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TITLE PAGE



VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 2, Randomized, Placebo-Controlled, Double-blind Study to Evaluate the Effect of VX-661 in Combination With Ivacaftor on Chest Imaging Endpoints in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

Vertex Study Number: VX15-661-112



Date of Protocol: 26 February 2018 (Version 5.0)

Replaces: Version 4.0 (24 October 2017)

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

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2 SYNOPSIS

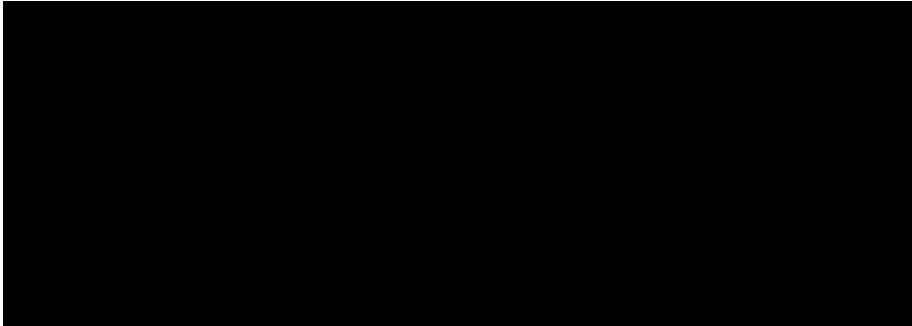
Title A Phase 2, Randomized, Placebo-Controlled, Double-blind Study to Evaluate the Effect of VX-661 in Combination With Ivacaftor on Chest Imaging Endpoints in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the *F508del CFTR* Mutation

Brief Title A Study to Evaluate the Effect of VX-661 in Combination With Ivacaftor on Chest Imaging Endpoints in Subjects With Cystic Fibrosis, Homozygous for the *F508del CFTR* Mutation

Clinical Phase and Clinical Study Type Phase 2 efficacy and safety

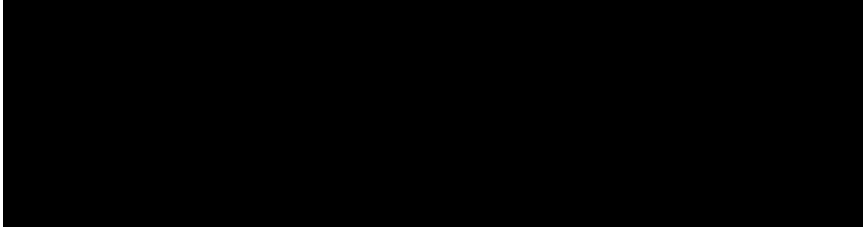
Objectives Primary:
To evaluate the treatment effect of VX-661 in combination with ivacaftor (VX-661/ivacaftor) on chest imaging endpoints as evaluated using low-dose computed tomography (LDCT) at Week 72 in subjects with CF who are homozygous for the *F508del* mutation on the CF transmembrane conductance regulator (*CFTR*) gene

Secondary:

- To evaluate the safety of VX-661/ivacaftor through Week 72
- 

Endpoints Primary:
• Absolute change in Total Brody/CF-CT score from baseline at Week 72 using LDCT

Secondary:

- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values (hematology, serum chemistry, lipid and vitamin levels, coagulation studies, and urinalysis), standard digital electrocardiograms (ECGs), vital signs, and pulse oximetry
- 

Number of Subjects Approximately 40

Study Population Subjects aged 12 years and older with CF, homozygous for the *F508del CFTR* mutation

Investigational Drug **Active Substance:** VX-661 and ivacaftor
Activity: cystic fibrosis transmembrane conductance regulator (CFTR) corrector and potentiator (increased chloride ion [Cl⁻] secretion)
Strength and Route of Administration: VX-661 100-mg/ivacaftor 150-mg fixed-dose combination (light yellow) film-coated tablet for oral administration (for morning dose)

Active Substance: ivacaftor
Activity: cystic fibrosis transmembrane potentiator (increased chloride ion [Cl⁻] secretion)

Strength and Route of Administration: ivacaftor 150-mg (light blue) film-coated tablet for oral administration (for evening dose)

Active Substance: not applicable

Activity: placebo

Strength and Route of Administration: 0-mg film-coated matching placebo tablets for oral administration (1 light yellow for morning dose and 1 light blue for evening dose)

Study Duration Excluding the Screening Period, the planned study duration is 76 weeks ± 7 days (from Day 1 to the Safety Follow-up Visit).

Study Design This is a Phase 2, randomized, placebo-controlled, double-blind, parallel-group, multicenter study in subjects with CF who are homozygous for the *F508del-CFTR* mutation. This study is designed to evaluate the treatment effect of VX-661/ivacaftor on chest imaging endpoints over 72 weeks of treatment; LDCT [REDACTED] will be used for chest imaging.

All subjects will undergo LDCT imaging at specified time points. [REDACTED]

[REDACTED] The images will be evaluated using the Brody/CF-CT scoring system.

Safety during 72 weeks of treatment will also be evaluated.

This study includes a Screening Period, a 72-week Treatment Period, and a Safety Follow-up Visit. Following a 28-day Screening Period, approximately 40 subjects will be randomized (1:1) to 1 of the 2 treatment arms, active or placebo, on Day 1. The active treatment regimen will be comprised of a morning dose of a fixed-dose combination tablet of VX-661 100-mg/ivacaftor 150-mg and an evening dose of ivacaftor 150-mg to be taken approximately 12 hours after the morning dose. The placebo regimen will be visually-matched tablets to be taken on the same schedule as the active treatment.

The study will be double-blind. Interim analyses are described below in the “Statistical Analyses” section.

Assessments **Efficacy:** LDCT, [REDACTED]

[REDACTED]
Safety: AEs, clinical laboratory assessments (hematology, serum chemistry, vitamin levels, lipid panel, coagulation studies, and urinalysis), vital signs, physical examinations, pulse oximetry, and ECGs

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 and treatment unblinding.

The primary endpoint is the change from baseline in Total Brody/CF-CT score at Week 72 using LDCT. The primary analysis will be based on an analysis of covariance (ANCOVA) model with the change from baseline in Total Brody/CF-CT score at Week 72 as dependent variable, and treatment, sex (male versus female), and age as covariates.

[REDACTED]
Safety data will be summarized descriptively by treatment group.

IDMC Reviews The independent data monitoring committee (IDMC) will conduct regular planned safety reviews of study data as outlined in the IDMC charter.

3 SCHEDULE OF ASSESSMENTS

Schedules of Assessments are shown in Table 3-1 and Table 3-2.

