestinal Inflammation

Fecal samples for assessment of fecal elastase-1, fecal calprotectin, and other markers of intestinal inflammation will be collected.

11.5.6 Multiple Breath Washout

MBW is optional and will only be performed on subjects for whom additional or separate informed consent was obtained. Also, MBW will only be performed at sites that are adequately trained and qualified and are equipped with a mass spectrometry MBW system. Therefore, only a subset of subjects will undergo MBW assessment. However, subjects from other sites may be referred to the sites that have capability to perform MBW. Detailed procedures for the MBW will be supplied in a separate study manual.

11.6 Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, 12-lead ECGs, physical examinations (PEs; with clinically significant abnormalities recorded as medical history or adverse events), and OEs.

11.6.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with ICH GCP guidelines. Section 13.1 outlines the definitions; collection periods; criteria; and procedures for documenting, grading, and reporting AEs. A separate document that details AE CRF completion guidelines for investigators as well as training will be provided.

11.6.2 Clinical Laboratory Assessments (Ivacaftor Arm Only)

Blood samples for clinical laboratory assessments will be analyzed at a central laboratory. Local laboratories may be used at the discretion of the local investigator for management of urgent medical issues. If a local laboratory test value is found to be abnormal and clinically significant, it will be verified by the central laboratory as soon as possible after the investigator becomes aware of the abnormal result. The Vertex medical monitor or authorized designee should be notified. 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 will be reported as AEs (see Section 13.1).

The safety laboratory test panels are shown in Table 11-1.

Table 11-1 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	Lymphocytes
Alanine transaminase	Monocytes
Lactate dehydrogenase	
Gamma-glutamyl transferase	
Protein	
Albumin	
Amylase	
Lipase	

Note: Screening Visit blood draws will be done after a minimum 4-hour fast. All subsequent blood draws do not require fasting.

***CFTR* Genotype**:

Subjects must have an approved ivacaftor-responsive mutation on at least 1 allele to meet inclusion criteria (see study manual and approved country/region ivacaftor label). The genotype results must be available before the first dose of study drug is administered to the subject. Subjects who had *CFTR* genotyping completed in Study 124 will not require repeat testing upon entry into this study.

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.

Subjects will not receive the study drug if *CFTR* genotype is not confirmed by a historic genotype result OR by genotype testing at screening.

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 levels 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 for 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 9.7). 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 any 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.

11.6.3 Physical Examinations and Vital Signs (Ivacaftor Arm Only)

A PE of all body systems and vital signs assessment will be performed at screening and select study visits. At other visits, symptom-directed PEs and symptom-directed vital sign assessments can be performed at the discretion of the investigator or health care provider.

A PE includes a review of the following systems: head/neck/thyroid; eyes/ears/nose/throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and

neurological. Anorectal and genital examinations will be performed when medically indicated. After screening, any clinically significant abnormal findings in PEs will be reported as AEs.

The abbreviated PE 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, respiratory rate, and pulse oximetry. The subject will be instructed to rest in the supine position (if possible) for at least 5 minutes before vital signs are assessed. The temperature must be obtained by the same method throughout the study.

11.6.4 Electrocardiograms (Ivacaftor Arm Only)

Standard 12-lead ECGs will be performed using a machine with printout. 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 will rest in the supine position for at least 5 minutes, if possible, before having an ECG performed.
- The ECG will be performed predose through the Week 24 Visit before any other procedures that may affect heart rate, such as blood draws. Following the Week 24 Visit, ECGs may be taken pre- or post-dose.

The ECG traces will be manually read at the study site at the Screening Visit and Safety Follow-up Visit. A printout of the ECG traces will be made for safety review by the investigator and maintained with source documentation. Clinically significant ECG abnormalities occurring during the study through the Safety Follow-up Visit will be recorded as AEs.

Study sites should use QTcF unless they receive approval in advance from the Vertex medical monitor or authorized designee to use QTcB.

