1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

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

Vertex Study Number: VX14-661-110

[redacted]

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2 PROTOCOL SYNOPSIS

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

Brief Title A Study to Evaluate the Safety and Efficacy of Long-term Treatment With VX-661 in Combination With Ivacaftor in Subjects With Cystic Fibrosis Who Have an *F508del-CFTR* Mutation

Clinical Phase and Clinical Study Type Phase 3, safety and efficacy

Objectives

Primary Objective

Treatment Cohort

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

Secondary Objectives

Treatment Cohort

- To evaluate the long-term efficacy of VX-661 in combination with ivacaftor for subjects in the Treatment Cohort

Observational Cohort

- To evaluate the post-treatment safety of VX-661 in combination with ivacaftor for subjects in the Observational Cohort

Endpoints

Primary Endpoints

Treatment Cohort

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

Observational Cohort

Not applicable

Secondary Endpoints

Treatment Cohort

The following efficacy endpoints will be analyzed:

- Absolute change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$)
- Relative change from baseline in $ppFEV_1$
- Number of pulmonary exacerbations
- Absolute change from baseline in body mass index (BMI)
- Absolute change from baseline in BMI z-score for subjects aged <20 years
- Absolute change from baseline in Cystic Fibrosis Questionnaire–Revised

(CFQ-R) respiratory domain score

- Absolute change from baseline in body weight
- Absolute change from baseline in body weight z-score for subjects aged <20 years
- Absolute change from baseline in height z-score for subjects aged <20 years
- Time-to-first pulmonary exacerbation
- Pharmacokinetic (PK) parameters of VX-661, a VX-661 metabolite (M1-661), ivacaftor, and an ivacaftor metabolite (M1-ivacaftor)

Observational Cohort

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

[redacted]

Number of Subjects

Study VX14-661-110 is a rollover study that plans to enroll subjects from Studies VX13-661-103, VX14-661-106, VX14-661-107, VX14-661-108, VX14-661-109, VX14-661-111, and other eligible Vertex studies investigating VX-661 in combination with ivacaftor who meet the eligibility criteria for this study. Approximately up to 1375 subjects are potentially eligible to be enrolled from the following parent studies: 40 subjects from Study VX13-661-103, 490 subjects from Study VX14-661-106, 300 subjects from Study VX14-661-107, up to 300 subjects from Study VX14-661-108, up to 200 subjects from Study VX14-661-109, and 45 subjects from Study VX14-661-111.

Study Population

Treatment Cohort

Male and female subjects 12 years of age and older with CF who are homozygous or heterozygous for the *F508del-CFTR* mutation

Observational Cohort

Male and female subjects <18 years of age (age on the date of informed consent/assent in the parent study) with CF who are homozygous or heterozygous for the *F508del-CFTR* mutation

Investigational Drug

Treatment Cohort

Active substance: VX-661 and ivacaftor

Activity: CFTR corrector and potentiator (increased chloride ion [Cl^-] secretion)

Strength and Route of Administration: VX-661 100 mg/ivacaftor 150-mg fixed-dose combination (FDC) film-coated tablet for oral administration

Active substance: ivacaftor

Activity: CFTR potentiator (increased Cl^- secretion)

Strength and Route of Administration: ivacaftor 150-mg film-coated tablet for oral administration

Study Duration

Treatment Cohort

Study drug will be administered for approximately 96 weeks [with a Safety Follow-up Visit 28 days (± 7 days) after the last dose.

Observational Cohort

For the Observational Cohort, maximum subject participation will be approximately 2 years.

Study Design

This is a Phase 3, multicenter, open-label, rollover study in subjects with CF who are homozygous or heterozygous for the *F508del-CFTR* mutation and who participated in Studies VX13-661-103, VX14-661-106, VX14-661-107, VX14-661-108, VX14-661-109, VX14-661-111, VX15-661-112, VX16-661-114, or other Vertex studies investigating VX-661 in combination with ivacaftor. The study is designed to evaluate the safety and efficacy of long-term treatment of VX-661 in combination with ivacaftor.

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

While participating in the Treatment Cohort, if allowed by another Vertex study protocol, subjects may screen for the other Vertex study of investigational CFTR modulators (including clinical studies of Next Generation CFTR modulators, hereafter referred to as "another qualified Vertex study"), but are not permitted to screen for studies of lumacaftor in combination with ivacaftor and ivacaftor monotherapy.

Subjects who completed at least 4 weeks of treatment before discontinuing Study VX14-661-110 to participate in another qualified Vertex study, and who meet the eligibility criteria (Sections 9.1 and 9.2) will be offered the opportunity to re-enroll once in the Study VX14-661-110 Treatment Cohort. Subjects who re-enroll will resume treatment with VX-661/ivacaftor at the next study day after their previous treatment discontinuation in Study VX14-661-110. Subjects who discontinue Study VX14-661-110 more than once to participate in another qualified Vertex study may not re-enroll in Study VX14-661-110 a second time.

During the course of study conduct, if VX-661 in combination with ivacaftor is approved and available for the treatment of CF in populations enrolled in Study VX14-661-110, subjects with the approved *CFTR* genotypes may be discontinued from this rollover study at the discretion of the sponsor. If a subject is continuing onto commercially available VX-661/ivacaftor, the Early Treatment Termination Visit will be completed before dosing with commercial drug begins, and the Safety Follow-up Visit will not be required. Alternatively, if local health authorities decline to approve, or if clinical benefit is not demonstrated for the use of VX-661 in combination with ivacaftor for the treatment of CF in populations enrolled in Study VX14-661-110, subjects with the relevant *CFTR* genotypes may be discontinued after communication to investigators and IRBs/IECs of the risks/benefits related to the safety and efficacy observed for the subset of subjects. If subjects are discontinued from the study, an Early Treatment Termination Visit should occur within 7 days of the last dose of study drug.

Observational Cohort

Subjects <18 years of age (age on the date of informed consent/assent in the parent study) who received at least 4 weeks of study drug in the parent study, who are not eligible for the Treatment Cohort or who elect not to enroll in the

Treatment Cohort, and meet eligibility criteria will be offered the opportunity to enroll in the Observational Cohort.

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

Assessments

Treatment Cohort

Safety Assessments

AEs, ophthalmologic examinations (subjects <18 years of age [age on the date of informed consent/assent in the parent study]), clinical laboratory values (serum chemistry, hematology, coagulation, lipids, vitamins, and urinalysis), standard digital ECGs, vital signs, and pulse oximetry

Efficacy Assessments

Spirometry, weight, height, BMI, CFQ-R, [redacted] and documentation of other events related to outcomes (e.g., pulmonary exacerbations)

Pharmacokinetic Assessments

VX-661, M1-661, ivacaftor, and M1-ivacaftor

Observational Cohort

Related SAEs

[redacted]

Statistical Analyses

Statistical analysis details will be provided in the Statistical Analysis Plan (SAP), which will be finalized before the clinical data lock for the study.

The safety analysis will be performed on all subjects pooled together irrespective of their CFTR mutations. The efficacy analysis will be the secondary analysis and will be performed on each of the CFTR mutation groups separately (*F508del/F508del*, *F508del*/Residual Function, and *F508del*/Gating). The methods used for the efficacy analyses will be similar for those used in the parent studies. For example, the analysis for absolute change from baseline in ppFEV$_1$ will be based on a mixed-effect repeated-measure model (MMRM). Descriptive summary statistics will be provided for relevant safety and efficacy parameters. In addition, the least square (LS) mean and the associated 95% CI at each defined analysis visit will be provided for the efficacy parameters.

3 SCHEDULE OF ASSESSMENTS

The schedules of assessments are provided in Table 3-1 (Treatment Cohort) and Table 3-2 (Observational Cohort). Subjects who received at least 4 weeks of study drug in the Treatment Cohort, discontinued Study VX14-661-110 to participate in another Vertex study of investigational CFTR modulators that allows participation of subjects in Study VX14-661-110 (hereafter referred to as "another qualified Vertex study"), and who meet the eligibility criteria (Sections 9.1 and 9.2) will be offered the opportunity to re-enroll once in the Treatment Cohort of Study VX14-661-110.

3.1 Treatment Cohort

Table 3-1 Study VX14-661-110: Treatment Cohort

Event/Assessment[a]	Day –28 to Day -1	Treatment Period[b]						ETT Visit/ Departing Visit (Within 7 Days of Last Dose of Study Drug)[b,c,d,e]	Safety Follow-up Visit 28 (± 7) Days After Last Dose[c,d,e]
		Day 1[f]/ Returning Visit[b,g]	Day 15 (± 3 days)	Weeks 8, 16, 24, 36 (± 5 days)	Week 48 (± 5 days)	Weeks 60, 72, 84 (± 5 days)	Week 96 (± 5 days)		
Clinic visit		X	X	X	X	X	X	X	X

[a] All assessments will be performed before dosing unless noted otherwise.

[b] Selected visits may overlap with visits in the other qualified Vertex study: the Screening Visit of the other qualified Vertex study and a scheduled Treatment Period visit; the last required visit of the other qualified Vertex study and the Returning Visit; and the visit with the first dose of study drug in the other qualified Vertex study and the ETT Visit (refer to Section 8.1.1.1 and Section 8.1.1.3 for the timing/order of assessments in these cases).

[c] If the subject prematurely discontinues study treatment, an ETT Visit should be scheduled as soon as possible after the subject decides to terminate study treatment (Section 8.1.1.3). Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 (± 7) days after their last dose of study drug. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

[d] If a subject is continuing onto commercially available VX-661/ivacaftor, the ETT Visit (Section 8.1.1.3) will be completed before dosing with commercial drug begins, and the Safety Follow-up Visit (Section 8.1.1.2) will not be required.

[e] If a subject discontinues treatment to participate in another qualified Vertex study, the ETT Visit (Section 8.1.1.3) will be completed, and the Safety Follow-up Visit (Section 8.1.1.2) will not be required if the subject enrolls in the other study within 28 (± 7 days) days of the last dose of study drug in Study VX14-661-110.

[f] **Initial enrollment**: The Day 1 Visit of Study VX14-661-110 will be on the **same day** as the last scheduled visit of the parent study for subjects at Study VX14-661-110 sites that have been activated by the time the subject has completed the last scheduled visit in the parent study. Subjects at these active sites will NOT have to repeat any Study VX14-661-110 Day 1 assessments that were specified to be performed at the last scheduled visit in the parent study. Subjects who were enrolled but had Day 1 study drug administration procedures (Section 10.2) delayed will have to repeat the safety (Section 11.8) and spirometry (Section 11.7.1) assessments that were specified to be performed at the Day 1 Visit before receiving their first dose of study drug. However, the Day 1 Visit of Study VX14-661-110 **will NOT coincide** with the last scheduled visit of the parent study for subjects at Study VX14-661-110 sites that have NOT been activated by the time the subject has completed the last scheduled visit in the parent study. Subjects at these nonactive sites will have to repeat any Study VX14-661-110 Day 1 assessments that were specified to be performed at the last scheduled visit in the parent study.

[g] **Re-enrollment**: Subjects who re-enroll in the Treatment Cohort will complete the Returning Visit and will resume treatment with VX-661/ivacaftor at the next study day after their previous treatment discontinuation from Study VX14-661-110. If the timepoint coincides with a scheduled Study VX14-661-110 visit (± 5 days), only the Returning Visit assessments will be completed. Subjects who were re-enrolled but had their Returning Visit study drug administration procedures (Section 10.2) delayed will have to repeat the safety (Section 11.8) and spirometry (Section 11.7.1) assessments that were specified to be performed at the Returning Visit before receiving their first dose of study drug.

Table 3-1 Study VX14-661-110: Treatment Cohort

Event/Assessment[a]	Day –28 to Day -1	Treatment Period[b]						ETT Visit/ Departing Visit (Within 7 Days of Last Dose of Study Drug)[b,c,d,e]	Safety Follow-up Visit 28 (± 7) Days After Last Dose[c,d,e]
		Day 1[f]/ Returning Visit[b,g]	Day 15 (± 3 days)	Weeks 8, 16, 24, 36 (± 5 days)	Week 48 (± 5 days)	Weeks 60, 72, 84 (± 5 days)	Week 96 (± 5 days)		
Informed consent/assent	X[h]	X[h]							
Inclusion and exclusion criteria review		X							
CFQ-R[i]		X	X	X	X	X	X	X	X
[redacted]									
Weight and height[j]		X		X	X	X	X	X	X
Ophthalmological history[k]		Day 1							
Ophthalmologic examination[l]	X[h,m]	X[n]			X		X	X[o]	X[p]
Complete physical examination[p]		X			X		X	X	
Pregnancy test[q]		urine		urine	urine	urine	serum	serum	serum

h If the baseline ophthalmologic examination (see Footnote m) is not conducted as a parent study assessment but is conducted during the Day -28 to Day -1 period of Study VX14-661-110, informed consent/assent will be obtained before this examination and will not be obtained again on Day 1 of Study VX14-661-110.

i Questionnaires must be completed before the start of any other assessments scheduled at that visit (Section 11.1). The CFQ-R must be completed first[redacted]

j Weight and height will be measured before dosing with shoes off (Section 11.7.2). Height will be collected only for subjects ≤21 years of age (age on the date of informed consent/assent in the parent study).

k Required on Day 1 for all subjects without a documented ophthalmological history from the parent study. Not required at the Returning Visit.

l Ophthalmologic examinations will be conducted on subjects < 18 years of age (age on the date of informed consent/assent in the parent study) by a licensed ophthalmologist.

m An ophthalmologic examination will be conducted on subjects < 18 years of age (age on the date of informed consent/assent in the parent study) by a licensed ophthalmologist within 28 days before enrollment on Day 1 (Section 11.8.7). This examination may be conducted while the subject is participating in the parent study. If this examination is not conducted during the Day -28 to Day -1 period, subjects are required to complete the Day 1 ophthalmologic examination.

n The Day 1 ophthalmologic examination is not required for subjects who complete the baseline ophthalmologic examination during the Day -28 to Day -1 period (this examination may be conducted while the subject is participating in the parent study).

o Subjects <18 years of age (age on the date of informed consent/assent in the parent study) who discontinue treatment after receiving at least 1 dose of study drug will have an ophthalmologic examination conducted by a licensed ophthalmologist (Section 8.1.1.3). The examination may be completed at either the ETT or Safety Follow-Up Visit, but must be completed by the date of the Safety Follow-Up Visit.

p Symptom-targeted physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator (Section 11.8.3).

q Pregnancy tests will be performed for all female subjects of childbearing potential. All urine pregnancy tests will be performed at the site.