Table 3-1 Study VX15-661-112: Screening

Event/Assessment	Screening Period (Day -28 through Day -1)
Informed consent (and assent, when applicable)	X
Demographics	X
Medical history	X
Ophthalmological history	X
CF genotype ^a	X
FSH ^b	X
Serum pregnancy test (all females of childbearing potential) ^c	X
Hematology	X
Coagulation	X
Serum chemistry	X
Urinalysis	X
Weight and height ^d	X
Ophthalmologic examination ^e	X
Complete physical examination	X
Vital signs ^f	X
Pulse oximetry ^f	X
Standard 12-lead ECG ^g	X
Spirometry ^h	X
Inclusion/exclusion criteria review	X
Prior and concomitant medications	X
Sweat chloride ⁱ	X
AEs and SAEs	Continuous from signing of the ICF and assent (where applicable) through the Safety Follow-up Visit

AE: adverse event; CF: cystic fibrosis; ECG: electrocardiogram; FSH: follicle-stimulating hormone; ICF: informed consent form; SAE: serious adverse event.

- ^a All subjects will be tested for CF genotype. Specific instructions will be provided in the Laboratory Manual. CF genotyping may be waived if the subject has a documented result from a previous Vertex study.
- ^b FSH will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be ≥ 40 mIU/mL to be considered postmenopausal.
- ^c Any female subject who does not meet the criteria for non-childbearing potential is considered to be of childbearing potential and must have a serum pregnancy test.
- ^d Weight and height will be measured with shoes off.
- ^e An ophthalmologic examination will be conducted on subjects of all ages by an ophthalmologist. The ophthalmologic examination does not need to be repeated if there is documentation of an examination that met the protocol criteria and was conducted within 3 months before the start of the Screening Period or if there is documentation of bilateral lens removal (Section 11.6.8).
- ^f Vital signs and pulse oximetry will be collected after the subject has been at rest (seated or supine) for 5 minutes.
- ^g A standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes.
- ^h Spirometry may be performed pre- or postbronchodilator [REDACTED]
- ⁱ A sweat chloride test must be performed at the Screening Visit if an eligible sweat chloride value is not available in the subject's medical records and the Screening Visit value is needed to establish eligibility. For subjects using sweat chloride values documented in their medical records to establish eligibility, the sweat chloride test at the Screening Visit is optional.

Table 3-2 Study VX15-661-112: Treatment Period (Day 1 to Week 72), Early Termination of Treatment Visit, and Safety Follow-up Visit Assessments

Event/Assessment ^a	Day 1	Day 15 (± 3 days)	Week 4, Week 12, (± 1 week)	Week 24 (± 1 week)	Week 36, Week 48, Week 60 (± 1 week)	Week 72 (± 1 week)	Early Termination of Treatment Visit (Within 7 days After Last Dose of Study Drug)	Safety Follow-up Visit 4 weeks (± 7 days) After Last Dose of Study Drug ^b
Clinic visit	X	X	X	X	X	X	X	X
Inclusion and exclusion criteria review ^c	X							
Randomization ^d	X							
Complete physical examination ^f	X					X	X	X
Pregnancy test ^g	urine		urine	urine	urine	urine	serum	serum

^a All assessments will be performed before dosing unless noted otherwise. If study drug is not administered on the day of the visit (i.e., study drug interruption or premature discontinuation of study drug treatment), only 1 set of assessments will be collected.

^b The Safety Follow-up Visit is not required for subjects who complete the Week 72 Visit and have enrolled in the TEZ/IVA open-label extension study, VX14-661-110, within 28 days after the last dose of study drug.

^c The screening inclusion and exclusion criteria should be re-reviewed before administration of study drug on Day 1.

^d Randomization must occur after the informed consent/assent has been obtained and all inclusion and exclusion criteria are met and before the first dose of study drug. Randomization will be done through an interactive web response system. Randomization may occur on Day -1 if the above conditions for randomization have been met.

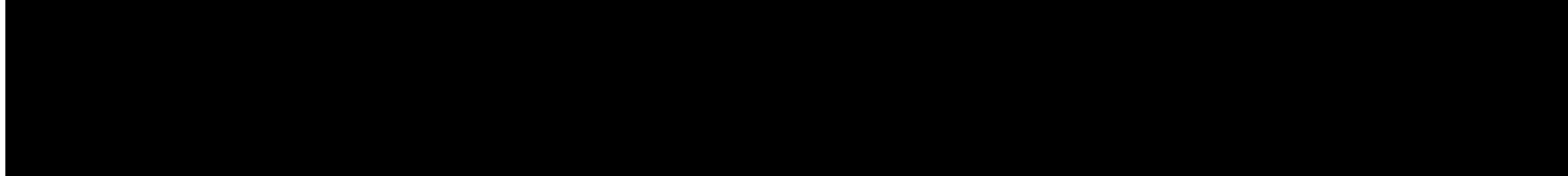
^f In addition to the indicated visits, a symptom-targeted physical examinations will occur at any time during the study if triggered by adverse events (AEs) or if deemed necessary by the investigator.

^g Pregnancy tests will be performed for all female subjects of childbearing potential. Day 1 results will be reviewed before dosing and the Low-dose CT scan. Week 72 results will be reviewed before the Low-dose CT scan.

Table 3-2 Study VX15-661-112: Treatment Period (Day 1 to Week 72), Early Termination of Treatment Visit, and Safety Follow-up Visit Assessments

Event/Assessment ^a	Day 1	Day 15 (± 3 days)	Week 4, Week 12, (± 1 week)	Week 24 (± 1 week)	Week 36, Week 48, Week 60 (± 1 week)	Week 72 (± 1 week)	Early Termination of Treatment Visit (Within 7 days After Last Dose of Study Drug)	Safety Follow-up Visit 4 weeks (± 7 days) After Last Dose of Study Drug ^b
Low-dose CT scan ^h	X					X		
Standard digital ECG ^m	X	X	X	X	X	X	X	X
Vital signs ⁿ	X	X	X	X	X	X	X	X
Pulse oximetry ⁿ	X	X	X	X	X	X	X	X

^h Low-dose CT scans [REDACTED] should be performed on the same day. If not possible for logistical reasons, Low-dose CT scans [REDACTED] should be performed within ± 4 days of the scheduled visit. Day 1 assessments must be completed before dosing. The Week 72 CT scan may be delayed for up to 60 days if the subject is recovering from a pulmonary exacerbation. The medical monitor should be notified about the extension. The scan should be done after the pulmonary exacerbation is resolved and at least 28 days after the antibiotic regimen for the treatment of pulmonary infection has been completed. If this antibiotic regimen is not completed by the end of the 60-day extension, the subject may complete the CT scan within the first 30 days of enrolling in Study VX14-661-110; or within 1 week of the end of the 60-day extension if they do not enroll in Study VX14-661-110. No extension is permitted for any other assessment.



All standard 12-lead ECGs will be performed before dosing and after the subject has been supine for at least 5 minutes. The predose ECGs collected at the Day 1 Visit will be performed in triplicate.

ⁿ 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. In addition to the indicated visits, symptom-targeted vital signs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.