To ensure safety of the subjects, a qualified individual at the study site will make comparisons to baseline measurements. If the QTcF is increased by >60 msec from the baseline or an absolute QTcF value is ≥500 msec for any scheduled ECG, 2 additional ECGs will be performed approximately 2 to 4 minutes apart to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (>60 msec from baseline or ≥500 msec), a single ECG will be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. A subject with a QTcF value above the threshold value will discontinue dosing.

11.6.5 Ophthalmologic Examinations

All subjects should have an OE approximately every 24 weeks while on ivacaftor treatment in this study. Subjects who did not participate in Study 124 Part B should have an additional OE exam at Week 12. The OE must be conducted by a licensed ophthalmologist, preferably a pediatric ophthalmologist. Whenever possible, the same ophthalmologist should perform the OEs throughout the study. The OE will include the following:

- Examination of the lens with a slit-lamp (portable or otherwise; pharmacologically dilated examination)
- Assessment of the red reflex (pharmacologically dilated examination)

- Screening OEs (subjects not from Study 124 Part B only): examination of the fundus (retina, optic nerve, and vessels), pupils, and eye movements

For subjects not from Study 124, relevant medical history (e.g., history of steroid use; history of trauma to the eye; and family history of glaucoma, congenital cataracts, or cataracts arising later in life) will be collected at screening. For subjects from Study 124 Part B with a Same-day Transition, the above relevant ophthalmological medical history will be collected in Study 124. For subjects from Study 124 Part B with a Gap Transition, the above relevant ophthalmological history will be collected before or at the Day 1 Visit.

During the screening period, if an adequate slit-lamp examination cannot be conducted, subjects will not be enrolled until an adequate repeat slit-lamp examination is completed (Sections 9.1.1.1.1 and 9.1.1.1.3) and eligibility criteria regarding the ophthalmologic findings are met.

If a new lens opacity or cataract is identified at any OE in subjects in the ivacaftor arm, study drug dosing must be discontinued. The-Vertex medical monitor should also be notified.

12 STATISTICAL AND ANALYTICAL PLANS

Analysis of all data will be performed by Vertex (or designee).

A detailed analysis plan for the analysis of safety and efficacy data will be presented in a statistical analysis plan (SAP). As the study design is open label, a draft SAP for the final analysis will be available before the first subject is dosed; the SAP will be approved before data lock.

12.1 Sample Size and Power

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

12.2 Analysis Sets

The All Subjects Set (defined as all enrolled subjects) will be used to summarize the disposition table and listings. The Safety Set (defined as enrolled subjects who receive at least 1 dose of ivacaftor in Study 126) will be used for all safety analyses. The Full Analysis Set (FAS) (defined as enrolled subjects who have at least 1 postbaseline efficacy assessment in Study 126) will be used for all efficacy analyses.

12.3 Statistical Analysis

Data from all endpoints will be summarized using descriptive statistics and presented by subjects from Study 124 Part B/subjects not from Study 124 Part B, and by study visit. No inferential analyses are planned.

12.3.1 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 using descriptive statistics.

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

Listings will display all subjects who were enrolled or dosed.

Definition of the baseline value: There are 2 baselines, the baseline from Study 124 Part B and the baseline in the current study.

The Study 124 Part B baseline value will be defined as the baseline measurement from Study 124 Part B. That is, the most recent non-missing measurement collected on or before the initial administration of study drug in Study 124 Part B will be the Study 124 Part B baseline. 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 Study 126 baseline value will be defined as the most recent non-missing measurement collected on or before the initial administration of study drug or enrollment in the observational arm, including both the scheduled and unscheduled measurements.

The absolute change from baseline value will be defined as the postbaseline value minus the baseline value.

For subjects from Study 124 Part B with a Same-day Transition (Section 9.1.1.2.1), absolute change will be determined from Study 124 Part B baseline and Study 126 baseline. For subjects from Study 124 Part B with a Gap Transition (Section 9.1.1.2.1), absolute change will be determined from Study 126 baseline.

For subjects who did not participate in Study 124 Part B (e.g., subjects from Study 124 Part A or subjects not from Study 124), absolute change will be determined from Study 126 baseline.