Table 3-1 Study VX14-661-110: Treatment Cohort

Event/Assessment[a]	Day –28 to Day -1	Treatment Period[b]						ETT Visit/ Departing Visit (Within 7 Days of Last Dose of Study Drug)[b,c,d,e]	Safety Follow-up Visit 28 (± 7) Days After Last Dose[c,d,e]
		Day 1[f]/ Returning Visit[b,g]	Day 15 (± 3 days)	Weeks 8, 16, 24, 36 (± 5 days)	Week 48 (± 5 days)	Weeks 60, 72, 84 (± 5 days)	Week 96 (± 5 days)		
Standard 12-lead ECG[r]		X	X	Weeks 8, 16, 24	X	Week 72	X	X	X
Vital signs[s]		X	X	X	X	X	X	X	X
Pulse oximetry[s]		X	X	X	X	X	X	X	X
Spirometry[t]		X	X	X	X	X	X	X	X
Hematology[u]		X[v]	X	X	X	X	X	X	X
Coagulation[u]		X[v]		X	X	X	X	X	X
Serum chemistry[u]		X[v]	X	X	X	X	X	X	X
Lipid panel[u]		X[v]		X	X	X	X	X	X
Vitamin levels[u]		X[v]		X	X	X	X	X	X
Urinalysis		X		X	X	X	X	X	X
PK sampling				Week 24[w]				X	
Other events related to outcome[x]		X	X	X	X	X	X	X	X
Meal(s) or snack(s) at site[y]		X	X	X	X	X			
Study drug count			X	X	X	X	X	X	

[r] All standard 12-lead ECGs will be performed before dosing and after the subject has been supine for at least 5 minutes (Section 11.8.4). At the Day 1 and 15 Visits, ECGs will be collected before dosing and at 1.5 and 4 hours after the morning dose. A window of ± 15 minutes will be allowed around the nominal times for all postdose ECG assessments. ECGs collected on Day 1 before dosing will be performed in triplicate. If study drug is not administered on the day of the visit (i.e., because of study drug interruption), only 1 ECG will be collected.

[s] Vital signs and pulse oximetry will be collected before dosing and after the subject has been at rest (seated or supine) for at least 5 minutes (Sections 11.8.3 and 11.8.5).

[t] Spirometry must be performed for all subjects before dosing and should be performed pre-bronchodilator (Section 11.7.1).

[u] With the exception of Day 15, all blood samples will require a 4-hour fast before collection.

[v] Blood samples will be collected before the first dose of study drug.

[w] A single blood sample for PK will be collected within 60 minutes before dosing (Section 11.5.1).

[x] Other events related to outcome include assessments relating to pulmonary exacerbations, administration of antibiotic therapy for sinopulmonary signs or symptoms, and hospitalizations (Section 11.7.5).

[y] Fat-containing food such as a standard CF high-fat, high-calorie meal or snack will be provided at the site to subjects after all predose assessments have occurred.

Table 3-1 Study VX14-661-110: Treatment Cohort

Event/Assessment[a]	Day –28 to Day -1	Treatment Period[b]						ETT Visit/ Departing Visit (Within 7 Days of Last Dose of Study Drug)[b,c,d,e]	Safety Follow-up Visit 28 (± 7) Days After Last Dose[c,d,e]
		Day 1[f]/ Returning Visit[b,g]	Day 15 (± 3 days)	Weeks 8, 16, 24, 36 (± 5 days)	Week 48 (± 5 days)	Weeks 60, 72, 84 (± 5 days)	Week 96 (± 5 days)		
Study drug dosing[z]		*Day 1 to Week 96*							
[redacted]									
Concomitant medications		*Continuous from signing of the ICF and Assent (where applicable) through the Safety Follow-up Visit*							
Concomitant treatments and procedures		*Continuous from signing of the ICF and Assent (where applicable) through the Safety Follow-up Visit*							
AEs and SAEs[bb]		*Continuous from signing of the ICF and Assent (where applicable) through the Safety Follow-up Visit*							

AE: adverse event; CF: cystic fibrosis; CFQ-R: CF Questionnaire–Revised; ECG: electrocardiogram; ETT: Early Treatment Termination; ICF: informed consent form; PK: pharmacokinetic; SAE: serious adverse event; [redacted]

[z] The study drug should be administered every 12 hours (± 2 hours) within 30 minutes of starting a meal with fat-containing food such as a standard CF high-fat, high-calorie meal or snack (Section 10.2). On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. The final dose of study drug will be administered the evening before the Week 96 Visit. If the Returning Visit coincides with the last Visit of the other Vertex study, the morning dose of VX-661/ivacaftor may be supplied by the other Vertex study.

[redacted]

[bb] 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** as described in Section 13.1.2.2.

3.2 Observational Cohort

Table 3-2 Study VX14-661-110: Observational Cohort

Event/Assessment	Day 1[a]	Long-term Follow-up	
		Approx. Every 3 to 4 Months for the First Year	Approx. 2 Years (± 4 weeks)
Clinic visit	X		
Telephone contact		X	X
Informed consent/assent	X		
Inclusion criteria review[b]	X		
Related serious adverse events	**Continuous from signing of ICF and Assent through last telephone contact**		

ICF: informed consent form.

[a] The Day 1 Visit of Study VX14-661-110 will be on the **same day** as the last scheduled visit of the parent study for subjects at Study VX14-661-110 sites that have been activated by the time the subject has completed the last visit in the parent study. Subjects at these active sites will NOT have to repeat any Study VX14-661-110 Day 1 assessments that were specified to be performed at the last scheduled visit of the parent study. However, the Day 1 Visit of Study VX14-661-110 **will NOT coincide** with the last scheduled visit of the parent study for subjects at Study VX14-661-110 sites that have NOT been activated by the time the subject has completed the last scheduled visit in the parent study. Subjects at these nonactive sites will have to repeat any Study VX14-661-110 Day 1 assessments that were specified to be performed at the last scheduled visit in the parent study.

[b] Subjects must be < 18 years of age (age on the date of informed consent/assent in the parent study) and meet the other inclusion criteria (Section 9.1) to be eligible for the Observational Cohort.

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5 INTRODUCTION

5.1 Background

Cystic fibrosis (CF) affects an estimated 70,000 children and adults worldwide[1] and is the most common fatal genetic disease in persons of European descent.[2] Based on the size of the population, CF qualifies as an orphan disease.[3,4] Despite progress in the treatment of CF with antibiotics and mucolytics, the predicted median age of survival for a person with CF is in the mid-40s.[2,5] Although the disease affects multiple organs, most morbidity and mortality is caused by progressive loss of lung function.[6]

CF is an autosomal recessive genetic disease caused by a defect in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR), an epithelial chloride ion (Cl^-) channel activated by cyclic AMP-dependent protein kinase A that is responsible for aiding in the regulation of salt and water absorption and secretion in various tissues.[2] This function is defective in patients with CF due to a loss of cell surface expression and/or function.

More than 1900 mutations in the *CFTR* gene have been identified.[7] Mutations in the *CFTR* gene have been classified based on the molecular and functional consequence of the mutation on the CFTR protein[8,9,10] and can be generally considered to reduce the quantity of functional CFTR protein that reaches the epithelial cell surface or reduce the function of CFTR protein located at the cell surface. *CFTR* gene mutations that affect the quantity of functional cell surface CFTR protein include defects that reduce CFTR protein synthesis and defects that impede the cellular processing and delivery of CFTR proteins to the cell surface.

CFTR gene mutations associated with minimal CFTR function include

- mutations associated with severe defects in ability of the CFTR channel to open and close, known as defective channel gating or “gating mutations”;
- severe defects in the cellular processing of CFTR and its delivery to the cell surface;
- no (or minimal) CFTR synthesis; and
- severe defects in channel conductance.

The most prevalent mutation is an in-frame deletion in the *CFTR* gene resulting in a loss of phenylalanine at position 508 in the CFTR protein (F508del-CFTR).[10] In the USA, almost 87% of patients with CF have at least 1 copy of the *F508del-CFTR* mutation, and approximately 47% have 2 copies.[11] In the European Union, approximately 83% of patients with CF have 1 or 2 copies of the *F508del-CFTR* mutation, and approximately 38.7% of patients with CF in the United Kingdom have 2 copies.[12] The *F508del-CFTR* mutation interferes with the ability of the CFTR protein to reach and remain at the cell surface, as well as to open and close, resulting in decreased Cl^- transport.[13,14] The combined effect is a marked reduction in F508del-CFTR-mediated Cl^- secretion that impairs fluid regulation and promotes accumulation of thick sticky mucus in the airway. The mucus build-up obstructs the airways and predisposes the patient to chronic lung infections.[15]

Two complementary approaches to increase CFTR-mediated Cl^- secretion in airway epithelia have been studied.[9] One approach is to treat with a compound that will modify the cellular processing and delivery of CFTR protein to the cell surface. This kind of compound has been termed a CFTR corrector. Another approach is to treat with a compound that increases channel gating activity of protein kinase A-activated CFTR at the cell surface to enhance ion transport. This kind of compound has been termed a potentiator. Depending on the amount of residual CFTR channel activity in the membrane and the pathophysiology of that activity (reflecting the CFTR genotype of the patient and possibly other factors), both approaches may be required to ameliorate lung disease in patients with CF. A modest restoration of Cl^- secretion through the action of a potentiator and/or corrector could prevent the hyperabsorption of water across the apical surface of epithelial cells, allowing for proper maintenance of airway hydration. Adequate airway hydration could alleviate the cycle of mucus plugging, infection, and inflammation that leads to irreversible structural changes in the lungs, and eventually respiratory failure for patients with CF.

VX-661 is a compound developed by Vertex Pharmaceuticals Incorporated (Vertex) that has been shown to have CFTR corrector properties. Several lines of in vitro evidence suggest that VX-661 works by promoting the proper folding of a fraction of F508del-CFTR protein during its biogenesis and processing in the endoplasmic reticulum, allowing it to exit the endoplasmic reticulum and traffic to the cell surface.[16] When added for more than 24 hours to human bronchial epithelial (HBE) cells isolated and cultured from lung explants obtained from donors with CF (CF-HBE cells) who are homozygous for the *F508del-CFTR* mutation, a concentration-dependent increase in levels of mature (i.e., plasma membrane) F508del-CFTR was observed. The increased trafficking of F508del-CFTR to the cell surface resulted in a significant increase in Cl^- secretion.[16] VX-661 did not correct the processing and localization of other misfolded or normally folded proteins other than CFTR, suggesting that the mechanism of VX-661 action is selective for CFTR (CFTR corrector).[17]

Ivacaftor (also known as VX-770) is the first CFTR modulator to show an improvement in CFTR function and clinical benefit in patients with CF. Results from several Phase 3 studies showed that ivacaftor is effective in the treatment of patients with CF who have mutations that result in gating defects as evidenced by sustained improvements in CFTR channel function (measured by reduction in sweat chloride concentration) and corresponding substantial, durable improvements in lung function, respiratory symptoms, and weight gain. Ivacaftor was also well tolerated, as evidenced by the rates and reasons for premature discontinuation and results of safety assessments.

In the US, ivacaftor (150-mg tablets; trade name Kalydeco) is indicated for the treatment of CF in patients aged 2 years and older who have 1 of the following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R,* or *R117H*. In the EU, Kalydeco is indicated for the treatment of CF in patients aged 6 years and older who have 1 of the following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*. In Canada, Kalydeco is indicated for the treatment of CF in patients aged 6 years and older who have 1 of the following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R,* or *G970R.* It is also indicated for the treatment of CF in patients aged 18 years and older who have the *R117H* mutation in the *CFTR* gene. In Australia, Kalydeco is indicated for the treatment of CF in patients aged 6 years and older who have a *G551D* or other gating (class III)

mutation in the *CFTR* gene. In New Zealand, Switzerland, and Liechtenstein, Kalydeco is currently indicated for the treatment of CF in patients 6 years of age and older who have the *G551D* mutation.

Details about the VX-661 and ivacaftor development programs can be found in the Investigator's Brochures.[18,19]

5.2 Study Rationale

To date, the long-term safety of VX-661 in combination with ivacaftor has not yet been evaluated. Therefore, the primary objective of this study is to evaluate the long-term safety and tolerability of VX-661 in combination with ivacaftor in subjects with CF, homozygous or heterozygous for the *F508del-CFTR* mutation. In addition, a secondary objective of this study is to evaluate the long-term efficacy and durability of treatment with VX-661 in combination with ivacaftor in the same subjects.

6 STUDY OBJECTIVES

6.1 Primary Objective

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

6.2 Secondary Objectives

Treatment Cohort

To evaluate the long-term efficacy of VX-661 in combination with ivacaftor for subjects in the Treatment Cohort

Observational Cohort

To evaluate the post-treatment safety of VX-661 in combination with ivacaftor for subjects in the Observational Cohort

7 STUDY ENDPOINTS

7.1 Primary Endpoints

Treatment Cohort

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

7.2 Secondary Endpoints

Treatment Cohort

The following efficacy endpoints will be analyzed:

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

Observational Cohort

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

[redacted]

8 STUDY DESIGN

8.1 Overview of Study Design

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

A schematic of the study design is shown in Figure 8-1.

This study consists of a Treatment Cohort (eligible subjects 12 years of age and older) and an Observational Cohort (eligible subjects <18 years of age [age on the date of informed consent/assent in the parent study]), which will enroll subjects from Studies VX13-661-103,

VX14-661-106, VX14-661-107, VX14-661-108, VX14-661-109, VX14-661-111, and other Vertex studies investigating VX-661 in combination with ivacaftor. The Treatment Cohort and the Observational Cohort will be open to enrollment in parallel.

Treatment Cohort

Subjects who completed study drug treatment (i.e., VX-661/ivacaftor, ivacaftor monotherapy, or placebo) during the Treatment Period in the parent study who meet the eligibility criteria (Sections 9.1 and 9.2) will be offered the opportunity to enroll in Study VX14-661-110. Subjects who permanently discontinue study drug treatment or who withdrew consent during the parent study are not eligible for enrollment in the Treatment Cohort.

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

Subjects may screen for another qualified Vertex study while participating in the Treatment Cohort.