Table 3-2 Study VX15-661-112: Treatment Period (Day 1 to Week 72), Early Termination of Treatment Visit, and Safety Follow-up Visit Assessments

Event/Assessment ^a	Day 1	Day 15 (± 3 days)	Week 4, Week 12, (± 1 week)	Week 24 (± 1 week)	Week 36, Week 48, Week 60 (± 1 week)	Week 72 (± 1 week)	Early Termination of Treatment Visit (Within 7 days After Last Dose of Study Drug)	Safety Follow-up Visit 4 weeks (± 7 days) After Last Dose of Study Drug ^b
Hematology	X			X	Wk 48 only	X	X	X
Lipid and vitamin levels	X			X	Wk 48 only	X	X	X
Coagulation	X					X		X
Serum chemistry ^p	X	X	X	LFT only	LFT only	X	X	X
Urinalysis	X					X		X
Study drug count		X	X	X	X	X		
Meal(s) or snack(s) at site ^q	X	X	X	X	X			

CT: computed tomography; ECG: electrocardiogram; LFT: liver function test;

^p Blood samples will be collected before the dose of study drug. At Weeks 24, 36, 48, and 60, only samples for LFT analysis will be collected.

^q Food will be provided after all predose assessments have occurred.

Table 3-2 Study VX15-661-112: Treatment Period (Day 1 to Week 72), Early Termination of Treatment Visit, and Safety Follow-up Visit Assessments

Event/Assessment ^a	Day 1	Day 15 (± 3 days)	Week 4, Week 12, (± 1 week)	Week 24 (± 1 week)	Week 36, Week 48, Week 60 (± 1 week)	Week 72 (± 1 week)	Early Termination of Treatment Visit (Within 7 days After Last Dose of Study Drug)	Safety Follow-up Visit 4 weeks (± 7 days) After Last Dose of Study Drug ^b
Study drug dosing ^f	Day 1 through Week 72							
Ophthalmologic examination						X ^s	X ^t	X ^t
Concomitant medications	X	X	X	X	X	X	X	X
Concomitant treatments and procedures	X	X	X	X	X	X	X	X
Adverse events and serious adverse events	Continuous from signing of the informed consent form and assent (where applicable) through the Safety Follow-up Visit							

^f Subjects will take study drug as specified in [Section 10.2](#). On days of scheduled visits, the subject’s dose of study drug will be administered at the site after predose assessments have been completed. Study drug administration should be completed within 5 minutes. At the Week 72 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 72 Visit. If the Week 72 CT scan is delayed to allow a subject to recover from a pulmonary exacerbation, study drug will continue for up to 60 days until the Week 72 CT scan has been completed or the subject has enrolled in Study VX14-661-110; for these subjects, the last dose of study drug will be the evening dose administered the day before the CT scan or before the Day 1 Visit of Study VX14-661-110.

^s All subjects <18 years of age at the Screening Visit will have an ophthalmologic examination conducted by a licensed ophthalmologist at Week 72. This exam may be completed within 4 weeks before the Week 72 Visit, but must be completed by the end of the Week 72 Visit.

^t Subjects <18 years of age at the Screening Visit who discontinue treatment after receiving at least 1 dose of study drug will have an ophthalmologic examination performed by a licensed ophthalmologist at the Safety Follow-up or the Early Termination of Treatment Visit. This examination may be completed at either the Early Termination of Treatment or Safety Follow-up Visit, but must be completed by the end of the Safety Follow-up Visit.



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5 INTRODUCTION

Cystic fibrosis (CF) affects an estimated 70,000 children and adults worldwide¹ 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 approximately 40 years.^{2,5} Although the disease affects multiple organs, most morbidity and mortality are caused by progressive loss of lung function.⁶

CF is an autosomal recessive genetic disease caused by a defect in the gene encoding the CF transmembrane conductance regulator (CFTR), an epithelial chloride ion (Cl⁻) channel activated by cyclic adenosine monophosphate-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.

CF affects approximately 30,000 individuals in the United States (US)⁵, 32,000 individuals in the European Union (EU)⁷, 4,000 individuals in Canada⁸, and 3,100 individuals in Australia.⁹ Of the more than 1900 mutations in the CFTR gene that have been identified,¹⁰ 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 (d I-CFTR).¹¹ In the US, almost 87% of patients with CF have at least 1 copy of the *F508del-CFTR* mutation.⁵ The proportion of patients with CF who have 2 copies of the *F508del-CFTR* mutation is similar in the US (approximately 47%), the EU (approximately 44%), Canada (49%), and Australia (52%).^{5,7,8,9} Orkambi™ (lumacaftor/ivacaftor) was recently approved in the US to treat patients 12 years and older with CF who have 2 copies of the *F508del-CFTR*, but no therapies to treat the underlying defect in this population are currently approved in other regions, including Australia.

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.^{12,13} 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.¹⁴

Two complementary approaches to increase CFTR-mediated Cl⁻ secretion in the airway epithelia have been studied.¹⁵ One approach is to treat with a compound that will modify the cellular processing and trafficking of the CFTR protein to increase the amount of functional CFTR at the cell surface. This kind of compound has been termed a CFTR corrector. Another approach is to treat with a compound that increases the 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 CFTR modulator, such as a potentiator and/or corrector, could prevent the hyperabsorption of

water across the apical surface of epithelial cells, allowing proper maintenance of airway hydration. Adequate airway hydration could alleviate the cycle of mucous 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 cellular processing and trafficking 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 the cell surface.¹⁶

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 and the EU, ivacaftor (150-mg tablets; trade name 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*. In Australia, Kalydeco is indicated for the treatment of CF in patients age 6 years and older who have a *G551D* or other gating (class III) mutation in the *CFTR* gene. Details about the VX-661 and ivacaftor development programs can be found in the Investigator's Brochures.

The improvement of lung function in Phase 2 studies supported the continued development of VX-661/ivacaftor combination treatment in Phase 3 studies, which are ongoing in subjects homozygous and heterozygous for the *F508del-CFTR* mutation ages 12 years and older. This study will evaluate the effect of VX-661/ivacaftor on CF disease as measured by lung imaging using [REDACTED] low-dose computed tomography (LDCT) [REDACTED]. In addition, the safety of VX-661/ivacaftor will be evaluated over a treatment period of 72 weeks.

6 STUDY OBJECTIVES

6.1 Primary Objective

- To evaluate the treatment effect of VX-661 in combination with ivacaftor (VX-661/ivacaftor) on chest imaging endpoints as evaluated using low-dose computed tomography (LDCT) at Week 72 in subjects with CF who are homozygous for the *F508del* mutation on the CF transmembrane conductance regulator (*CFTR*) gene

6.2 Secondary Objective

- To evaluate the safety of VX-661/ivacaftor through Week 72

7 STUDY ENDPOINTS

7.1 Primary Endpoint

- Absolute change in Total Brody/CF-CT score from baseline at Week 72 using LDCT

7.2 Secondary Endpoints

- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values (hematology, serum chemistry, lipid and vitamin levels, coagulation studies, and urinalysis), standard digital electrocardiograms (ECGs), vital signs, and pulse oximetry

8 STUDY DESIGN

8.1 Overview of Study Design

This is a Phase 2, randomized, placebo-controlled, double-blind parallel-group, multicenter study in subjects with CF who are homozygous for the *F508del-CFTR* mutation. This study is designed to evaluate the treatment effect of VX-661/ivacaftor on chest imaging endpoints during 72 weeks of treatment. LDCT [REDACTED] will be used for chest imaging. The images will be evaluated using the Brody/CF-CT scoring system. Safety over 72 weeks of treatment will also be evaluated.