The definitions will apply to all analysis variables: demographics, medical history (including prior and concomitant medications), baseline characteristics, efficacy, and safety, unless otherwise specified.

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

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

- Enrolled
- Enrolled and dosed (Safety Set)
- Observational arm
- Last treatment visit completed
- Prematurely discontinued the study during the Treatment Period and the reasons for discontinuations

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

12.3.2.2 Demographics and Baseline Characteristics

Demographic background (e.g., medical history) and baseline characteristics (Study 124 Part B baseline or current study baseline) will be summarized. No statistical tests will be carried out to evaluate any baseline imbalance between dose groups.

For subjects from Study 124 Part B with a Same-day Transition, medical history (including prior and concomitant medications) will be taken from Study 124. For subjects from Study 124 Part B with a Gap Transition and subjects not from Study 124 Part B, medical history (including prior and concomitant medications) will be taken before (e.g., during screening) or at Day 1.

12.3.2.3 Prior and Concomitant Medications (Ivacaftor Arm Only)

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 as frequency tables in 2 parts:

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

If medication start date is at or after the date of the first dosing of ivacaftor in Study 126, 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 the first dosing of ivacaftor in Study 126, then the medication will be summarized as prior medication regardless of whether the medication start date is missing or not. Note that medication that is started before the first dosing of ivacaftor in Study 126 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.

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.

12.3.2.4 Study Drug Exposure and Compliance (Ivacaftor Arm Only)

Exposure to ivacaftor (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 ivacaftor 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.

12.3.3 Efficacy Analysis (Ivacaftor Arm Only)

12.3.3.1 Analysis of Primary Variables

Not applicable (see Section 12.3.4).

12.3.3.2 Analysis of Secondary Variables

Sweat chloride results (including changes from baseline) will be summarized by either treatment duration or time on study and presented by treatment group (subjects from Study 124 Part B and subjects not from Study 124 Part B).

12.3.3.3 Analysis of Tertiary Variables

- Weight
- Length
- Weight-for-length
- Weight-for-age z-score
- Length-for-age z-score
- Weight-for-length-for-age z-score
- BMI
- BMI-for-age z-score

Data (including changes from baseline) will be summarized by either treatment duration or time on study and presented by treatment group (subjects from Study 124 Part B and subjects not from Study 124 Part B).

Weight, length, and weight-for-length, adjusted for sex and age, will be summarized as weight-for-age z-score, length-for-age z-score, and weight-for-length z-score, respectively. Z-scores will be calculated using the Nutrition Examination Survey (NCHS) Growth Chart Equations for children and adolescents 0 to 48 months of age.[78]

- LCI (including changes from baseline) will be summarized by either treatment duration or time on study and presented by treatment for subjects who had their LCIs evaluated.
- Measure of pancreatic function (fecal elastase-1): This parameter will be summarized descriptively as a continuous parameter, and results (including changes from baseline) will be summarized by either treatment duration or time on study and presented by treatment.
- Markers of intestinal inflammation (e.g., fecal calprotectin): This parameter will be summarized descriptively as a continuous parameter, and results (including changes from baseline) will be summarized by either treatment duration or time on study and presented by treatment.
- Qualitative microbiology cultures: The presence of bacteria will be descriptively summarized by subject counts and percentages by visit and treatment. Shifts from baseline may be presented, as appropriate.
- Pulmonary exacerbations: Pulmonary exacerbations will be identified using the definitions provided in Section 11.5.3 and will be analyzed in 3 ways:
    - The number of pulmonary exacerbations will be normalized to an annual period to adjust for differences in time spent on study and summarized as a continuous variable using descriptive summary statistics and presented by treatment.

- The number of days with pulmonary exacerbations (cumulative duration) will be normalized to an annual period to adjust for differences in time spent on study and summarized as a continuous variable using descriptive summary statistics and presented by treatment.
- The time-to-first pulmonary exacerbation will be analyzed using the Kaplan-Meier method (provided the number of subjects with events observed is adequate) and the event-free rate presented by treatment.