Subjects who completed at least 4 weeks of treatment before discontinuing Study VX14-661-110 to participate in another qualified Vertex study, and who meet the eligibility criteria (Sections 9.1 and 9.2), will be offered the opportunity to re-enroll in the Treatment Cohort of Study VX14-661-110. Subjects who re-enroll will resume treatment with VX-661/ivacaftor at the next study day after their previous treatment discontinuation from Study VX14-661-110 (e.g., a subject who discontinued at Study Day 50 would resume treatment at Study Day 51). Subjects who discontinue Study VX14-661-110 more than once to participate in another qualified Vertex study may not re-enroll in Study VX14-661-110 a second time.

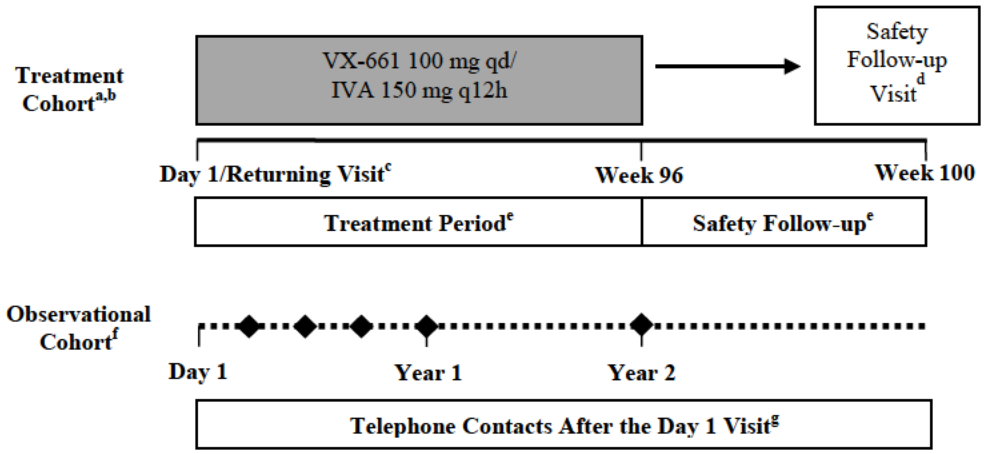
During the course of study conduct, if VX-661 in combination with ivacaftor is approved and available for the treatment of CF in populations enrolled in Study VX14-661-110, subjects with the approved *CFTR* genotypes may be discontinued from this rollover study at the discretion of the sponsor (Section 10.6). If a subject is continuing onto commercially available VX-661/ivacaftor, the Early Treatment Termination Visit (Section 8.1.1.3) will be completed before dosing with commercial drug begins, and the Safety Follow-up Visit (Section 8.1.1.2) will not be required. Alternatively, if local health authorities decline to approve, or if clinical benefit is not demonstrated for the use of VX-661 in combination with ivacaftor for the treatment of CF in populations enrolled in Study VX14-661-110, subjects with the relevant *CFTR* genotypes may be discontinued after communication to investigators and IRBs/IECs of the risks/benefits related to the safety and efficacy observed for the subset of subjects. If subjects are discontinued from the study, an Early Treatment Termination Visit should occur within 7 days of the last dose of study drug and a Safety Follow-up Visit should occur within 28 (± 7) days after the last dose of study drug.

Observational Cohort

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

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

Figure 8-1 Study Design



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

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

[a] Subjects may be eligible to enroll in the Treatment Cohort if they completed study drug treatment in the parent study and meet eligibility criteria for the Treatment Cohort.

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

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

[d] The Safety Follow-up Visit is scheduled to occur 28 (± 7 days) after the last dose of study drug (Section 8.1.1.2).

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

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

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

8.1.1 Treatment Cohort (Eligible Subjects 12 Years of Age and Older)

8.1.1.1 Treatment Period

After obtaining informed consent and assent (where applicable), and eligibility has been confirmed, subjects will receive VX-661 100 mg/ivacaftor 150-mg FDC tablet qd in the morning and ivacaftor 150-mg tablet qd in the evening. Study drug will be administered for approximately 96 weeks.

Initial Enrollment

Timing of Treatment Cohort Day 1 Visit in Study VX14-661-110 Active Sites

The Day 1 Visit of Study VX14-661-110 will be on the **same day** as the last scheduled visit of the parent study for subjects at Study VX14-661-110 sites that have been activated by the time the last scheduled visit of the parent study has been completed. Subjects at these active sites MAY have to repeat any Day 1 assessments of Study VX14-661-110 that were specified to be performed at the last scheduled study visit of the parent study. Assessments for the Treatment Cohort are listed in Table 3-1.

Subjects who were enrolled but had Day 1 study drug administration procedures (Section 10.2) delayed will have to repeat the safety (Section 11.8) and spirometry (Section 11.7.1) assessments that were specified to be performed at the Day 1 Visit before receiving their first dose of study drug.

Timing of Day 1 Visit in Study VX14-661-110 Nonactive Sites

The Day 1 Visit of Study VX14-661-110 **will NOT coincide** with the last scheduled visit of the parent study for subjects at Study VX14-661-110 sites that have NOT been activated by the time the last scheduled visit of the parent study has been completed. Subjects at these nonactive sites will have to repeat any Study VX14-661-110 Day 1 assessments that were specified to be performed at the last scheduled visit of the parent study. Assessments for the Treatment Cohort are listed in Table 3-1.

Re-enrollment

Subjects who re-enroll in the Treatment Cohort will complete the Returning Visit and resume treatment with VX-661/ivacaftor at the next study day after their previous treatment discontinuation from Study VX14-661-110. If the timepoint coincides with a scheduled Study VX14-661-110 visit (± 5 days), only the Returning Visit assessments will be completed. Assessments for the Treatment Cohort are listed in Table 3-1.

Subjects who re-enroll in the Treatment Cohort but have a delay in their Returning Visit study drug administration procedures (Section 10.2) will have to repeat the safety (Section 11.8) and spirometry (Section 11.7.1) assessments that are specified to be performed at the Returning Visit before receiving their first dose of study drug.

Timing of Overlapping Visits With Another Qualified Vertex Study

The Returning Visit in Study VX14-661-110 may be on the **same day** as the last required visit of the other qualified Vertex study. If completed on the same day, the order/timing in the Schedule of Assessments in the other qualified Vertex study should be followed and subjects MAY have to repeat Study VX14-661-110 assessments that were specified to be performed at the last

required visit of the other qualified Vertex study. Assessments for the Treatment Cohort are listed in Table 3-1.

Screening for Another Qualified Vertex Study

Timing of Overlapping Visits With Another Qualified Vertex Study

Subjects may screen for another qualified Vertex study while participating in the Treatment Cohort. The Screening Visit of the other qualified Vertex study may be on the **same day** as a scheduled Treatment Period visit in Study VX14-661-110. If completed on the same day, the order/timing in the VX14-661-110 Schedule of Assessments should be followed and subjects MAY have to repeat any Screening Visit assessments that were specified in the other qualified Vertex study in order to maintain the integrity of the data for the other qualified Vertex study.

8.1.1.2 Safety Follow-up

Treatment Cohort

Subjects who do not complete the Day 1 Visit in Study VX14-661-110 within 28 days after the last dose of study drug in the parent study are to complete the Safety Follow-Up Visit in the parent study before receiving the first dose of study drug in Study VX14-661-110.

The Safety Follow-up Visit is scheduled to occur 28 (± 7) days after the last dose of study drug. The Safety Follow-up Visit assessments are listed in Table 3-1.

If a subject is continuing onto commercially available VX-661/ivacaftor, the Early Treatment Termination Visit (Section 8.1.1.3) will be completed before dosing with commercial drug begins, and the Safety Follow-up Visit will not be required.

If a subject discontinues treatment to participate in another qualified Vertex study, the Early Treatment Termination Visit (Section 8.1.1.3) will be completed, and the Safety Follow-up Visit will not be required if the subjects enrolls in the other study within 28 (±7) days of the last dose of study drug in Study VX14-661-110.

8.1.1.3 Early Treatment Termination

Treatment Cohort

If a subject prematurely discontinues study treatment, an Early Treatment Termination Visit should be scheduled as soon as possible after the subject decides to terminate study treatment and should occur within 7 days after the last dose of study drug. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 (± 7) days after their last dose of study drug as described in Section 8.1.1.2. The assessments performed at the Safety Follow-up Visit are listed in Table 3-1.

If the Early Treatment Termination Visit occurs 3 weeks or later following the last dose of study drug, then the Early Treatment Termination Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required. If a subject discontinues Study VX14-661-110 to participate in another qualified Vertex study, and the subject does not re-enroll in Study VX14-661-110, the Early Treatment Termination Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

During the course of study conduct, if VX-661 in combination with ivacaftor is approved and available for the treatment of CF in populations enrolled in Study VX14-661-110, subjects with

the approved *CFTR* genotypes may be discontinued from this rollover study at the discretion of the sponsor (Section 10.6). If a subject is continuing onto commercially available VX-661/ivacaftor, the Early Treatment Termination Visit will be completed before dosing with commercial drug begins, and the Safety Follow-up Visit (Section 8.1.1.2) will not be required. Alternatively, if local health authorities decline to approve, or if clinical benefit is not demonstrated for the use of VX-661 in combination with ivacaftor for the treatment of CF in populations enrolled in Study VX14-661-110, subjects with the relevant *CFTR* genotypes may be discontinued after communication to investigators and IRBs/IECs of the risks/benefits related to the safety and efficacy observed for the subset of subjects. If subjects are discontinued from the study, an Early Treatment Termination Visit should occur within 7 days of the last dose of study drug and a Safety Follow-up Visit should occur within 28 (± 7) days after the last dose of study drug.

If a subject withdraws from the study and also withdraws consent for disclosure of future information, 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.

Timing of Overlapping Visits With Another Qualified Vertex Study

If a subject enrolls in another qualified Vertex study and is discontinued from Study VX14-661-110, the Early Treatment Termination Visit in Study VX14-661-110 may be on the **same day** as the visit with the first dose of study drug in the other qualified Vertex study. If completed on the same day, the order/timing in the Schedule of Assessments in the other qualified Vertex study should be followed and subjects MAY have to repeat any Study VX14-661-110 assessments that were specified to be performed at the visit with the first dose of study drug in the other qualified Vertex study.

8.1.2 Observational Cohort (Eligible Subjects <18 Years of Age)

8.1.2.1 Day 1

Following consent and assent (where applicable) and confirmation of eligibility, subjects will undergo the Day 1 assessments as shown in Table 3-2.

Timing of Day 1 Visit in Study VX14-661-110 Active Sites

The Day 1 Visit of the Observational Cohort will be on the **same day** as the last scheduled visit of the parent study for subjects at Study VX14-661-110 sites that have been activated by the time the last scheduled visit of the parent study has been completed. Subjects at these active sites MAY have to repeat any Study VX14-661-110 Day 1 assessments that were specified to be performed at the last scheduled study visit of the parent study. Assessments for the Observational Cohort are listed in Table 3-2.

Timing of Day 1 Visit in Study VX14-661-110 Nonactive Sites

The Day 1 Visit of the Observational Cohort of Study VX14-661-110 **will NOT coincide** with the last scheduled visit of the parent study for subjects at Study VX14-661-110 sites that have NOT been activated by the time the last scheduled visit of the parent study has been completed. Subjects at these nonactive sites will have to repeat any Study VX14-661-110 Day 1 assessments that were specified to be performed at the last scheduled visit of the parent study. Assessments for the Observational Cohort are listed in Table 3-2.

8.1.2.2 Long-term Follow-up

Subjects will be followed for approximately 2 years. A telephone contact will be made approximately every 3 to 4 months during the first year and at approximately 2 years (± 4 weeks) as shown in Table 3-2.

8.1.3 Lost to Follow-up

A subject will be considered lost to follow-up if both of the following occur:

- The subject misses 2 consecutive study visits (telephone contact and/or clinic visit) and is subsequently unable to be contacted by telephone (3 documented attempts by telephone within 2 weeks following the second missed visit)
- The subject does not respond within 2 weeks to a registered letter sent after the 3 attempted telephone contacts.

8.2 Rationale for Study Design and Study Drug Regimens

8.2.1 Study Design

The *F508del-CFTR* mutation is the most prevalent of the *CFTR* mutations. In vitro studies in primary cultures of HBE from subjects with CF who are homozygous for the *F508del-CFTR* mutation have demonstrated significant increases in CFTR activity with the addition of VX-661 in combination with ivacaftor when compared to no treatment, VX-661 alone, or ivacaftor alone. Clinical studies of subjects with CF have demonstrated significant increases in lung function (FEV_1) in subjects with CF who are homozygous or heterozygous for the *F508del-CFTR* mutation when treated with VX-661 in combination with ivacaftor when compared to placebo (Study VX11-661-101).[18] Four Phase 3 studies are investigating the efficacy and safety of VX-661 in combination with ivacaftor in subjects with CF who are homozygous (Study VX14-661-106) or heterozygous (Studies VX14-661-107, VX14-661-108, and VX14-661-109) with *F508del-CFTR* mutation. Study VX14-661-107 was terminated early because the study met the prespecified futility criteria. In addition, 3 Phase 2 studies are investigating the safety and efficacy of VX-661 in combination with ivacaftor in subjects with CF who are homozygous for *F508del-CFTR* (Study VX13-661-103, Study VX14-661-111, and Study VX15-661-112). Study VX16-661-114 is a Phase 3b study being conducted in subjects with CF who are homozygous for *F508del*.

Study VX14-661-110 will enroll subjects with CF who participated in a qualifying parent study of VX-661 in combination with ivacaftor (Studies VX13-661-103, VX14-661-106, VX14-661-107, VX14-661-108, VX14-661-109, VX14-661-111, and other eligible Vertex studies investigating VX-661 in combination with ivacaftor). Study VX14-661-110 will enroll subjects with CF who participated in a qualifying parent study (Studies VX15-661-112, VX16-661-114, and other eligible Vertex studies investigating VX-661 in combination with ivacaftor) or who completed study drug treatment.

Results from Study VX14-661-110 will provide information on the safety and efficacy of long-term treatment with VX-661 in combination ivacaftor in subjects with CF who are aged 12 years and older and homozygous or heterozygous for the *F508del-CFTR* mutation. Study VX14-661-110 offers an opportunity to continue treatment with VX-661 in combination with ivacaftor for subjects in qualifying parent studies who had completed their assigned treatment with combination therapy. For subjects who received placebo in their qualifying parent study,

Study VX14-661-110 offers the opportunity to receive treatment with VX-661 in combination with ivacaftor. For subjects <18 years of age (age on the date of informed consent/assent in the parent study) not eligible for further treatment with VX-661 and ivacaftor or who choose not to continue treatment, participation in the Observational Cohort of this study provides an opportunity for long-term safety data collection after subjects discontinue VX-661 in combination with ivacaftor in an eligible parent study.