Figure 8-1 shows a schematic of the study design. This study includes a Screening Period, a 72-week Treatment Period, and a Safety Follow-up Visit. Following a 28-day screening

period, approximately 40 subjects will be randomized (1:1) to 1 of the 2 treatment arms, active or placebo, on Day 1.

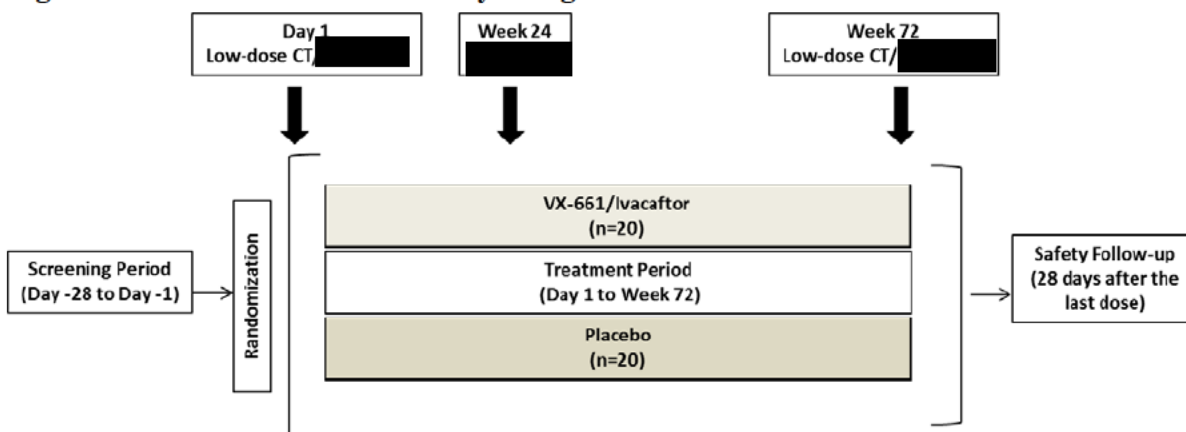
The active treatment regimen will be comprised of a morning dose of a fixed-dose combination (FDC) tablet of VX-661 100-mg/ivacaftor 150-mg and an evening dose of ivacaftor 150-mg to be taken approximately 12 hours after the morning dose. The placebo regimen will be visually-matched tablets to be taken on the same schedule as the active treatment.

The study will be double-blind.

The independent data monitoring committee (IDMC) will conduct regular planned safety reviews of study data as outlined in the IDMC charter.

Subjects who complete the study may have the opportunity to receive VX-661/ivacaftor, provided they meet criteria, until VX-661/ivacaftor is commercially available to them or development is terminated. After completing Study VX15-661-112 (Study 112), subjects who meet the criteria may have the opportunity to participate in future Vertex programs with VX-661/ivacaftor, which may include additional scans.

Figure 8-1 VX15-661-112: Study Design



CT: computed tomography; [redacted]

Note: The Safety Follow-up Visit is not required for subjects who complete the Week 72 Visit and have enrolled in the TEZ/TVA open-label extension study, VX14-661-110, within 28 days after the last dose of study drug.

8.1.1 Screening

Screening Visit assessments are listed in [Table 3-1](#).

Screening will occur within 28 days before administration of study drug. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent from each subject.

To prepare for study participation, subjects will be instructed on the study restrictions ([Section 9.3](#)).

8.1.1.1 Repetition of Screening Assessment(s)

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

- If there is clear evidence of a laboratory error (e.g., hemolyzed sample) or equipment malfunction, collection of a repeat sample for the appropriate laboratory test or assessment may be permitted with the approval of the medical monitor.
- Exclusionary liver function test (LFT) levels, which may be retested within 14 days of the original screening date.

If screening spirometry measurements fail to meet acceptability and repeatability criteria as specified by American Thoracic Society/European Respiratory Society guidelines,¹⁷ repeat spirometry evaluation may be performed once.

If repeat values of the individual assessment(s) are within the eligibility criteria and completed within the screening window, then the subject is eligible for the study.

8.1.1.2 Rescreening

Subjects may only be rescreened with the approval of the medical monitor. If a subject is rescreened, all screening assessments will be repeated except for CF genotyping, follicle-stimulating hormone (FSH) level (if serum FSH level was ≥ 40 mIU/mL during prior screening), sweat chloride level, and the ophthalmologic examination (if performed within the last 3 months). If a subject is rescreened, the screening window will begin once the first rescreening assessment has been initiated.

8.1.1.3 Extension of Screening Period Window

A subject may have the Screening Period window extended by 1 week for the following reasons:

- Repetition of the Screening Period assessments (Section 8.1.1.1)
- Unexpected operational or logistic delays, or to meet the eligibility criteria.

The Screening Period window may be extended by 2 weeks for the following reason:

- Additional time to conduct ophthalmologic examinations (Section 11.6.8).

8.1.2 Treatment Period

The Treatment Period will last approximately 72 weeks. The Treatment Period can be extended up to 60 days in the event of a pulmonary exacerbation. Antibiotics taken for a pulmonary infection or exacerbation must be completed at least 28 days before the Week 72 CT scan. Subjects will be randomized to 1 of 2 treatment arms: 1 active combination treatment arm and 1 placebo arm. The dosing regimen for each treatment arm is as follows:

- VX-661/ivacaftor: VX-661 100-mg /ivacaftor 150-mg FDC (light yellow) film-coated tablet for oral administration (morning dose); ivacaftor 150-mg (light blue) film-coated tablet for oral administration (evening dose)

- Placebo: 0-mg film-coated matching placebo tablets for oral administration (1 light yellow for morning dose and 1 light blue for evening dose)

The first dose of the study drug will be administered after randomization on Day 1. Study drug administration details are given in [Section 10](#).

Study visits during the Treatment Period will occur as shown in [Table 3-2](#). Subjects will be outpatients during the Treatment Period. All visits should occur within the windows specified.

8.1.3 Follow-up

The Safety Follow-up Visit assessments are listed in [Table 3-2](#). There will be an outpatient Safety Follow-up Visit approximately 28 (\pm 7) days after the last dose of study drug for subjects who complete study drug dosing and for subjects who prematurely discontinue study drug dosing.

The Safety Follow-up Visit is not required for subjects who complete the Week 72 Visit and have enrolled in the TEZ/IVA open-label extension study, VX14-661-110 (Study 110), within 28 days after the last dose of study drug.

8.1.4 Early Termination of Treatment

If the subject prematurely discontinues study drug treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after termination of study drug treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 (\pm 7) days after their last dose of study drug. The assessments performed at the ETT Visit and Safety Follow-up Visit are listed in [Table 3-2](#).