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

12.3.4 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:

- Treatment-emergent adverse event (TEAEs)
- Clinical laboratory results (serum chemistry and hematology)
- ECG outcomes
- PEs (clinically significant abnormalities recorded as medical history or adverse events)
- Vital signs (systolic blood pressure, diastolic blood pressure, temperature, pulse rate, and respiratory rate)
- OEs

TEAEs are the key safety assessment and will be assessed overall. Descriptive analysis of other safety endpoints will be performed; raw values, changes from baseline, shifts-from-baseline, and clinical abnormalities will be summarized for other endpoints.

12.3.4.1 Adverse Events

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

- 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.

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

Pretreatment AEs are defined as AEs that were reported or worsened after signing the ICF up to the start of study drug dosing.

Treatment-emergent AEs are defined as AEs that were reported or worsened on or after the start of study drug dosing through the the end of participation (as applicable) in this study.

Only TEAEs will be summarized in tables. All summaries of TEAEs will be presented by the severity of the AE and relationship to the study drug. Some rules that will apply to the summarization of AEs are as follows: (1) a subject with multiple occurrences of the same AE or a continuing AE will only be counted once; (2) only the maximum severity level will be presented in the severity summary; and (3) only the worst relationship level will be presented in the relationship summary.

AEs leading to death, SAEs, dose interruption, and permanent discontinuation will be listed separately. All AEs through the Safety Follow-up Visit will be listed in an individual subject data listing, including pretreatment AEs.

12.3.4.2 Clinical Laboratory Assessments (Ivacaftor Arm Only)

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. Changes from baseline will also be summarized.

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.

12.3.4.3 Electrocardiogram (Ivacaftor Arm Only)

Continuous ECG measurements will be summarized by visit and treatment. 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 QTcF intervals will be presented.

12.3.4.4 Vital Signs (Ivacaftor Arm Only)

The following vital signs will be summarized by visit and treatment: systolic and diastolic blood pressure (mm Hg), temperature (°C), pulse oximetry (%), heart rate (beats per minute), and respiratory rate (breaths per minute). Changes from baseline will also be summarized.

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

12.3.4.5 Physical Examination (Ivacaftor Arm Only)

PE results will be presented in individual subject data listings only. Clinically relevant results identified after screening will be reported as AEs.

12.3.4.6 Ophthalmological Examination

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

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

Results of OEs (incidence of cataracts) will be summarized as a categorical variable and presented by treatment.

Red reflex will be analyzed as continuous variables using descriptive summary statistics and presented by visit and treatment.

12.3.5 Interim and IDMC Analyses

12.3.5.1 Interim Analysis

Interim analyses for regulatory or operational purposes may be performed.

12.3.5.2 IDMC Analysis

Details of the IDMC (Section 9.1.5) analyses will be provided in the IDMC Analysis Plan.

12.3.6 Pharmacokinetic Analysis

Not applicable.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

An AE 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 ICF is signed.

An AE is considered serious if it meets the definition in Section 13.1.2.1.

13.1.1.2 Clinically Significant Assessments

Study assessments including laboratory tests, ECGs, PEs, and vital signs will be assessed, and those deemed to have clinically significant worsening from baseline will be documented as an AE. 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 AE (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 subject's clinical status indicates a life-threatening AE.

13.1.1.3 Documentation of Adverse Events

All AEs 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 enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit, with the exception of ocular adverse events noted during the Follow-up OE
- For enrolled subjects who do not have a Safety Follow-up Visit: the earliest of 4 weeks ± 7 days after the last dose of study drug, or the ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (see Section 9.1.1.5)

All subjects will be queried, using nonleading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms will be identified as 1 overall event or diagnosis. All AEs for enrolled subjects will be recorded in the CRF and source document. AEs 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 AE:

- 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(s)
- Action taken
- Outcome
- Concomitant medication or other treatment given

For the purposes of study analysis, if the event has not resolved at the end of the study reporting period (the Safety Follow-up Visit), it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the adverse event to symptom resolution or until the condition stabilizes.