If an evaluation of the efficacy data from the Phase 3 studies suggests that the VX-661/ivacaftor treatment does not provide clinically meaningful benefit for subsets of subjects included in these studies, Vertex may recommend that subjects with relevant genotypes discontinue from the Treatment Cohort. In addition, if local health authorities decline to approve, or if clinical benefit is not demonstrated for the use of VX-661 in combination with ivacaftor for the treatment of CF in populations enrolled in Study VX14-661-110, subjects with the relevant *CFTR* genotypes may be discontinued after communication to investigators and IRBs/IECs of the risks/benefits related to the safety and efficacy observed for the subset of subjects.

8.2.2 Study Drug Dose and Duration

All subjects enrolled in the Treatment Cohort will receive the same regimen of study drug that is being administered in the Phase 3 studies of VX-661 in combination with ivacaftor in subjects with CF who are 12 years of age or older. Subjects will receive a morning dose of VX-661 100 mg/ivacaftor 150 mg (FDC tablet) and an evening dose of ivacaftor 150 mg. These dosages were selected based on efficacy, safety, and tolerability results from Study VX11-661-101.[18] The dose regimen of ivacaftor planned for this study (150 mg q12h) is the current labeled dose regimen for patients with CF with gating mutations who are 12 years of age and older. Dosages for subjects 12 to 17 years of age (same as the adult dosage) were determined based on the historical data on weight as a function of age in patients with CF from the ivacaftor Phase 3 program and the US CF Foundation Registry, weights in the 12- to 17-year old population are expected to be only slightly lower than those of the adult CF population.[20]

All subjects in the Treatment Cohort will receive VX-661 in combination with ivacaftor. Subjects who received VX-661 in combination with ivacaftor in the parent study and continue to receive this combination in Study VX14-661-110 may receive treatment for up to approximately 2.5 years, providing further information on the safety and efficacy of long-term treatment with VX-661 in combination with ivacaftor.

8.2.3 Rationale for Study Assessments

The safety and PK assessments are standard parameters for clinical studies in drug development. The efficacy assessments are widely accepted and generally recognized as reliable, accurate, and relevant to the study of patients with CF.

Spirometry: As lung disease is the major cause of morbidity and mortality for patients with CF, CF lung disease is the desired primary target of VX-661/ivacaftor combination therapy. Spirometry (as measured by FEV_1) is the most widely implemented standardized assessment to evaluate lung function.

Nutritional Status (measured by weight and BMI): Malnutrition is common in patients with CF because of increased energy expenditures due to lung disease and fat malabsorption. Given that VX-661 in combination with ivacaftor is a systemic therapy, it has the potential to improve extrapulmonary manifestations of CF, including those in the gastrointestinal system. Improved

nutritional status, defined as an increase in weight and/or BMI, is considered an appropriate endpoint for therapies targeting CFTR and was used in previous clinical studies of CFTR-targeted therapies (Studies VX08-770-102 and VX08-770-103). To evaluate the effect of VX-661 in combination with ivacaftor on growth, change in weight and BMI will be measured.

As children gain weight and height 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 VX-661 in combination with ivacaftor on growth and nutrition adjusted for age and sex, weight-for-age, height-for-age, BMI-for-age, and the respective z-scores will be determined. Height and weight will be collected at the study visits indicated in the schedule of assessments.

CFQ-R: The CFQ-R is a frequently used CF-specific instrument that measures the health-related quality of life of patients with CF.[21,22,23] As VX-661 in combination with ivacaftor is a systemic therapy, it has the potential to improve respiratory symptoms as well as other extrapulmonary manifestations of CF. These improvements can be captured by the non-respiratory symptoms domains of the CFQ-R. Linguistically validated versions of the CFQ-R[24,25] are available, thereby allowing consistent interpretation of the results in this global study. The CFQ-R will be used to capture and evaluate the impact of VX-661 in combination with ivacaftor on patient report of respiratory symptoms and other aspects of health-related quality of life.

[redacted]

Other Events Related to Outcome: Pulmonary exacerbations, administration of antibiotic therapy for sinopulmonary signs and symptoms, and hospitalizations are other outcomes used to assess efficacy in therapies targeting improvement in CF disease. CF pulmonary exacerbations are a compilation of patient signs and symptoms that often result in the need for aggressive treatment, including the use of intravenous (IV) antibiotics administered at home, at the site, or in the hospital and/or pulmonary exacerbations that may require hospitalization. To date, there is no generally accepted objective definition of a pulmonary exacerbation,[26] and large multicenter CF clinical studies have used many variations of physician-derived definitions.[27,28,29,30] Despite the lack of a standard definition, reduction in pulmonary exacerbation rate has served as a key clinical efficacy measure in definitive CF clinical studies, supporting the registration of 2 chronic CF pulmonary therapies (inhaled recombinant human DNase and inhaled tobramycin).[26] To evaluate the potential effect of VX-661 in combination with ivacaftor on pulmonary exacerbations, count, duration, and time-to-first event of hospitalizations and count and time-to-first event of IV courses of antibiotics for pulmonary exacerbations will be derived. For data consistency, this protocol specifies 1 definition of pulmonary exacerbation which is based on the definition used for the other studies including the ivacaftor monotherapy initial registration studies (Section 11.7.5.1). Because signs and symptoms in the definition may occur without meeting the overall definition of a pulmonary exacerbation, the number and timing of

outpatient sick visits to the clinic or hospital for CF that are unrelated to the study protocol will also be collected.

9 STUDY POPULATION

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

9.1 Inclusion Criteria

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

1. Signed and dated an informed consent form (ICF), and where appropriate, signed and dated an assent form.
2. Did not withdraw consent from the parent study.
3. Able to understand and comply with protocol requirements, restrictions, and instructions, and likely to complete the study as planned, as judged by the investigator and Vertex, based in part on study compliance in Studies VX13-661-103, VX14-661-106, VX14-661-107, VX14-661-108, VX14-661-109, VX14-661-111, or other Vertex studies investigating VX-661 in combination with ivacaftor.
4. The following criteria apply to the Treatment and Observational Cohorts:
    - Subjects entering the **Treatment Cohort** must meet all of the following criteria:
        1. Elect to enroll in the Treatment Cohort
        2. Completed study drug treatment during the Treatment Period in a parent study (Studies VX13-661-103, VX14-661-106, VX14-661-107, VX14-661-108, or VX14-661-109), study drug treatment and the Safety Follow-up Visit for subjects from Study VX14-661-111, or study drug treatment and follow-up as specified in other Vertex studies investigating VX-661 in combination with ivacaftor. (Note: studies VX11-661-101 and VX15-661-113 are not eligible parent studies.)
            - Subjects who had study drug interruptions, but completed study visits up to the last scheduled visit of the Treatment Period of the parent study (and the Safety Follow-up Visit for subjects from Study VX14-661-111 or study drug treatment and follow-up as specified in other parent Vertex studies investigating VX-661 in combination with ivacaftor) are eligible.
            - Subjects who had a study drug interruption at the last scheduled visit of the Treatment Period of the parent study, subjects who required interruption to be continued or initiated at Day 1 in Study VX14-661-110, or subjects who resumed study drug in the parent study 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 the Treatment Period of the parent study) must meet eligibility criteria and have received approval from the Vertex medical monitor in order to be enrolled into the Treatment Cohort of Study VX14-661-110.

Note: Subjects who permanently discontinue study drug treatment during the parent study, including at the last visit of the Treatment Period are not eligible to enroll into the Treatment Cohort.

3. Willing to remain on a stable CF medication (and supplement) regimen through the Safety Follow-up Visit of Study VX14-661-110.

- Subjects **re-enrolling in the Treatment Cohort** must meet all of the following criteria:

1. Previously received at least 4 weeks of study drug before discontinuing Study VX14-661-110 to participate in another qualified Vertex study, which is defined as a Vertex study of investigational CFTR modulators that allows participation of subjects in Study VX14-661-110. Note: other qualified Vertex studies do not include studies of lumacaftor in combination with ivacaftor or ivacaftor monotherapy.
2. Completed the last required visit of another qualified Vertex study before or during the Returning Visit in Study VX14-661-110. (If the last required visit of the other qualified Vertex study is more than 60 days from the Returning Visit in Study VX14-661-110, approval of the medical monitor is required.) Subjects who discontinue Study VX14-661-110 to screen for another qualified Vertex study, and do not enroll into the other study, are eligible to re-enroll in Study VX14-661-110.
3. Willing to remain on a stable CF medication (and supplement) regimen through the Safety Follow-up Visit of Study VX14-661-110.
4. Subjects who discontinue Study VX14-661-110 more than once to participate in another qualified Vertex study may not re-enroll in Study VX14-661-110 a second time.

- Subjects entering the **Observational Cohort** must meet the following criteria:

1. <18 years of age (age on the date of informed consent/assent in the parent study)
2. Completed study drug treatment during the Treatment Period in a parent study (Studies VX13-661-103, VX14-661-106, VX14-661-107, VX14-661-108, or VX14-661-109), study drug treatment and the Safety Follow-up Visit for subjects from Study VX14-661-111, or study drug treatment and follow-up as specified in other parent Vertex studies investigating VX-661 in combination with ivacaftor, but do not elect to enroll in the Study VX14-661-110 Treatment Cohort (note: Studies VX11-661-101, and VX15-661-113 are not eligible parent studies); or
3. Received at least 4 weeks of study drug treatment and completed visits up to the last scheduled visit of the Treatment Period of a parent study (and the Safety Follow-up Visit for subjects from Study VX14-661-111 or study drug treatment and follow-up as specified in other parent Vertex studies investigating VX-661 in combination with ivacaftor), but do not meet eligibility criteria for enrollment into the Treatment Cohort

   Note: Subjects who permanently discontinued study drug in the parent study must have completed the last scheduled study visit of the Treatment Period (and the Safety Follow-up Visit for subjects from Study VX14-661-111 or study drug treatment and

follow-up as specified in other parent Vertex studies investigating VX-661 in combination with ivacaftor).

9.2 Exclusion Criteria

Treatment Cohort

Subjects who meet any of the following exclusion criteria will NOT be eligible for this study.

1. History of any comorbidity that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject. For example:

   History of cirrhosis with portal hypertension, and/or history of risk factors for Torsade de Pointes (e.g., familial long QT syndrome, hypokalemia, heart failure, left ventricular hypertrophy, bradycardia, myocardial infarction, cardiomyopathy, history of arrhythmia [ventricular and atrial fibrillation], obesity, acute neurologic events [subarachnoid hemorrhage, intracranial hemorrhage, cerebrovascular accident, and intracranial trauma], and autonomic neuropathy)

2. Pregnant and nursing females. Females of childbearing potential must have a negative urine pregnancy test at the Day 1 Visit (and the Returning Visit for subjects who re-enroll) and before receiving the first dose of study drug.
3. Sexually active subjects of reproductive potential who are not willing to follow the contraception requirements outlined in Section 11.8.8.1.
4. History of drug intolerance in the parent study or other qualified Vertex study that would pose an additional risk to the subject in the opinion of investigator or Vertex. Examples of subjects who may not be eligible for the Treatment Cohort include the following:
   - Subjects with a history of allergy or hypersensitivity to the study drug
   - Liver function test (LFT) abnormality during study drug treatment in the parent study or other qualified Vertex study that required permanent study drug discontinuation
   - ECG abnormality (e.g., persistent QTc >450 msec) during study drug treatment in the parent study or other qualified Vertex study that required permanent study drug discontinuation
   - Other severe or life-threatening reactions to the study drug in the parent study or other qualified Vertex study.
5. History of poor compliance with study drug and/or procedures in the parent study or other qualified Vertex study as deemed by the investigator.
6. Participation in an investigational drug trial (other than Studies VX13-661-103, VX14-661-106, VX14-661-107, VX14-661-108, VX14-661-109, VX14-661-111, other Vertex studies investigating VX-661 in combination with ivacaftor, or other qualified Vertex study) or use of a commercially available CFTR modulator (e.g., Kalydeco) as defined in Table 9-1. NOTE: participation in a noninterventional study (including observational studies, registry studies, and studies requiring blood collections without administration of study drug), and screening for other qualified Vertex studies is permitted.

7. Subjects who are enrolled in a qualified Vertex parent study with more than 1 blinded-treatment periods but who have not completed treatment in all blinded-treatment periods are not eligible to enroll in the Treatment Cohort but may be eligible to enroll in the Observational Cohort if inclusion criteria are met.
8. Previous re-enrollment in the Treatment Cohort of Study VX14-661-110, after participating in other qualified Vertex studies.

9.3 Study Restrictions (Treatment Cohort)

For subjects enrolled in the Treatment Cohort, prohibited medications and certain foods are not allowed in this study while subjects are receiving study drug (Table 9-1). Both VX-661 and ivacaftor are metabolized predominantly via the hepatic enzymatic pathway utilizing CYP3A4. Co-administration of VX-661 and ivacaftor with moderate and strong CYP3A inducers such as rifampin, phenobarbital, carbamazepine, phenytoin, and St. John's wort (*Hypericum perforatum*) has the potential to significantly reduce VX-661 and ivacaftor exposure and is restricted in this study. Case-by-case exceptions for concomitant use of a moderate CYP3A inducer with VX-661/ivacaftor may be granted by the Vertex MM if it is the PI's opinion that the benefits outweigh the risks for the subject in question.

A more detailed but nonexhaustive list of study prohibitions and cautions for food and medication will be provided in the Study Reference Manual.

Table 9-1 Study Restrictions in Treatment Cohort of Study VX14-661-110

Restricted Medication/Food	Study Period
Certain fruits and fruit juices (grapefruit, grapefruit juice, Seville oranges, marmalade)	None allowed within 14 days before the first dose of the study drug through the Safety Follow-up Visit
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of the study drug through the Safety Follow-up Visit
Commercially available CFTR modulators (e.g., ivacaftor [Kalydeco])	None allowed within 30 days before the first dose of the study drug through the Safety Follow-up Visit

CFTR: cystic fibrosis transmembrane conductance regulator; CYP: cytochrome P450.