The ETT Visit should occur within 7 days after the 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.

During the course of study conduct, if VX-661 in combination with ivacaftor is approved by local health authorities and is available for the treatment of the population enrolled in this study, subjects may be discontinued from this study at the discretion of the sponsor ([Section 10.6](#)). If a subject is continuing onto commercially available VX-661/ivacaftor, the ETT Visit will be completed before dosing with commercially available drug begins, and the Safety Follow-up Visit will not be required.

Alternatively, if after review of a marketing application, local health authorities decline to approve, or if clinically meaningful benefit is not demonstrated for the use of VX-661/ivacaftor for the treatment of CF in populations enrolled in this study, subjects within those populations may be discontinued after communication to investigators and institutional review boards (IRBs)/independent ethics committees (IECs) of the risks/benefits related to the safety and efficacy. If subjects are discontinued from the study, an ETT Visit should occur within 7 days after the last dose of study drug and a Safety Follow-up Visit should occur within 28 (\pm 7) days after the last dose of study drug.

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

8.1.5 Independent Data Monitoring Committee

Safety and tolerability data will be reviewed by an IDMC to ensure the safety of the subjects in the study (Section 12.3.5.2). Procedural details of the IDMC's structure and function, frequency of meetings, and data planned for review will be included in the IDMC charter. The IDMC charter will be finalized before the first subject is screened.

8.2 Rationale for Study Design and Study Drug Regimens

8.2.1 Study Design

This is a Phase 2, randomized, placebo-controlled, double-blind, parallel-group, multicenter study in subjects aged 12 years and older with CF who are homozygous for the *F508del-CFTR* mutation with a percent predicted forced expiratory volume in 1 second ($ppFEV_1$) ≥ 70 . A randomized, double-blind study design will avoid observer bias and reduce symptoms or outcomes arising from the subjects' knowledge of treatment.

8.2.2 Study Drug Dose and Duration

VX-661 was studied at different doses alone and in combination with ivacaftor in the Phase 2 proof-of-concept Study VX11-661-101 (Study 101). The regimen of VX-661 100 mg once daily (qd) in combination with ivacaftor 150 mg every 12 hours (q12h) (VX-661 100 mg qd/ivacaftor 150 mg q12h) provided clinically meaningful and statistically significant improvement in $ppFEV_1$ compared to placebo, while VX-661 100 mg monotherapy did not (see VX-661 Investigator's Brochure). Based on the data in Study 101, VX-661 100 mg qd/ivacaftor 150 mg q12h was selected for continued development in the ongoing Phase 3 program and this study.

Placebo control is necessary to assess the effect of VX-661/ivacaftor combination treatment over time. Use of placebo is justified because there is no approved treatment available to address the underlying cause of CF for this population in Australia. All subjects will maintain their current standard of care and concomitant medication regimen throughout the study, including the use of antibiotics and hypertonic saline. Additionally, only subjects with mild to moderate pulmonary disease (baseline $ppFEV_1 \geq 70$) will be enrolled. Furthermore, subjects who have had an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug) will be excluded. A study showed that patients who had pulmonary exacerbations that were treated with intravenous (IV) antibiotics showed good resolution of structural and functional abnormalities comparable to CF patients in clinically stable condition [REDACTED] within 1 month of completion of antibiotic therapy.¹⁸

CF is a chronic, slowly progressive disease. It is hypothesized that a notable change will be observed during the 72-week duration of this study, based on review of the natural history progression of radiographic changes demonstrated on longitudinal studies seen on CT scans. In a 2-year natural history study in 48 children with CF, with a mean age of 11 years at the

start of the study, the mean change in the Total Brody score was +2.2 points per year.¹⁹ Based on these longitudinal studies, it is estimated that the progression of disease observed in the proposed study population is a 3.3 point increase in the Total Brody Score at Week 72. There has been 1 study that has examined the impact of CFTR modulation on structural lung disease. In 10 subjects (ages 10 to 44 years) who carried the *CFTR-G551D* mutation, Sheikh et al reported a within-treatment annual improvement of 13.6 points in the Total Brody/CF-CT score after 1 year of ivacaftor treatment.²⁰

8.2.3 Rationale for Study Assessments

CT [REDACTED] will be used for chest imaging. Chest CT, considered the gold standard for pulmonary imaging, is widely used in the clinical care of CF patients to diagnose structural lung abnormalities and to monitor disease progression. Chest CT offers advantages over other pulmonary endpoints because it has greater sensitivity to detect early structural lung disease even while the commonly used endpoint, ppFEV₁, is within normal range and respiratory symptoms are absent.¹⁹ Additionally, CT can demonstrate the structural abnormalities that are specific to CF lung disease and can be performed similarly in all age groups. Chest CT does carry theoretical risks due to the cumulative exposure to ionizing radiation, which is particularly important in young children who would be exposed to repeated testing sessions during a clinical trial and who now have increased life expectancy. For this reason, an LDCT algorithm will be used to minimize exposure to ionizing radiation.

[REDACTED]

[REDACTED]

For LDCT [REDACTED] the Brody/CF-CT scoring system will be used. The Brody/CF-CT scoring system has been the most frequently employed scoring system to measure structural lung disease as shown on CT in CF patients, semiquantitatively scoring the degree of structural lung disease.^{24,25,26,27,28,29} This scoring system has been extensively tested and validated.³⁰ Analyses will include change from baseline in the total Brody/CF-CT score [REDACTED]

[REDACTED]

Images will be read by 2 independent, expert central readers blinded to treatment

group. This will avoid observer bias arising from the readers' knowledge of treatment.

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. Subject (or his or her legally appointed and authorized representative) will sign and date an informed consent form (ICF), and where appropriate, assent form
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures
3. Subjects (males and females), will be 12 years of age or older on the date of informed consent or, where appropriate, date of assent
4. Homozygous for the *F508del-CFTR* mutation, genotype to be confirmed with testing performed at the Screening Visit. If the *CFTR* screening genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used to establish eligibility. *Note: Subjects who have been randomized and whose screening genotype results do not confirm study eligibility must be discontinued from the study as described in Section 9.5. CFTR genotyping may be waived if the subject has a documented result from a previous Vertex study.*
5. Confirmed diagnosis of CF³¹ defined as a sweat chloride value ≥ 60 mmol/L by quantitative pilocarpine iontophoresis. A sweat chloride test must be performed at the Screening Visit if an eligible sweat chloride value is not available in the subject's medical records and the Screening Visit value is needed to establish eligibility. For subjects using sweat chloride values documented in their medical records to establish eligibility, the sweat chloride test at the Screening Visit is optional.
6. $ppFEV_1 \geq 70\%$ of predicted normal for age, sex, and height (equations of Wang et al. or Hankinson et al.)^{36,37} during screening. Spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria¹⁷ for acceptability and repeatability.
7. Stable CF disease as judged by the investigator
8. Willing to remain on a stable CF medication regimen through the end of the treatment period (up to 72 weeks) and, if applicable, the ETT visit and the Safety Follow-up Visit