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. 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 August 2015). In 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 given in the vaccine scale. The severity of an AE that does not appear in this scale will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

Classification	Definition
Mild (Grade 1)	Mild level of discomfort and does not interfere with regular activities
Moderate (Grade 2)	Moderate level of discomfort and significantly interferes with regular activities
Severe (Grade 3)	Significant level of discomfort and prevents regular activities
Life-threatening (Grade 4)	Any adverse drug event that places the subject, in the view of the investigator, at immediate risk of death

13.1.1.5 Adverse Event Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug(s). Causality will be classified using the categories presented in Table 13-2.

Table 13-2 Classifications for AE 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.
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).

13.1.1.6 Study Drug Action Taken

The investigator will classify the study drug action taken with regard to the AE. The action taken will be classified according to the categories shown in Table 13-3.

Table 13-3 Classifications for Study Drug Action Taken With Regard to an AE

Classification	Definition
Dose not changed	Study drug dose not changed in response to an AE
Dose reduced	Study drug dose reduced in response to an AE
Drug interrupted	Study drug administration interrupted in response to an AE
Drug withdrawn	Study drug administration permanently discontinued in response to an AE
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 AE began and no opportunity to decide whether to continue, interrupt, or withdraw treatment is possible.

13.1.1.7 Adverse Event Outcome

An AE 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 13-4.

Table 13-4 Classifications for Outcome of an AE

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

13.1.1.8 Treatment Given

The investigator ensures adequate medical care is provided to subjects for any AEs, including clinically significant laboratory values related to study drug. In addition, the investigator will describe whether any treatment was given for the AE. "Yes" is used if any treatment was given in response to an AE, and may include treatments such as other medications, hospitalization, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an AE.

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

An SAE is any AE 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 signed the ICF, and the hospitalization or procedure was planned before the subject signed the ICF, the hospitalization or procedure will not be considered to indicate an SAE, unless an AE 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 AE (e.g., social hospitalization for purposes of respite care) will 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.

13.1.2.2 Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent through the Safety Follow-up Visit, regardless of causality, will be reported by the investigator to Vertex Global Patient Safety (GPS). In addition, all SAEs that occur after the Safety Follow-up Visit and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours**.

SAEs 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(s) and possible etiologies. On the SAE Form, relationship to study drug(s) 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.

13.1.2.3 Reporting Serious Adverse Events

The investigator is responsible for notifying the sponsor within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational study drug. 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: globalpatientsafety@vrtx.com (preferred choice)

Fax: + 1-617-341-6159

Contact Telephone: + 1-617-341-6677

13.1.2.4 Expedited Reporting and Investigator Safety Letters

Vertex, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) 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 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.

13.2 Administrative Requirements

13.2.1 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, 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.

13.2.2 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 ICH GCP and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

13.2.3 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 the protocol will be fully documented in the source documentation and in a protocol deviation log.

13.2.4 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.

13.2.5 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.

13.2.6 Record Retention

The investigator will maintain all study records according to ICH 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.

13.2.7 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.

13.3 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.

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.

13.4 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.

13.5 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, AEs, 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.

13.6 Publications and Clinical Study Report

13.6.1 Publication of Study Results

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.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between Vertex and the investigator and/or the investigator's institution.

13.6.2 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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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX15-770-126	Version #: 2.0	Version Date: 05 October 2017
Study Title: A Phase 3, 2-Arm, Open-label Study to Evaluate the Safety and Pharmacodynamics of Long-term Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have an Approved Ivacaftor-Responsive Mutation		

This Clinical Study Protocol has been reviewed and approved by the sponsor.

Printed Name	Title
Signature	Date

15.2 Investigator Signature Page

Protocol #: VX15-770-126	Version #: 2.0	Version Date: 05 October 2017
Study Title: A Phase 3, 2-Arm, Open-label Study to Evaluate the Safety and Pharmacodynamics of Long-term Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age at Treatment Initiation and Have an Approved Ivacaftor-Responsive Mutation		

I have read Protocol VX15-770-126, Version 2.0, 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