9.4 Prior and Concomitant Medications (Treatment Cohort)

Medicinal products affected by VX-661/ivacaftor

CYP3A, P-gp, or CYP2C9 substrates

Co-administration with (oral) midazolam, a sensitive CYP3A substrate, did not affect midazolam exposure. No dose adjustment is required when co-administered with CYP3A substrates.

Based on in vitro data, ivacaftor and its M1 metabolite have the potential to inhibit P-glycoprotein (P-gp). Co-administration of VX-661/ivacaftor with digoxin, a sensitive P-gp substrate, increased digoxin exposure by 1.3-fold, consistent with weak inhibition of P-gp by ivacaftor. Administration of VX-661/ivacaftor may increase systemic exposure of medicinal products that are sensitive substrates of P-gp, which may increase or prolong their therapeutic effect and adverse reactions. Use with caution and appropriate monitoring when using concomitant digoxin or other substrates of P-gp with a narrow therapeutic index. Ivacaftor may

inhibit CYP2C9; therefore, monitoring of the international normalized ratio (INR) during co-administration of VX-661/ivacaftor with warfarin is recommended.

Information regarding all prior and concomitant medications, including the subject's CF medications, other medications, and herbal and naturopathic remedies administered at or after completion of treatment in the parent study through the Safety Follow-up Visit, if applicable, will be recorded in each subject's source documents.

- Subjects must remain on a stable CF medication (and supplement) regimen through the Safety Follow-up Visit. Stable medication regimen is defined as the current medication regimen for CF that subjects have been following for at least 28 days before Day 1. **Subjects must not initiate long-term treatment with new medication from 28 days before Day 1 through the Safety Follow-up Visit unless it is discussed and approved by the Vertex medical monitor.** Guidelines for stable medication regimens for CF are as follows:
  - Subjects who are taking daily inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.
  - Subjects who are on inhaled cycling antibiotics should continue on their prior schedule. The timing of the first dose of study drug should be synchronized as closely as possible to the first day of inhaled cycling antibiotics in the cycle.
  - Subjects who alternate 2 different antibiotics monthly should remain on the same schedule during the study. The timing of the first dose of study drug should be synchronized as closely as possible to the first day of 1 of the inhaled alternating antibiotics.
- There are no restrictions on the concomitant use of corticosteroids.

For subjects in the Treatment Cohort, information on bronchodilator use during the study will be collected and documented.

Subjects who are using a bronchodilator must have their spirometry assessments performed according to the guidelines provided in Section 11.7.1.

9.5 Removal of Subjects (Treatment Cohort)

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 will continue to be followed, provided the subject has not withdrawn consent.

Subjects who discontinue study treatment early should continue to return for study assessments at the Early Treatment Termination Visit and/or the Safety Follow-up Visit, as noted in Section 8.1.1.3.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. 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 return all unused investigational product(s), request that the subject return for a Safety Follow-up Visit, if applicable (see Section 8.1.1.2), and follow up with the subject regarding any unresolved AEs.

If the subject 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.

9.6 Replacement of Subjects (Treatment Cohort)

Subjects who withdraw or are withdrawn during the study drug Treatment Period will not be replaced.

10 STUDY DRUG ADMINISTRATION AND MANAGEMENT (TREATMENT COHORT)

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 Administration

Study drug tablets will be administered orally as shown in Table 10-1. Subjects in the Observational Cohort will not receive study drug.

Table 10-1 Study Drug Administration – Treatment Period

Treatment Cohort	Time	Drug(s) and Dose(s) Administered Route of Administration
VX-661/ivacaftor	AM	VX-661 100-mg/IVA 150-mg fixed-dose tablet oral
	PM	IVA 150-mg tablet oral

AM: morning; IVA: ivacaftor; PM: evening.

Treatment Cohort

Study drug should be administered within 30 minutes of starting a meal with fat-containing food, such as a standard CF high-fat, high-calorie meal or snack, according to the following guidelines:

1. Study drug should be administered q12h (± 2 hours). For each subject, all doses (morning and evening) of study drugs will be taken at approximately the same time each day. For example, the morning dose could be taken at 08:00 every morning and the evening dose could be taken at 20:00 every evening throughout the study.
2. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. A meal or snack will be provided by the site for the morning dose of study drug.
3. If a subject's scheduled visit is to occur in the afternoon, the following guidelines must be used for administering either the morning or evening dose:
    - If the dose in the clinic will be within 6 hours of the subject's scheduled morning dose, the subject should withhold their morning dose of study drug, and the morning dose will be administered in the clinic.

- If the dose in the clinic will be more than 6 hours after the subject's scheduled morning dose, the subject should take the morning dose at home, and the evening dose will be administered in the clinic. In this event, all assessments will be collected relative to the evening dose.

4. For visits after the Day 1 Visit, subjects will be instructed to bring all used and unused study drug to the site; study drug will be dispensed at each visit, as appropriate.
5. At the Week 96 Visit, the morning dose of study drug will NOT be administered. The last dose of study drug will be the evening dose administered the day before the Week 96 Visit.

Treatment Cohort Only:

The date, amount taken, and time of study drug administration, including whether food was taken with each dose, will be recorded for 2 days before PK sample collection and on the days of PK sample collection.

10.3 Method of Assigning Subjects to Treatment Groups

This is an open-label study. Randomization is not required because all subjects will be treated identically in the Treatment Cohort.

Subjects in the Observational Cohort will not receive study drug.

10.4 Dose Modification for Use With Concomitant CYP3A Inhibitors (Treatment Cohort)

The dosage of VX-661/ivacaftor can be altered only when co-administered with moderate or strong inhibitors of CYP3A.

Table 10-2 Dosing Recommendations for Subjects Taking Concomitant CYP3A Inhibitors

Type of Inhibitor	Example of Inhibitor	VX-661 100 mg/Ivacaftor 150 mg	Ivacaftor 150 mg
Strong CYP3A inhibitor	ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin[a]	One tablet twice a week in the morning (3 to 4 days between doses)	No evening dose
Moderate CYP3A inhibitor	fluconazole, erythromycin	One tablet of VX-661 100 mg/ivacaftor 150 mg or one ivacaftor 150 mg in the morning, taken on alternate days. No evening dose.	

[a] A more detailed but nonexhaustive list of study prohibitions and cautions for food and medication will be provided in the Study Reference Manual.

The dosage of VX-661/ivacaftor cannot be otherwise altered, but the investigator can interrupt or stop treatment (Sections 10.5 and 10.6).

10.5 Study Drug Interruption (Treatment Cohort)

If study drug dosing must be interrupted for more than 72 hours, the medical monitor must be notified. In these instances, study drug dosing may only resume after approval by the medical monitor. Specific instructions for interruption for elevated LFT levels and increased QTc intervals are provided in Section 11.8.6 and Section 11.8.4, respectively.

Missed Doses

If a subject misses a dose and recalls the missed dose within 6 hours, the subject should take his/her dose with food. If more than 6 hours have elapsed after his/her usual dosing time, the subject should skip that dose and resume his/her normal schedule for the following dose. For example,

- if the morning dose of study drug should have been taken at approximately 08:00, and the subject remembers at 12:00 that he/she forgot to take his/her dose, he/she should take the dose with food as soon as possible.
- if the morning dose of study drug should have been taken at approximately 08:00, and more than 6 hours have elapsed beyond the scheduled dosing time (i.e., the time is past 14:00), the subject would resume dosing with the evening dose at approximately 20:00.

10.6 Discontinuation of Study Participation (Treatment Cohort)

If after review of a marketing application, local health authorities decline to approve, or if clinical benefit is not demonstrated for the use of VX-661 in combination with ivacaftor for the treatment of CF in populations enrolled in Study VX14-661-110, subjects with the relevant *CFTR* genotypes may be discontinued after communication to investigators and IRBs/IECs of the risks/benefits related to the safety and efficacy observed for the subset of subjects. In addition, if evaluation of efficacy data from the Phase 3 studies suggests that the VX-661/ivacaftor treatment does not provide clinically meaningful benefit for a population enrolled in Study VX14-661-110, Vertex may recommend that subjects with relevant *CFTR* genotypes discontinue from the Treatment Cohort of the study.

Subjects who become eligible to receive commercially-available VX-661/ivacaftor by prescription of a physician may be discontinued from this rollover study at the discretion of the sponsor. If a subject is continuing onto commercially available VX-661/ivacaftor, the Early Treatment Termination Visit (Section 8.1.1.3) will be completed before dosing with commercial drug begins, and the Safety Follow-up Visit (Section 8.1.1.2) will not be required.

Subjects may be discontinued from the Treatment Cohort at any time due to safety reasons. If a cataract or lens opacity is identified and determined to be clinically significant by the ophthalmologist after dosing, the subject will be notified. After discussion with the site principal investigator and in collaboration with the Vertex medical monitor, the subject may elect to continue or discontinue the study. If the subject discontinues study drug, they should complete the Early Treatment Termination Visit and Safety Follow-up Visit (see Section 8.1.1.3 for Early Treatment Termination). If the subject continues, more frequent ophthalmologic monitoring should be considered.

10.7 Packaging and Labeling

Study drug tablets will be supplied in blister cards by Vertex. Study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing for VX-661 and ivacaftor will be included in the Pharmacy Manual.

10.8 Study Drug Supply, Storage, and Handling

Blister cards must be stored at room temperature according to Table 10-3 and to the instructions provided in the Pharmacy Manual. While at the clinical site, 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 in Section 10.9.

Instructions regarding the storage and handling of study drug after dispensation to subjects will be provided to sites in the Pharmacy Manual.

Table 10-3 Identity of Study Drugs, Dosage, and Storage

Drug Name	Strength/Formulation/Route	Dosage	Storage Condition
VX-661/ivacaftor fixed-dose tablet	100-mg/150-mg tablet; oral	100 mg/ 150 mg, morning dose	≤25°C (77°F) with excursions to 30°C (86°F)
Ivacaftor	150-mg tablet, oral	150 mg, evening dose	≤25°C (77°F) with excursions to 30°C (86°F)

10.9 Drug Accountability (Treatment Cohort)

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. Subjects 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.

10.10 Disposal, Return, or Retention of Unused Drug (Treatment Cohort)

The study site staff or pharmacy personnel will retain all materials returned by the subjects until the study monitor has performed drug accountability. The site monitor will instruct the site when it is appropriate to return or destroy study drug. If the site monitor authorizes destruction at the study site, the investigator, or designee, must 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.

10.11 Compliance (Treatment Cohort)

To ensure treatment compliance, the investigator or designee will supervise all study drug dosing that occurs at the site. At each visit, site personnel will review that the subject is compliant with study drug dosing and remind the subject of study drug dosing requirements. Compliance will also be assessed by ongoing study drug count.

If a subject demonstrates continued noncompliance of study drug dosing despite educational efforts, the investigator should contact the medical monitor to discuss discontinuation of the subject from the study

10.12 Blinding and Unblinding

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

11 ASSESSMENTS

11.1 Timing of Assessments

The timing of assessments is shown in Table 3-1 (Treatment Cohort) and Table 3-2 (Observational Cohort).

If study drug is not administered on the day of the visit (i.e., study drug interruption), assessments will still be collected unless otherwise noted.

The CFQ-R questionnaire must be completed before any other assessment at the clinic visits. For the remaining assessments, the following assessments must be performed in the following order when more than 1 assessment is required at a particular time point.

[redacted]

2. standard 12-lead ECG recording
3. vital signs and pulse oximetry (interchangeable order is acceptable)
4. spirometry
5. safety laboratory assessments and PK sampling (i.e., blood draws)

All other assessments may be completed in any order as shown in Table 3-1 and Table 3-2.

11.2 Informed Consent/Assent

Each subject of age of consent (per local requirements) must sign and date a study-specific ICF before any study-specific procedures can be performed **and before the subject receives the first dose of study drug**. Subjects not of age of consent must assent, if applicable per local requirements, to participate in the study, and the subject's parent or legal guardian must sign and date a study-specific ICF **before any study-specific procedures can be performed**, **and before the subject receives the first dose of the study drug**. The consent/assent forms will comply with all applicable regulations governing the protection of human subjects. An ICF and Assent Form, approved by Vertex and the site's institutional review board (IRB) or independent ethics committee (IEC), must be used.

Subjects who re-enroll in the Treatment Cohort must re-consent/assent (Table 3-1) **before any study-specific procedures can be performed and before the subject receives the first dose of the study drug**.

11.3 Assigning Subject Number

All subjects will retain their subject number from the parent study.

11.4 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history, height, and weight. Select demographic and baseline characteristic data and medical history will be derived from the parent study.

Age, sex, race, and ethnicity will be derived from the parent study because these data are required for the normalization of spirometry values using either the Wang or Hankinson methods (Section 11.7.1).

11.5 Pharmacokinetics (Treatment Cohort Only)

11.5.1 Blood Sampling

Blood samples will be collected as shown in Table 3-1 for the determination of the plasma concentrations of VX-661, M1-661, ivacaftor, and M1-ivacaftor. Blood samples must be collected within 60 minutes before dosing.

Samples from the PK sampling will be kept frozen by Vertex or its designee until all analyses have been completed and then disposed of according to Vertex or designee standard operating procedures.

For each visit with a PK blood draw, a record of study drug administration will be collected as described in Section 10.2. The collection date and time that each PK blood sample is drawn will also be recorded.

Details on sample collection, processing, and shipping will be provided in a separate protocol-specific Laboratory Manual.

11.5.2 Processing and Handling of Pharmacokinetic Samples

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

11.5.3 Bioanalysis

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

[redacted]

[redacted]

11.7 Efficacy

11.7.1 Spirometry (Treatment Cohort)

Spirometry will be performed according to the American Thoracic Society Guidelines[32], according to the additional guidelines that follow.

Pre-bronchodilator spirometry is defined as spirometry testing performed for subjects who have

- withheld their short-acting bronchodilators (e.g., albuterol) or anticholinergic (e.g., ipratropium bromide [Atrovent®]) for more than 4 hours before the spirometry assessment;
- withheld their long-acting bronchodilator (e.g., salmeterol) for more than 12 hours before the spirometry assessment; and
- withheld their once-daily, long-acting bronchodilator (e.g., tiotropium bromide [Spiriva®]) for more than 24 hours before the spirometry assessment.