9.2 Exclusion Criteria

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. Any of the following abnormal laboratory values at Screening:
 - Hemoglobin <10 g/dL
 - Abnormal liver function defined as any 2 or more of the following: $\geq 3 \times$ upper limit of normal (ULN) aspartate aminotransferase (AST), $\geq 3 \times$ ULN alanine aminotransferase (ALT), $\geq 3 \times$ ULN gamma-glutamyl transpeptidase (GGT), $\geq 3 \times$ ULN alkaline phosphatase (ALP), or $\geq 2 \times$ ULN total bilirubin
 - Abnormal liver function defined as any increase of $\geq 5 \times$ ULN in AST or ALT
 - Abnormal renal function defined as glomerular filtration rate ≤ 50 mL/min/1.73 m² (calculated by the Modification of Diet in Renal Disease Study Equation)^{32,33} for subjects ≥ 18 years of age and ≤ 45 mL/min/1.73 m² (calculated by the Counahan-Barratt equation)³⁴ for subjects aged 12 to 17 years (inclusive)
 3. For an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease before Day 1 (first dose of study drug), antibiotic regimen for the treatment of a pulmonary infection must have been completed at least 28 days before Day 1 (first dose of study drug).
 4. A 12-lead ECG demonstrating QTc >450 msec at Screening. If QTc exceeds 450 msec for the screening ECG, the ECG should be repeated 2 more times during the Screening Period, and the average of the 3 QTc values should be used to determine the subject's eligibility.
 5. History of solid organ or hematological transplantation
 6. History or evidence of cataract, lens opacity, Y-suture, or lamellar rings determined to be clinically significant by the ophthalmologist during the ophthalmologic examination during the Screening Period. The ophthalmologic examination does not need to be repeated if there is documentation of an examination meeting protocol criteria that was conducted within 3 months before the Screening Period. If the subject has documentation of bilateral lens removal, an ophthalmologic examination is not required and this criterion is not applicable ([Section 11.6.8](#)).
 7. History of alcohol or drug abuse, as deemed by the investigator, in the past year, including but not limited to cannabis, cocaine, and opiates.

8. Ongoing participation in an investigational drug study (including studies investigating VX-661, lumacaftor [VX-809], and/or ivacaftor) within 30 days of screening
 - A washout period of 5 terminal half-lives of the previous investigational study drug or **30** days, whichever is longer, must elapse before screening. The duration of the elapsed time may be longer if required by local regulations.
 - Ongoing participation in a noninterventional study (including observational studies and studies requiring assessment without administration of study drug) is permitted.
9. Use of restricted medications or foods within the specified window before the first dose of study drug as defined in Section 9.3.
10. Pregnant or nursing females (females of childbearing potential must have a negative pregnancy test at Screening and Day 1 [results reviewed before dosing]).
11. Sexually active subjects of reproductive potential who are not willing to follow the contraception requirements outlined in [Section 11.6.6.1](#)
12. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study. An adult (aged 18 years or older) who is a relative of a study staff member may be randomized in the study provided that
 - the adult lives independently of and does not reside with the study staff member or
 - the adult participates in the study at a site other than the site at which the family member is employed.
13. Colonization with organisms associated with a more rapid decline in pulmonary status (e.g., *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*). For subjects who have had a history of a positive culture in the past, the investigator could be guided by the following suggested criteria for a subject to be considered free of colonization:
 - The subject should have had 2 respiratory tract cultures negative for these organisms within the past 12 months, with no subsequent positive cultures.
 - These 2 respiratory tract cultures should have been separated by at least 3 months.
 - One of these 2 respiratory tract cultures should have been obtained within the past 6 months.
14. Any contraindication to undergoing LDCT [REDACTED] as per the site's institutional guidelines

9.3 Study Restrictions

9.3.1 Additional Dietary Restrictions

Prohibited medications and certain foods are not allowed in this study (Screening Period through Safety Follow-up Visit) ([Table 9-1](#)). Both ivacaftor and VX-661 are metabolized at least in part via hepatic enzymatic pathway using cytochrome P450 (CYP) 3A4, hence the need to restrict usage of known CYP3A4 inducers and inhibitors.

A nonexhaustive list of study prohibitions and cautions for food and medication will be provided in the Study Reference Manual. This list may be updated throughout the study and updates will be communicated by the study team.

Table 9-1 Study Restrictions

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

CYP: cytochrome P450.

Note: The use of restricted medication by subjects with medical needs will be addressed on a case-by-case basis with the medical monitor.

9.4 Prior and Concomitant Medications

Information regarding all prior and concomitant medications, including the subject's CF medications, other medications, and herbal and naturopathic remedies, administered from 28 days before the Screening Period through the Safety Follow-up Visit, if applicable, will be recorded in each subject's source documents. For subjects who are screened but are not subsequently randomized into the study, details of prior medication will only be documented in the subjects' source documents.

Subjects must remain on a stable medication (and supplement) regimen for their CF from 28 days before Day 1 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 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.

- Subjects may receive doses of prednisone or prednisolone of up to 10 mg/day (chronically), or prednisone or prednisolone 60 mg qd for up to 5 days without prior approval of the medical monitor.
- Information about 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 [REDACTED].

9.5 Removal of Subjects

Subjects may withdraw from the study at any time at their own request. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons.

If a subject 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 the subject's 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 8.1.3](#)), and follow up with the subject regarding any unresolved AEs.

If the subject withdraws consent, no further evaluations will be performed and no additional data will be collected. Vertex may retain and continue to use any data collected before such withdrawal of consent. Subjects who discontinue study treatment early should continue to return for study assessments as noted in [Section 8.1.4](#).

The investigator should inquire about the reason for withdrawal of consent.

Subjects must return all unused study drug and return for all scheduled visits.

A subject will be withdrawn from study drug treatment for any of the following reasons:

- A female subject or a female partner of a male subject has a confirmed pregnancy.
- A subject's treatment is unblinded by the investigator.

A subject may be withdrawn from study drug treatment after a discussion between the investigator and the medical monitor for any of the following reasons:

- A subject develops a medical condition that requires prolonged concomitant therapy with a prohibited medication or prolonged interruption of the study drug.
- A subject develops a life-threatening AE or a serious AE (SAE) that places him/her at immediate risk, and discontinuation of study drug treatment and withdrawal from the study are deemed necessary.
- A subject is noncompliant with study requirements.
- A subject has an increase in transaminases (ALT or AST) according to evaluations and management described in [Section 11.6.3](#).

- A subject has an increase in QTc according to evaluations and management described in [Section 11.6.5](#).
- A subject develops a cataract or lens opacity.

Subjects who are randomized and whose screening *CFTR* genotype results do not confirm study eligibility must be discontinued from study drug treatment, undergo ETT and/or Safety Follow-up Visits per [Section 8.1.3](#) and [Section 8.1.4](#), and be discontinued from the study. After discontinuation of study drug treatment, these subjects will not undergo any further assessments other than those performed at the ETT and/or Safety Follow-up Visits.