All spirometry assessments should be performed "pre-bronchodilator." During the Treatment Period, spirometry assessments must be performed before dosing. In the event that a subject forgets to withhold bronchodilator(s), spirometry should be performed according to the following:

- If a subject's Day 1 spirometry is pre-bronchodilator, but, on a subsequent visit, the subject forgets to withhold bronchodilator use, a post-bronchodilator spirometry assessment will be obtained for that visit only, and the visit will not be rescheduled.
- If, on Day 1, the subject forgets to withhold his/her dose of bronchodilator, spirometry should be performed post-bronchodilator, and all subsequent spirometric measurements should be performed post-bronchodilator.
- Each spirometry assessment will be recorded in the source documents as pre- or post-bronchodilator.

All sites will be provided with spirometers to be used for all study assessments. Spirometry data will be transmitted to a centralized spirometry service for quality review.

The parameters listed below will be normalized using the standards of Wang et al.[33] (for female subjects aged 12 to 15 years [inclusive] and male subjects aged 12 to 17 years [inclusive]) or Hankinson et al.[34] (for female subjects aged 16 years and older and male subjects aged 18 years and older).

- FEV_1 (L)
- Forced vital capacity (FVC) (L)
- FEV_1/FVC (ratio)
- Forced expiratory flow ($FEF_{25\%-75\%}$) (L/s)

11.7.2 Height and Weight (Treatment Cohort)

Height and weight will be measured with shoes off. Height and weight will be measured before the morning dose of the study drug during the Treatment Period. During the Treatment Period and at the Safety Follow-up Visit, height will be collected only for subjects ≤ 21 years of age (age on the date of informed consent/assent in the parent study).

11.7.3 Cystic Fibrosis Questionnaire-Revised (Treatment Cohort)

Subjects will be asked to complete the CFQ-R in their native language. The CFQ-R will be completed before the start of any other assessments, as noted in Table 3-1.

- Subjects who are 12 and 13 years of age at Day 1 will complete the CFQ-R Child version themselves, and their parents/caregivers will complete the CFQ-R Parent version, on all visits, regardless of whether the subject subsequently turns 14 years of age during the study.
- Subjects who have turned 14 years of age during their participation in the parent study and have their Day 1 Visit for Study VX14-661-110 on the same day as the last parent study visit will complete the CFQ-R per the parent protocol requirement. At Day 15 and all subsequent visits, these subjects will complete the CFQ-R Adolescent/Adult version themselves.
- Subjects 14 years of age and older at Day 1 who do not have their Day 1 Visit for Study VX14-661-110 on the same day as the last parent study visit will complete the Adolescent/Adult version of the questionnaire themselves at all visits.

The questionnaires provide information about demographics; general quality of life, school, work, or daily activities; and symptom difficulties (pertaining to CF). Copies of the CFQ-R used in this study will be provided in the Study Reference Manual. Validated translations[24,25] of the CFQ-R, if available, will be provided for participating centers in non-English-speaking countries.

[redacted]

11.7.5 Other Events Related to Outcome (Treatment Cohort)

11.7.5.1 Antibiotic Therapy for Sinopulmonary Sign/Symptoms (Treatment Cohort)

New or changed antibiotic therapy (IV, inhaled, or oral) for the following sinopulmonary signs/symptoms will be determined and documented at visits:

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

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

For this study, a pulmonary exacerbation is defined as a change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the above signs/symptoms. This definition is based on the definition of a pulmonary exacerbation used in the parent clinical studies including those investigating ivacaftor and VX-661/ivacaftor.[35,36]

It is recommended that the study drug should not be interrupted during a pulmonary exacerbation unless, in the opinion of the investigator, it would be in the best interest of the subject.

The following information will be determined for protocol-defined pulmonary exacerbations:

- Number of pulmonary exacerbations
- Number of days with pulmonary exacerbations
- Time-to-first pulmonary exacerbation
- Number of pulmonary exacerbations requiring hospitalizations
- Number of days hospitalized for pulmonary exacerbations*
- Time-to-first hospitalization for pulmonary exacerbation
- Number of pulmonary exacerbations requiring IV antibiotic therapy
- Number of days on IV antibiotic therapy for pulmonary exacerbations
- Time-to-first IV antibiotic therapy for pulmonary exacerbations

*For each treatment group, the number of days hospitalized for pulmonary exacerbations will be analyzed as 48 weeks times the total numbers of days in hospital for pulmonary exacerbation, divided by the total number of weeks on treatment, for all subjects in the same treatment group.

11.7.5.2 Hospitalization for CF (Treatment Cohort)

At the visits indicated in Table 3-1, subjects will be queried about planned and unplanned hospitalizations lasting ≥24 hours. The dates of hospitalizations and the reasons for hospitalizations will be documented.

For any hospitalization (unplanned and planned), the procedures for safety reporting should be followed (see Section 13.1.2.3).

The following information will be determined:

- Number of planned hospitalizations for CF (i.e., prophylactic antibiotic therapy)

- Number of all unplanned hospitalizations
- Number of days of all unplanned hospitalizations
- Time-to-first unplanned hospitalization

11.8 Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, ECGs, pulse oximetry, ophthalmologic examinations (subjects <18 years of age [age on the date of informed consent/assent in the parent study]), and PEs.

11.8.1 Adverse Events (Treatment Cohort)

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 eCRF completion guidelines for investigators as well as training will be provided.

11.8.2 Clinical Laboratory Assessments (Treatment Cohort)

Blood and urine samples will be analyzed at a central laboratory. With the exception of Day 15 (when a lipid panel is not required), all blood samples will require a 4-hour fast before collection (at least a 4-hour fast is needed for the lipid panel). Fasting is not required at other time points unless specified in the assessment table. On Day 1/Returning Visit, blood samples will be collected before the first dose of the study drug. At all other scheduled visits, these samples will be collected at any time during the visit. Although blood samples are to be collected and analyzed at a central laboratory, a local laboratory may be used if a subject cannot return to the clinical study site for the mandatory liver function testing (Section 11.8.6). All urine pregnancy tests will be performed at the site.

Blood and urine samples for clinical laboratory assessments will be collected as shown in Table 3-1. Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1.1).

Table 11-1 Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urinalysis[a]
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen	Erythrocytes	Nitrite
Creatinine	Mean corpuscular hemoglobin	Urobilinogen
Sodium	Mean corpuscular hemoglobin concentration	Urine protein
Potassium	Mean corpuscular volume	pH
Calcium	Reticulocytes	Urine blood
Chloride	Platelets	Specific gravity
Magnesium	Leukocytes	Urine ketones
Bicarbonate	Differential (absolute and percent):	Urine bilirubin
Inorganic phosphate	Eosinophils	Urine glucose
Total bilirubin, direct bilirubin	Basophils	
Alkaline phosphatase	Neutrophils	
Aspartate aminotransferase	Lymphocytes	
Alanine aminotransferase	Monocytes	
Lactate dehydrogenase	**Coagulation Studies**	
Gamma-glutamyl transpeptidase	Activated partial thromboplastin time	
Total protein	Prothrombin time	
Albumin	Prothrombin time International Normalized Ratio	
Creatine kinase		
Amylase		
Lipase		
Vitamin Levels		
Vitamins A, D, E, K, and B12		
Lipid Panel		
Total cholesterol, triglycerides		
Low-density lipoprotein (LDL)		
High-density lipoprotein (HDL)		

[a] If urine is positive for leukocyte esterase, nitrite, protein, or blood, microscopic examination of urine will be performed for leukocytes, erythrocytes, crystals, bacteria, and casts.

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

Pregnancy (β-human chorionic gonadotropin) testing for female subjects who are of childbearing potential from the time of the Day 1 Visit or at any point through the Safety Follow-up Visit (as defined in Section 11.8.8.1): Serum samples will be obtained as specified and analyzed at the central laboratory. Urine samples will be obtained as specified and all urine pregnancy tests will be performed at the site. **The urine pregnancy test on Day 1 (and the Returning Visit for subjects who re-enroll) must be negative before the first dose of study drug.**

Additional evaluations: Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate.

For purposes of study conduct, only laboratory tests done in the central laboratory may be used. At the discretion of the local investigator, local laboratories may be used for management of urgent medical issues. If a local laboratory test value is found to be abnormal and clinically significant, it should be verified by the central laboratory as soon as possible after the investigator becomes aware of the abnormal result. If it is not possible to send a timely specimen

to the central laboratory (e.g., the subject was hospitalized elsewhere), the investigator may base the assessment of an AE on the local laboratory value.

11.8.3 Physical Examinations and Vital Signs (Treatment Cohort)

A PE of all body systems and vital signs assessment will be performed at Day 1 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 healthcare 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. Breast, anorectal, and genital examinations will be performed when medically indicated. Any clinically significant abnormal findings in physical examinations will be reported as AEs.

Vital signs include blood pressure (systolic and diastolic), temperature (oral), pulse rate, and respiration rate. These will be assessed following a 5-minute rest in the seated or supine position.

11.8.4 Electrocardiograms (Treatment Cohort)

Standard 12-lead ECGs will be performed using a machine with printout according to the Schedule of Assessments (Table 3-1). Additional standard 12-lead ECGs will be performed at any other time if clinically indicated. A window of ± 15 minutes will be allowed around the nominal times for all postdose ECG assessments.

The performance of all ECGs will adhere to the following guidelines:

- The subject will be instructed to rest in the supine position for at least 5 minutes before having an ECG performed.
- The ECG will be performed before any other procedures that may affect heart rate, such as blood draws.

The ECG traces will be manually read at the study site at the Day 1 and Safety Follow-up Visits. 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.

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 >45 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 (>45 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.

If the QTcF value remains above the threshold value (>45 msec from the average of the 3 predose values on Day 1 or ≥500 msec) on repeated measurement or is noted on >2 occasions with no identified alternative etiology for the increased QTcF study drug, then discontinuation from study drug treatment may be required after discussion with the medical monitor. Subjects in whom treatment is discontinued for increased QTc should have their QTc monitored closely until it normalizes or returns to baseline.

Further details pertaining to ECGs will be provided to sites in a separate document (ECG Manual).

11.8.5 Pulse Oximetry (Treatment Cohort)

Arterial oxygen saturation by pulse oximetry will be measured at visits noted in Table 3-1. This will be assessed following a 5-minute rest (seated or supine) and before study drug dosing. At visits when study drug is taken at the site, pulse oximetry will be collected before the morning dose. This is a noninvasive measure of oxygen delivery to the tissues and has been correlated with clinical status and lung function.

11.8.6 Liver Function Test Parameters (Treatment Cohort)

Liver Function Testing

Liver function testing (ALT, AST, GGT, ALP, direct bilirubin, and total bilirubin) must be performed as noted for serum chemistry, while subjects are receiving study drug treatment and at the Early Treatment Termination Visit and the Safety Follow-up Visit. These blood samples should be processed and shipped immediately per the Laboratory Manual.

Subjects with new treatment-emergent ALT or AST elevations of >3 × ULN and clinical symptoms 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 is >5 × ULN, repeat follow-up levels must be obtained within 7 ± 2 days.

If a subject cannot return to the site for liver function testing, a local laboratory may be used. Elevations in LFTs at the local laboratory must be reported immediately to the 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).

Study Drug Interruption

Study drug administration **must be interrupted** immediately (prior to confirmatory testing), and the medical monitor must be notified, if any of the following criteria is met:

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

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., acetaminophen use, viral hepatitis, or alcohol ingestion) for the confirmed elevated transaminases is identified, regardless of whether ALT or AST levels have improved, study drug treatment must be permanently discontinued if repeat testing within 48 to 72 hours confirms the initial elevation. Subjects in whom treatment is discontinued for elevated transaminases should have their transaminases monitored closely until levels normalize or return to baseline.

Resumption of Study Drug

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

11.8.7 Ophthalmologic Examination (Treatment Cohort)

Subjects <18 years of age (age on the date of informed consent/assent in the parent study) will undergo a baseline ophthalmologic examination performed by a licensed ophthalmologist within 28 days before enrollment on Day 1 of Study VX14-661-110, which includes:

- measurement of best corrected distance visual acuity of each eye,
- measurement of lens refracting power following cycloplegia (e.g., autorefractor or ophthalmoscopy streak), and
- pharmacologically dilated examination of the lens with a slit lamp.

The baseline ophthalmologic examination must be completed and the results reviewed before enrollment. This examination may be conducted while the subject is participating in the parent study.

If a cataract or lens opacity is identified and determined to be clinically significant by the ophthalmologist at the baseline examination, the subject will be notified. After discussion with the site principal investigator and in collaboration with the Vertex medical monitor, the subject may elect to participate or not to participate in the study. If the subject elects to participate, more frequent ophthalmologic monitoring should be considered.

Subjects who are enrolled in the Treatment Cohort will have ophthalmologic exams as noted in Table 3-1. If a cataract or lens opacity is identified and determined to be clinically significant by the ophthalmologist after dosing, the subject will be notified. After discussion with the site principal investigator and in collaboration with the Vertex medical monitor, the subject may elect to continue or discontinue the study. If the subject discontinues study drug, they should complete the Early Treatment Termination Visit and Safety Follow-up Visit (Sections 8.1.1.3 and 8.1.1.2). If the subject continues, more frequent ophthalmologic monitoring should be considered.

In addition to the baseline examination, an ophthalmologic examination will be performed by a licensed ophthalmologist at the Early Treatment Termination or Safety Follow-Up Visit for subjects < 18 years of age (age on the date of informed consent/assent in the parent study) who discontinue treatment after receiving at least 1 dose of study drug. This examination may be completed at either the Early Treatment Termination or Safety Follow-Up Visit, but must be completed by the date of the Safety Follow-Up Visit.

In addition, on Day 1 of Study VX14-661-110, the following history will be obtained for all subjects, if it was not documented in the parent study:

- history of steroid use
- history or presence of diabetes

- any prior ophthalmologic or optometric examinations
- history of trauma to the eye
- any family history of glaucoma, congenital cataracts, or cataracts arising later in life
- use of corrective lenses (contact lenses or eyeglasses)
- history of prolonged exposure to sunlight or ultraviolet light and use of sunglasses
- history of exposure to secondhand smoke.

11.8.8 Contraception and Pregnancy (Treatment Cohort)

11.8.8.1 Contraception

Participation in this study requires a commitment from the subject and his/her partner to use at least 1 acceptable method of contraception, which must be used correctly with every act of sexual intercourse. Methods of contraception should be in successful use from at least 14 days before the first dose of study drug (unless otherwise noted) and until 90 days following the last dose of study drug.

For female subjects using oral hormonal contraceptives:

1. The oral hormonal contraceptives should be in successful use from at least 60 days before the first dose of study drug (unless otherwise noted) and until 90 days following the last dose of study drug.

2. Female subjects who change their method of contraception to hormonal contraceptive during Study VX14-661-110 must use a second form of approved contraception for at least 60 days after beginning oral contraceptives.

Contraception for the couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
- If the male is infertile (e.g., bilateral orchiectomy). Infertility may be documented through examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound before the first dose of the study drug.
- If the female is of non-childbearing potential, per the following:
  - Documented hysterectomy or a bilateral oophorectomy/salpingo-oophorectomy.
  - Postmenopausal: continuous amenorrhea for at least 12 months and serum FSH levels ≥ 40 mIU/mL.
  - Has not achieved menarche (has not had her first menstrual period). If a female achieves menarche during the study, she will need to follow acceptable methods of contraception or abstinence.

For subjects for whom contraception methods are not waived due to at least 1 of the reasons cited above, the following are acceptable contraceptive methods for male subjects and their female (non-study) partners, and for female subjects and their male (non-study) partners:

Table 11-2 Acceptable Methods of Contraception

- Male vasectomy 6 months or more previously, with a documented negative post-vasectomy semen analysis for sperm.
- Male or female condom with or without spermicide (either as a single product if commercially available and/or as allowed according to local regulations; otherwise condom and spermicide as separate products).
- Female bilateral tubal ligation performed at least 6 months previously.
- Female diaphragm, cervical cap, or vaginal sponge, each with spermicide (where available).
- Female continuous use of an intrauterine device (non-hormone releasing or hormone releasing) for at least 90 days before the first dose of study drug
- Female combined (estrogen and progestogen-containing) or progestogen-only oral hormonal contraception associated with inhibition of ovulation if successfully used for at least 60 days before the first dose of study drug or with a second form of approved contraception for at least 60 days after beginning hormonal contraception.

Important notes:

- Local requirements may prohibit the use of some of these acceptable methods listed above. Please contact the medical monitor with any questions.
- If applicable, additional contraception requirements may need to be followed according to local regulations and/or requirements.
- Male and female subjects who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study if they become sexually active.
- Female condom used with male condom (as a double method of contraception) is not an acceptable method of contraception due to risk of tearing; a different acceptable method of birth control must be used as described in Table 11-2.
- Male subjects must not donate sperm after the first dose of study drug, throughout the study, and for 90 days following the last dose of study drug.
- Female subjects and female partners of male subjects should not plan to become pregnant during the study through 90 days following the last dose of study drug.
- Female subjects should not nurse a child from the start of study drug dosing through 90 days following the last dose of study drug.

Other situations that do not fall within the above specifications may be discussed with the Vertex medical monitor on an individual basis.

11.8.8.2 Pregnancy

Subjects will be counseled to inform the investigator of any pregnancy that occurs during study treatment and within 90 days after the last dose of the study drug.

If a female subject or the female partner of a male subject becomes pregnant while participating in the study, study drug must be permanently discontinued immediately. For male subjects, study drug does not need to be permanently discontinued if the female partner's pregnancy resulted from donated sperm or sperm banked before study drug exposure (Section 11.8.8.1). The investigator must notify the medical monitor and Vertex GPS within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy using the Pregnancy Information Collection Form.

If the subject is confirmed to be on study drug, the subject or partner will be followed until the end of the pregnancy and the infant will be followed for 1 year after the birth, provided informed consent/assent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

12 STATISTICAL AND ANALYTICAL PLANS

This section presents a summary of the planned analyses for the Treatment Cohort in this protocol. Statistical analysis details for the Treatment Cohort will be provided in the Statistical Analysis Plan (SAP) will be finalized before the clinical data lock for the study.

No analysis will be performed for the Observational Cohort.

12.1 Sample Size and Power

Study VX14-661-110 is a rollover study that plans to enroll subjects from Studies VX13-661-103, VX14-661-106, VX14-661-108, VX14-661-109, VX14-661-111, and other eligible Vertex studies investigating VX-661 in combination with ivacaftor who meet the eligibility criteria for this study. Approximately up to 1375 subjects are potentially eligible to be enrolled from the following parent studies: 40 subjects from Study VX13-661-103, 490 subjects from Study VX14-661-106, up to 300 subjects from Study VX14-661-108, up to 200 subjects from Study VX14-661-109, and 45 subjects from Study VX14-661-111, if eligible.

12.2 Analysis Sets

For subjects in the Treatment Cohort, the assignment to analysis sets will be done before the clinical data lock for the study.

The All Subjects Set is defined as all subjects who signed inform consent (enrolled) and have received at least 1 dose of study drug in Study VX14-661-110. This analysis set will be used in subject listings and disposition summary tables unless otherwise specified.

The Full Analysis Set (FAS) is defined as all enrolled subjects who have received at least 1 dose of study drug in Study VX14-661-110 and have one of the following mutations: *F508del/F508del*, *F508del/Residual function*, and *F508del/Gating*. The FAS is to be used in the efficacy analyses unless otherwise specified.

The Safety Set is defined as all subjects who received at least 1 dose of study drug in Study VX14-661-110. The Safety Set is to be used for the safety analyses unless otherwise specified.

12.3 Statistical Analysis

12.3.1 General Considerations

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

Categorical variables will be summarized using counts and percentages.

Baseline value, unless otherwise specified, for efficacy and safety analyses, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of VX-661/ivacaftor or ivacaftor alone (in the parent study or Study VX14-661-110, but

after the washout period, if applicable). For subjects who received VX-661 and ivacaftor combination therapy in the parent study, the baseline will be the same as the baseline in the parent study. For subjects who received placebo or ivacaftor in the parent study and transitioned to VX-661/ivacaftor in Study VX14-661-110, the baseline will be the baseline in Study VX14-661-110. For subjects from Study VX14-661-108, the parent study baseline will be the baseline for Treatment Period 2 in Study VX14-661-108. For subjects from Study VX13-661-103, the parent study baseline will be the baseline in the Open-label Phase of Study VX13-661-103 for subjects who participated in the Open-label Phase or the baseline in Study VX14-661-110 for subjects who did not participate in the Open-label Phase of Study VX13-661-103.

Change (absolute change) from baseline will be calculated as postbaseline value - baseline value.

Relative change from baseline will be calculated as (postbaseline value - baseline value)/baseline value.

Efficacy Analysis Period will include the time from the first dose of VX-661/ivacaftor or ivacaftor alone (in the parent study or Study VX14-661-110, but after the washout period, if applicable) to the last scheduled efficacy visit in Part of Study VX14-661-110. For subjects who participate in another qualified Vertex study before completing Study VX14-661-110 assessments and re-enroll in Study VX14-661-110, the Efficacy Analysis Period will exclude the time between the last dose before the discontinuation from Study VX14-661-110 and the first dose after re-enrollment in Study VX14-661-110.

Treatment-emergent (TE) Period will include the time from the first active dose of VX-661/ivacaftor or ivacaftor alone (in the parent study or Study VX14-661-110, but after the washout period, if applicable) to the Safety Follow-up Visit or 28 days after the last dose of the study drug for subjects who do not have a Safety Follow-up Visit or who have their Safety Follow-up Visit more than 35 days after the last dose of Study VX14-661-110. For subjects who participate in another qualified Vertex study before completing Study VX14-661-110 (96 weeks) and re-enroll in Study VX14-661-110, the TE Period will exclude the time spent in the other study. Specifically, the TE Period will be interrupted 28 days after the last dose of study drug in Study VX14-661-110 and will restart with re-enrollment into Study VX14-661-110 when the subject takes the first dose of study drug.

Note, in the Efficacy Analysis and TE Periods, for subjects who received the active study drugs in Study VX14-661-108, the first active dose will be the first dose of VX-661/ivacaftor or ivacaftor monotherapy in the Treatment Period 2 of Study VX14-661-108. For subjects who received the active study drug from Study VX13-661-103, the first active dose will be the first active dose of study drug in the Open-label Phase of Study VX13-661-103.

12.3.2 Overview of Analysis Strategies

- Study VX14-661-110 data will not be analyzed in isolation as patients received different durations of treatment in the parent studies. Study VX14-661-110 data will be integrated with the parent study data for each subject from the first active dose of VX-661/ivacaftor or ivacaftor alone (after the washout period, if applicable).
- The analysis baseline will be the last non-missing measurement prior to the first active dose of VX-661/ivacaftor or ivacaftor alone [in the parent study (after the washout period, if

applicable) or Study VX14-661-110]. All post-baseline measurements will be mapped to the uniform analysis visit windows based on the study days counted from the first active dose of VX-661/ivacaftor or ivacaftor alone (after the washout period in the parent study, if applicable) to make the results more comparable and interpretable.

- For subjects in Study VX14-661-110, the safety analyses will be performed on all of the subjects pooled together. The efficacy analysis will be performed on each CFTR mutation group separately *(F508del/F508del, F508del/Residual Function, and F508del/Gating).*

12.3.3 Background Characteristics

Subject disposition, demographic and baseline characteristics, prior and concomitant medications, study drug exposure and compliance, and other background characteristics will be summarized. Additionally, all subject data will be presented in subject data listings.

12.3.3.1 Subject Disposition

All summaries in this section will be performed on all subjects pooled together based on the Safety Set, and performed on each CFTR mutation group separately (*F508del/F508del*, *F508del/Residual Function*, and *F508del/Gating*) based on the FAS, unless otherwise specified in the SAP. No statistical hypothesis testing will be performed.

Subject disposition analysis will be performed. The number and percentage of subjects in the following categories will be summarized as appropriate:

- All Subjects Set
- Safety Set
- FAS
- Completed study drug treatment
- Prematurely discontinued treatment and the reasons for discontinuation
- Prematurely discontinued the study during the Safety Follow-up and the reasons for discontinuations

12.3.3.2 Demographics and Baseline Characteristics

All summaries in this section will be performed on all subjects pooled together based on the Safety Set, and performed on each CFTR mutation group separately (*F508del/F508del*, *F508del/Residual Function*, and *F508del/Gating*) based on the FAS, unless otherwise specified in the SAP. No statistical hypothesis testing will be performed. Demographics and baseline characteristics of Study VX14-661-110 will be based on the demographics and baseline characteristics in the parent studies.

Demographic, background (e.g., medical history), and baseline characteristics will be summarized. Baseline characteristics will be the based on the parent study baseline characteristics. Protocol deviations/violations will be provided as a subject data listing only. Important protocol deviations/violations will be listed or summarized.

The following demographics and baseline characteristics will be summarized for the FAS: sex, race, ethnicity, age, weight, height, BMI, region, baseline ppFEV$_1$, and baseline score of CFQ-R respiratory domain.

12.3.3.3 Prior and Concomitant Medications

All summaries in this section will be performed on all subjects pooled together based on the Safety Set, unless otherwise specified in the SAP. No statistical hypothesis testing will be performed.

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

- **Prior medication:** any medication that started before the first active dose of study drug (in the parent study or in Study VX14-661-110, after the washout period, if applicable), regardless of when it ended. In addition, for subjects who participate in another qualified Vertex study before completing Study VX14-661-110 assessments and re-enroll in Study VX14-661-110, any medication that was collected with a start date after the informed consent/assent for re-enrollment is signed and before the first dose of VX-661/ivacaftor after re-enrollment in Study VX14-661-110 will also be considered as prior medication, regardless of when medication was discontinued.
- **Concomitant medication:** medication continued or newly received at, or after, initial dosing of study drug through the end of the TE Period.
- **Post-treatment medication:** medication continued or newly received beyond the TE Period.

A given medication can be classified as a prior medication, a concomitant medication, or a post-treatment medication; both prior and concomitant; both concomitant and post-treatment; or prior, concomitant, and post-treatment. If a medication has a missing or partial missing start/end date or time and it cannot be determined whether it was taken before initial dosing, concomitantly, or beyond the TE Period, it will be considered as prior, concomitant, and post-treatment.

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

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

12.3.3.4 Study Drug Exposure and Compliance

All summaries in this section will be performed on all subjects pooled together based on the Safety Set, and performed on each CFTR mutation group separately (*F508del/F508del*, *F508del/Residual Function*, and *F508del/Gating*) based on the FAS, unless otherwise specified in the SAP. No statistical hypothesis testing will be performed.

Treatment Cohort

Exposure to study drug (i.e., duration of treatment) will be summarized for the FAS in terms of duration of treatment a subject received (in days), defined as the last day minus the first day of dosing with VX-661/ivacaftor or ivacaftor monotherapy in the parent study (but after the washout period, if applicable) or VX-661/ivacaftor in Study VX14-661-110, plus 1.

Dosing compliance will be summarized for the FAS and is calculated as the actual number of days at which study drug was administered, as a percentage of the duration of study drug exposure.

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

12.3.4 Efficacy Analysis

Treatment Cohort

Assessment of the long-term efficacy and tolerability of VX-661 /ivacaftor for subjects in the Treatment Cohort is a secondary or other objective of this study. The efficacy analysis will be performed on each CFTR mutation group separately (*F508del/F508del, F508del/Residual function, and F508del/Gating*). All data collected during the efficacy analysis period through the end of Study VX14-661-110 will be summarized.

12.3.4.1 Analysis of Primary Efficacy Variables

Not applicable since efficacy is not a primary objective.

12.3.4.2 Analysis of Secondary [redacted] Efficacy Variables (Treatment Cohort)

- **Absolute change from baseline in $ppFEV_1$**

One of the secondary efficacy endpoints is the absolute change from baseline in $ppFEV_1$. The primary analysis for this secondary endpoint will be based on a mixed-effect repeated-measure model (MMRM), as applicable. The model will include the absolute change from baseline in $ppFEV_1$ as the dependent variable; treatment group, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect with or without adjustment for sex, age, baseline $ppFEV_1$.

In the model, visit will be treated as a class variable, assuming an unstructured covariance matrix to model the within-subject variability. This model imposes no assumptions on the correlational structure and is considered robust. Denominator degrees of freedom for the F test for fixed effects will be estimated using the Kenward-Roger approximation. If there is a convergence problem due to the use of an unstructured covariance matrix, a compound symmetry covariance structure will be used to model the within-subject errors. With a mixed-effects model based on a restricted maximum likelihood estimation used for the primary analysis and assuming that, conditional on fixed and random effects, data are missing at random, no imputation of missing data will be performed.

Descriptive summary statistics including number of subjects, mean, standard error, and least square mean (LS mean), along with the associated 95% CI will be provided for each visit.