9.6 Replacement of Subjects

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

10 STUDY DRUG ADMINISTRATION AND MANAGEMENT

Study drug refers to VX-661/ivacaftor and matching placebo.

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. Subjects will receive the same number of tablets each day to maintain the blind. Refer to Table 10-1.

Table 10-1 Study Drug Administration: Treatment Period

Treatment Arm	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
Placebo	AM	VX-661/IVA matching placebo tablet oral
	PM	IVA matching placebo tablet oral

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

Study drug should be administered within 30 minutes after 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. Throughout the Treatment Period, study drugs will be administered after the start and before the end of a meal. It is recommended that the duration of each meal associated with study drug intake (i.e., breakfast and dinner/snack, as applicable) should not exceed 30 minutes.
2. Study drug should be administered q12h (\pm 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.
3. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. The meal or snack will be provided by the site for the morning dose of study drug.
4. If a subject’s scheduled visit is to occur in the afternoon, the following guidelines must be used:
 - If the dose in the clinic will be within 6 hours of the subject’s scheduled morning dose, the subject should withhold his or her 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.
5. For visits after the Day 1 Visit, subjects will be instructed to bring all unused study drug to the site; study drug will be dispensed at each visit, as appropriate.
6. At the Week 72 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 72 Visit.
7. If the Treatment Period has been extended and the Week 72 CT scan is delayed because of a pulmonary exacerbation ([Section 11.1](#)), subjects should continue to take study drug until the Week 72 CT scan has been completed or the subject enrolls in Study 110. The last dose of study drug for these subjects will be the evening dose administered the day before the CT scan or the evening dose administered before the Day 1 Study 110 Visit, whichever occurs first.

10.3 Method of Assigning Subjects to Treatment Groups

Approximately 40 subjects who meet the eligibility criteria will be randomized (1:1) to 1 of 2 treatment arms.

An interactive web response system (IWRS) will be used to assign subjects to treatment. The randomization code will be produced by Vertex Biostatistics or a qualified randomization vendor. The Vertex study biostatistician will review and approve the production of the final

randomization list, which will be reviewed and approved by a designated unblinded biostatistician who is not a member of the Study Execution Team.

10.4 Dose Modification for Toxicity

The dosage of individual study drugs or the regimen cannot be altered, but the investigator can interrupt or stop treatment with all study drugs.

10.5 Study Drug Interruption and Missed Doses

10.5.1 Study Drug Interruption

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 resume only after approval by the medical monitor. Specific instructions for interruption for elevated LFT levels are provided in [Section 11.6.3](#) and instructions for elevated QTc levels are provided in [Section 11.6.5](#).

10.5.2 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, the subject 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

If after review of a marketing application, local health authorities decline to approve, or if clinically meaningful benefit is not demonstrated for the use of VX-661/ivacaftor for the treatment of CF in populations enrolled in this study, subjects within those populations may be discontinued after communication to investigators and IRBs/IECs of the risks/benefits related to the safety and efficacy. In addition, if evaluation of efficacy data from the Phase 3 studies (Studies VX14-661-106, VX14-661-107, VX14-661-108, and VX14-661-109) suggest that the VX-661/ivacaftor treatment does not provide clinically meaningful benefit, Vertex may recommend that subjects are discontinued or the study is terminated (see [Section 13.2.7](#)).

Subjects who are able to receive commercially-available VX-661/ivacaftor by prescription of a physician may be discontinued from the study at the discretion of the sponsor. If a subject is continuing onto commercially available VX-661/ivacaftor, the ETT Visit ([Section 8.1.4](#)) will be completed before dosing with commercial drug begins, and the Safety Follow-up Visit ([Section 8.1.3](#)) will not be required.

A subject may be discontinued at any time due to safety reasons. If a subject discontinues study drug, he/she should complete the ETT Visit ([Section 8.1.4](#)) and Safety Follow-up Visit ([Section 8.1.3](#)).

If during the time when a subject is participating in the study a cataract or lens opacity is identified and determined to be clinically significant by the ophthalmologist after dosing, discussion as to that subject's continuance in the study is provided in [Section 11.6.8](#).

10.7 Packaging and Labeling

Vertex will supply the study drug tablets in blister cards. Study drug cards will be provided and replaced via the IWRS. A detailed study drug dispensation plan will be provided in the Pharmacy Manual.

Study drug labeling will be in compliance with applicable local and national regulations.

10.8 Study Drug Supply, Storage, and Handling

VX-661/ivacaftor (100 mg/150 mg) and matching placebo will be supplied as light yellow film-coated tablets of similar size and appearance containing VX-661 100-mg/ivacaftor 150-mg and VX-661 0-mg/ivacaftor 0-mg, respectively.

Ivacaftor (150 mg) and matching placebo will be supplied as light blue film-coated tablets of similar size and appearance containing ivacaftor 150-mg and ivacaftor 0-mg, respectively.

Blister cards must be stored at room temperature according to Table 10-2 and to the instructions provided in the Pharmacy Manual. 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 study conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for as detailed in [Section 10.10](#).

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

Table 10-2 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)
VX-661/ivacaftor-matching placebo	0-mg/0-mg tablet; oral	0 mg/0 mg, morning dose	≤ 25°C (77°F) with excursions to 30°C (86°F)
Ivacaftor-matching placebo	0-mg tablet; oral	0 mg, evening dose	≤ 25°C (77°F) with excursions to 30°C (86°F)

10.9 Drug Accountability

The pharmacist or designated site staff will maintain records documenting the dates and amounts of

- study drug received,
- study drug dispensed to the subjects, and
- study drug returned by the subjects.

Subjects will be instructed to return all used, partially used, and full study drug blister cards 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 verify study drug records and inventory throughout the study.

10.10 Disposal, Return, or Retention of Unused Drug

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

10.11 Compliance

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 treatment.

10.12 Blinding and Unblinding

10.12.1 Blinding

This is a double-blind study.

The subjects and all site personnel, including the investigator, the site monitor, and the study team, will be blinded with the exception of the following:

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of the subject and her fetus in the event of a pregnancy
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy SAE processing and reporting regulations