- **Relative change from baseline in $ppFEV_1$**

Analysis of this variable will be performed using the same MMRM model as described for the absolute change from baseline in $ppFEV_1$.

- **Number of pulmonary exacerbations**

The number of pulmonary exacerbations will be analyzed using a negative binomial regression model as applicable. The independent variables will include visit, sex, age, baseline $ppFEV_1$. The event rate and 95% CI will be reported.

- **Absolute change from baseline in body mass index (BMI)**

Analysis of this variable will be similar to the model as described for the absolute change in $ppFEV_1$ from baseline, with the addition of baseline BMI as the covariate.

- **Absolute change from baseline in BMI z-score**

Analysis of this variable will be similar to the model as described for the absolute change in $ppFEV_1$ from baseline, with the addition of the BMI z-score at baseline as a covariate for subjects <20 years old at the time of the Screening Visit in the parent study.

- **Absolute change from baseline in CFQ-R respiratory domain score**

Analysis of this domain will be similar to the model as described for the absolute change in $ppFEV_1$ from baseline, with the addition of the CFQ-R respiratory domain score at baseline as the covariate.

- **Absolute change from baseline in body weight**

Analysis for this variable will be similar to the model as described for the absolute change in $ppFEV_1$ from baseline, with the addition of the body weight at baseline as a covariate.

- **Absolute change from baseline in body weight z-score for subjects aged <20 years at screening in the parent study**

Analysis of this variable will be similar to the model as described for the absolute change in $ppFEV_1$ from baseline, with the addition of the body weight z-score at baseline as a covariate for subjects <20 years old at the time of the Screening Visit in the parent study.

- **Absolute change from baseline in height z-score for subjects aged <20 years at screening in the parent study**

Analysis of this variable will be similar to the model as described for the absolute change in $ppFEV_1$ from baseline, with the addition of the height z-score at baseline as a covariate for subjects <20 years old at the time of the Screening Visit in the parent study.

- **Time-to-first pulmonary exacerbation**

Time-to-first pulmonary exacerbation is defined as days starting from the first dose of VX-661 and ivacaftor combination therapy to the first event of pulmonary exacerbation. A subject without exacerbation before the end of the Efficacy Analysis Period of Study VX14-661-110 will be considered censored at the end of the Efficacy Analysis Period. Kaplan-Meier method will be used to produce graphical presentation of the survival distribution (exacerbation-free survival) and to estimate cumulative survival rates by the CFTR mutation groups.

[redacted]

[redacted]

- **Absolute change in Brody/CF-CT scores from baseline using LDCT scans for subjects enrolling from Study VX15-661-112**

Only applicable for the subjects enrolling from Study VX15-661-112. The absolute values and changes from baseline of the Total Brody/CF-CT scores [redacted] will be summarized descriptively.

[redacted]

12.3.5 Safety Analysis (Treatment Cohort)

Evaluating the long-term safety and tolerability of VX-661 in combination with ivacaftor treatment in the Treatment Cohort is the primary objective of this study. All safety analyses will be based on TE Period for subjects in the Safety Set.

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

- Treatment-emergent adverse events (TEAEs), SAEs, TEAEs leading to treatment discontinuations, TEAEs leading to treatment interruptions, deaths.
- Clinical laboratory results (i.e., hematology, serum chemistry, coagulation studies, vitamin levels, lipid panel, and urinalysis)
- Standard 12-lead ECGs
- Vital signs
- Pulse oximetry
- Pregnancy test

Descriptive analysis of safety will be performed for subjects in the Safety Set of Study VX14-661-110.

12.3.5.1 Adverse Events

For analysis purposes, AEs will be classified as pretreatment AEs, TEAEs, or post-treatment AEs.

- **Pretreatment AE:** any AE that increased in severity or newly developed before the first active dose of VX-661/ivacaftor or ivacaftor alone in the TE Period. For subjects who participate in another qualified Vertex study before completing Study VX14-661-110 assessments and re-enroll in Study VX14-661-110, pretreatment AEs include any AE that increased in severity or began before the first dose of VX-661/ivacaftor in the TE Period, and any AE that increased in severity or began after signing informed consent/assent for re-

enrollment and before the first dose of VX-661/ivacaftor after re-enrollment in Study VX14-661-110.

- **TEAE:** any AE that increased in severity or began at, or after, the first active dose of VX-661/ivacaftor or ivacaftor alone in the TE Period.
- **Post-treatment AE:** any AE that increased in severity or began beyond the TE Period.

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

An overview of AEs table will include the following.

- All TEAEs
- TEAEs by strongest relationship
- Related TEAEs
- TEAEs by maximum severity
- Grade 3/4 TEAEs
- Serious TEAEs
- Related serious TEAEs
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- TEAEs leading to death

The following summary tables of TEAEs will also be provided:

- All TEAEs by PT and by SOC/PT
- Related TEAEs by SOC/PT
- Serious TEAEs by PT and by SOC/PT
- Related serious TEAEs by SOC/PT
- Grade 3/4 TEAEs by SOC/PT
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- TEAEs leading to death
- Treatment-emergent elevated transaminases events by PT
- Treatment-emergent respiratory events or symptoms by PT

Summaries will be presented by MedDRA system organ class and preferred term using frequency counts and percentages (i.e., number and percentage of subjects with an event as well as total number of events). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once, only the maximum severity level will be presented in the severity summaries, and the

worst/highest relationship level in the relationship summaries. An AE overview table will be provided. A separate table will summarize all TEAEs when each of them is considered unique, hereafter referred to as an AE count table. In addition, a listing containing individual subject AE data for all deaths and other serious and significant AEs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

12.3.5.2 Clinical Laboratory Assessments

For the treatment-emergent laboratory measurements, the raw values and change from baseline values of the continuous laboratory parameters will be summarized in SI units at each scheduled time point during the TE Period. Mean value at each visit will be plotted for each of the liver function parameters. In addition, a listing containing individual subject laboratory assessment values outside the reference ranges will be provided.

The number and percentage of subjects with at least 1 threshold analysis event during the TE Period will be summarized for selected laboratory parameters. The shift of the threshold analysis criteria from baseline to postbaseline will also be summarized for selected laboratory parameters. The threshold analysis and parameter-selection criteria will be provided in the SAP.

Results of abnormal urinalysis and positive serum/urine pregnancy tests will be listed in individual subject data listings only.

12.3.5.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of raw values and change from baseline values will be provided at each scheduled time point during the TE Period for the following standard digital ECG measurements: PR, QT, and QTc for HR interval (QTcF), QRS duration, and HR. In addition, the mean value at each visit will be plotted by treatment groups for QTc.

The number and percentage of subjects with at least 1 threshold analysis event during the TE Period will be summarized by treatment group. The threshold analysis criteria will be provided in the SAP.

12.3.5.4 Vital Signs

For the treatment-emergent vital signs measurements, the raw values and change from baseline values will be summarized at each scheduled time point during the TE Period: systolic and diastolic blood pressure (mm Hg), body temperature (°C), HR (beats per minute [bpm]), and respiratory rate (breaths per minute).

The number and percentage of subjects with at least 1 threshold analysis event during the TE Period will be summarized. The threshold analysis criteria will be provided in SAP.

12.3.5.5 Physical Examination

No tables/figures/listings will be provided for physical examination.

12.3.5.6 Pulse Oximetry

For the treatment-emergent pulse oximetry measurements, a summary of raw values and change from baseline values will be provided at each scheduled time point during the TE Period for the percent of oxygen saturation by pulse oximetry. In addition, the mean value at each visit will be plotted by treatment groups for the percent of oxygen saturation.

The number and percentage of subjects with shift changes from baseline (normal/missing and low according to the reference range) to the lowest percent of oxygen saturation during the TE Period will be tabulated.

12.3.5.7 Ophthalmologic Examination

Ophthalmologic examination results will be listed for subjects < 18 years old (age on the date of informed consent/assent in the parent study) with cataracts anytime during the TE period.

12.3.5.8 Pregnancy Tests

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

12.3.6 Interim Analyses, DMC Analyses, and Data Monitoring

12.3.6.1 Interim Analysis

Interim analyses may occur at any time during the study as determined by Vertex. During any interim analysis time, if any parent study is still not completely unblinded to the relevant study personnel, the analysis will be performed according to the relevant unblinding plans. In general, Vertex Biometrics will use blinded data to program tables, figures, and listings (TFLs) based on the relevant SAP for the interim analysis. An independent biometrics team (internal or external as defined in the Unblinding Plan) will then rely on the programs to prepare unblinded TFLs using unblinded data. The details of the unblinding process will be provided in the Unblinding Plan.

12.3.6.2 DMC Analysis

A DMC (Data Monitoring Committee) will be formed. The DMC's objectives and operational details will be defined in a separate document (the DMC Charter). The DMC will conduct regular planned safety reviews of study data as outlined in the DMC Charter.

12.3.6.3 Data Monitoring

Vertex will continuously monitor unblinded safety data. If in the course of evaluating safety events from other blinded studies, data from the open-label study may be shared with an external data monitoring committee in order to better understand any potential safety signals.

12.4 Clinical Pharmacology Analysis

12.4.1 Pharmacokinetic Analysis (Treatment Cohort)

A detailed description of the clinical pharmacology analyses will be provided in the CPAP. Listings of plasma concentration data of VX-661, ivacaftor, and their metabolites will be provided in the clinical study report. A population approach may be used to analyze the time-versus-plasma concentration data of VX-661, ivacaftor, and their metabolites. The PK/pharmacodynamic (PD) relationship between concentrations of VX-661 and ivacaftor (and their metabolites as appropriate) and efficacy and safety measurements may be investigated. The results of the PK and PK/PD analyses using a population approach will be presented in a separate report, if 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 preexisting 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 a clinically significant worsening from baseline 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 clinical status of the subject indicates a life-threatening AE.

13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time ICF is signed, or assent, if applicable, until the following time points:

- Until time of withdrawal of consent
- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit, the **earliest** of:
  - 28 days after the last dose of study drug, or
  - the Early Treatment Termination Visit, if that visit is 3 weeks or later following the last dose of study drug (see Section 8.1.1.3), or

- the Early Treatment Termination Visit, or until the time of enrollment in another qualified Vertex study

All subjects will be queried, using non-leading 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 eCRF and source document. 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

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and non-serious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed August 2012). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." 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 CTCAE.

The severity of an AE that does not appear in the CTCAE 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 experience 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 re-appeared 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

For the Treatment Cohorts, all SAEs that occur after obtaining informed consent and assent (where applicable) through the Safety Follow-up Visit, regardless of causality, will be reported by the investigator to Vertex 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**.

For the Observational Cohort, all related SAEs that occur after obtaining informed consent and assent (where applicable) through the Long-term Follow-up telephone contact at Year 2 will be reported by the investigator to GPS within 24 hours.

SAEs will be recorded on the Vertex Organized 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 Clinical Trials 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 Vertex Clinical Trials 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 Vertex Clinical Trial 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 Global Patient Safety via
Email: [redacted] (Preferred Choice)
Or via Fax: [redacted]
Contact Telephone: [redacted]

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 independent ethics committees (IECs).

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

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 (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or Vertex, as allowable by local applicable laws and regulations.

13.2.2 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject or legal representative or guardian (if applicable), and assent will be obtained from the subject (if applicable), before study participation. The method of obtaining and documenting the informed consent and assent (if applicable) 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 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 eCRFs, 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 doctor 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 eCRFs/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 an eCRF 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 eCRF 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 eCRFs/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 eCRFs/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 eCRFs on the subjects for which they are responsible.

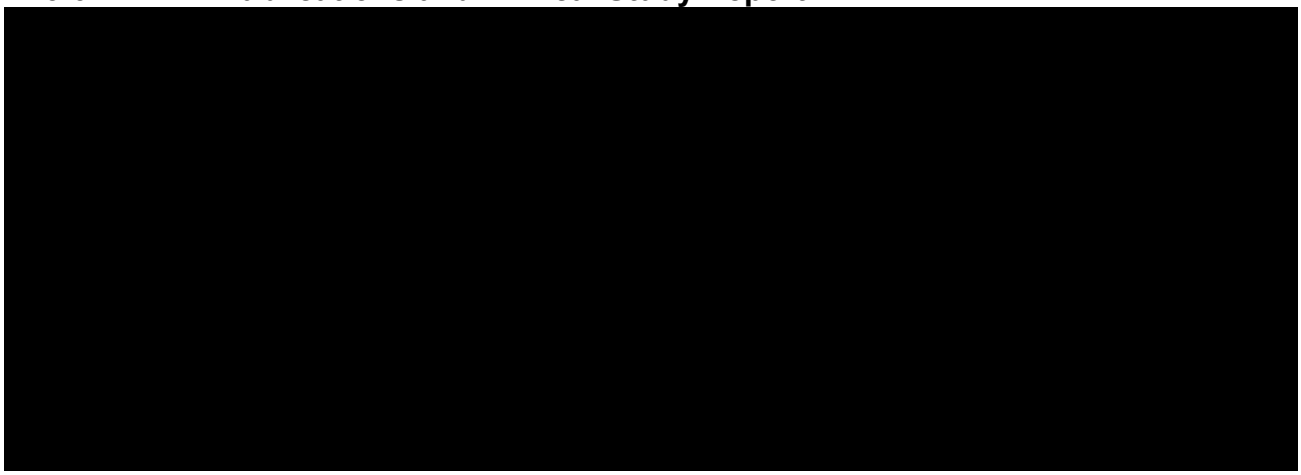
An eCRF will be completed for each enrolled study subject. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's eCRF. Source documentation supporting the eCRF data will indicate the subject's participation in the study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

The investigator, or designated representative, will complete the eCRF 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 eCRFs, including any changes made to the eCRFs, to endorse the final submitted data for the subjects for whom the investigator is responsible.

Vertex will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF 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



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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 #: VX14-661-110	Version #: 3.4 IRE, ESP, ISR, US	Version Date: 09 June 2017
Study Title: A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the *F508del-CFTR* Mutation		

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

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15.2 Investigator Signature Page

Protocol #: VX14-661-110	Version #: 3.4 IRE, ESP, ISR, US	Version Date: 09 June 2017
Study Title: A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the *F508del-CFTR* Mutation		

I have read Protocol VX14-661-110, Version 3.4 IRE, ESP, ISR, US and agree to conduct the study according to its terms. I understand that all information concerning VX-661 and ivacaftor and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date