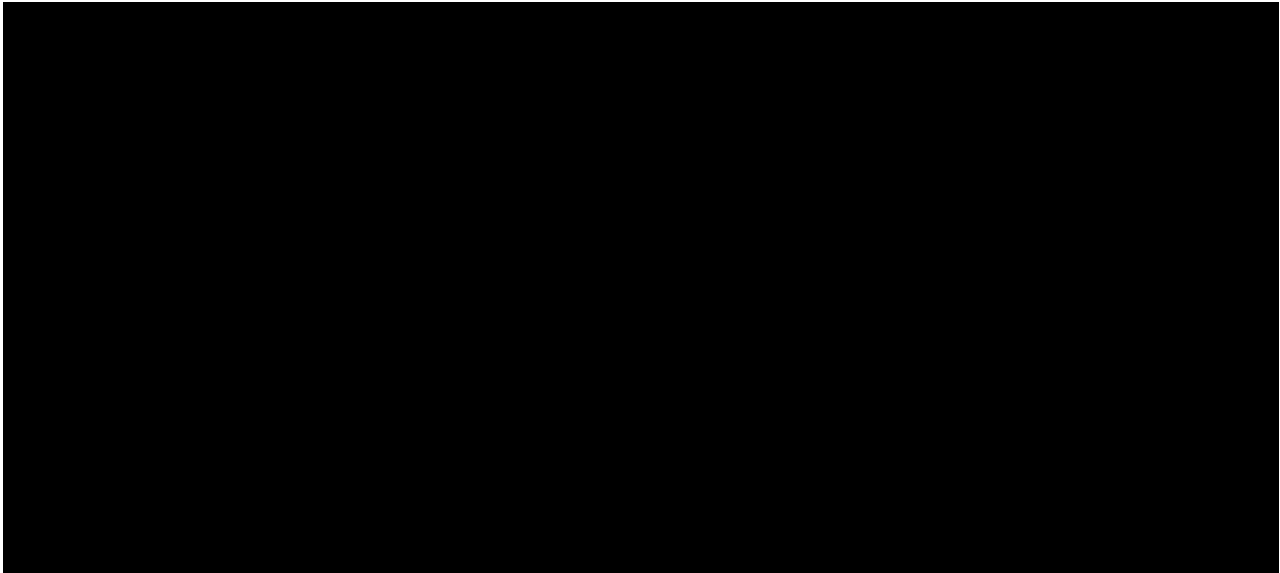
- Unblinded statistician preparing the final (production) randomization list who is not part of the study team
- Vertex Clinical Operations IWRS management
- Vertex Clinical Supply Chain
- IDMC
- Vendor preparing the unblinded analysis for the IA and IDMC ([Section 12.3.5](#))
- Vertex medical monitor may unblind individual subjects at any time for matters relating to safety concerns.

For the purpose of the IA described in [Section 12.3.5.1](#), a small team at Vertex, who are not involved with study conduct, will be unblinded. The members of this IA team will be documented in an unblinding plan.

Imaging Data Blinding

Despite treatment blinding, knowledge of the LDCT [REDACTED] results has the potential to suggest whether a subject has been administered active study drug or placebo. Therefore, during the conduct of the study, the Vertex study team will have no access to the postdose imaging data. The vendor for central reading of the imaging data will send only the blinded files (blinded treatment group, with real scores for baseline, but with dummy scores for all the imaging assessments after baseline) to Vertex to be used for developing the statistical programs. Furthermore, subjects and their caregiver should not be informed of their study-related imaging results during the Treatment Period regardless of whether the subject has prematurely discontinued treatment.

CT scans [REDACTED] will have a clinical over-read by a site radiologist blinded to study drug assignment. Any urgent safety-related findings should be communicated to the Vertex medical monitor, who may recommend follow-up by the site principal investigator. The Vertex medical monitor will facilitate any discussion with the central readers as needed.



10.12.2 Unblinding

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The unblinding method will be either a manual or electronic process.

Unblinding of the individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, investigators will use their best judgment as to whether to unblind without first attempting to contact the medical monitor to discuss and agree to the need for unblinding. If investigators deem it not necessary to unblind immediately, they will first attempt to contact the medical monitor to discuss and agree to the need for unblinding. If investigators have tried but are unable to reach the medical monitor, they will use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding without having successfully reached and discussed the situation with the medical monitor.

Contact information for the medical monitor (or appropriate backup) will be provided in a separate document.

In addition, the Vertex Medical Information Call Center [REDACTED] will answer calls 24 hours a day, 7 days a week, 365 days of the year, and will triage these calls to the study medical monitor or appropriate backup.

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor will be notified within 24 hours of the unblinding event. The reason and the date of the unblinding will be documented clearly in the subject's study file. Information about the treatment assignment obtained from the unblinding will be maintained in a secure location with controlled access and will not be shared with the sponsor (Vertex), contract research organization (CRO), or any site personnel (other than the physician treating the subject). In addition, the investigator will consider whether the clinical event that prompted unblinding will be considered an SAE, according to the regulatory definitions or criteria for SAEs, and, if so, submit an SAE report to Vertex GPS or designee, per [Section 13.1.2](#).

Vertex GPS or designee will also unblind any SAE reports in compliance with regulatory reporting requirements. In addition, Vertex may, for matters relating to safety concerns, unblind individual subjects at any time.

11 ASSESSMENTS

11.1 Timing of Assessments

The timing of assessments is shown in [Table 3-1](#) and [Table 3-2](#).

[REDACTED] 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 recordings
3. Vital signs and pulse oximetry

5. Safety laboratory assessments (i.e., blood draws)

LDCTs [REDACTED] should be performed on the same day. If that is not possible for logistical reasons, LDCT [REDACTED] should be performed within ± 4 days of the scheduled visit. Day 1 LDCTs [REDACTED] must be completed before dosing. The Week 72 CT scan may be delayed for up to 60 days if the subject is recovering from a pulmonary exacerbation. The antibiotic regimen for the treatment of pulmonary exacerbation or infection must be completed at least 28 days before the Week 72 CT scan. If the 28-day antibiotic-free period is not completed before the 60-day extension ends, the subject may roll over into Study 110 and complete the CT scan within the first 30 days of enrolling in Study 110. For subjects who have not completed the 28-day antibiotic-free period after the 60-day extension ends and who choose not to enroll in Study 110, the CT scan should be completed within 1 week of the end of the 60-day extension. The medical monitor should be notified about extensions for the Week 72 CT scan. No extension is permitted for any other assessment. [REDACTED]

11.1.1 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. 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. The consent 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 IRB or IEC, must be used.

11.1.2 Assigning Subject Number

Once a subject has signed an ICF or assent, if applicable, a subject number will be assigned. The subject will retain this number for the entire study. Detailed instructions on assigning subject numbers will be provided in the Study Reference Manual. If a subject is rescreened, the subject retains the original subject number.

11.2 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history, height, weight, and sweat chloride.

Medical history will be elicited from each subject during screening. Based on the medical history, the subject will be assessed for any disqualifying medical conditions as specified in the inclusion and exclusion criteria. The medical history shall include a complete review of systems, past medical and surgical histories, and any allergies.

Sputum microbiology, as documented in the subject's medical record over the past 2 years, will be collected during screening.

A sweat chloride test must be performed at the Screening Visit if an eligible sweat chloride value is not available in the subject's medical records and the Screening Visit value is needed to establish eligibility. For subjects using sweat chloride values documented in their medical records to establish eligibility, the sweat chloride test at the Screening Visit is optional. Collection of sweat samples will be performed using an approved collection device. Sweat samples will be sent to a central laboratory for testing and interpretation of results. Specific instructions for collection, handling, processing, and shipping of sweat chloride samples to the central laboratory will be provided separately.

11.3 Pharmacokinetics

Not applicable

11.4 Pharmacodynamics

Not applicable

11.5 Efficacy

11.5.1 Chest Imaging

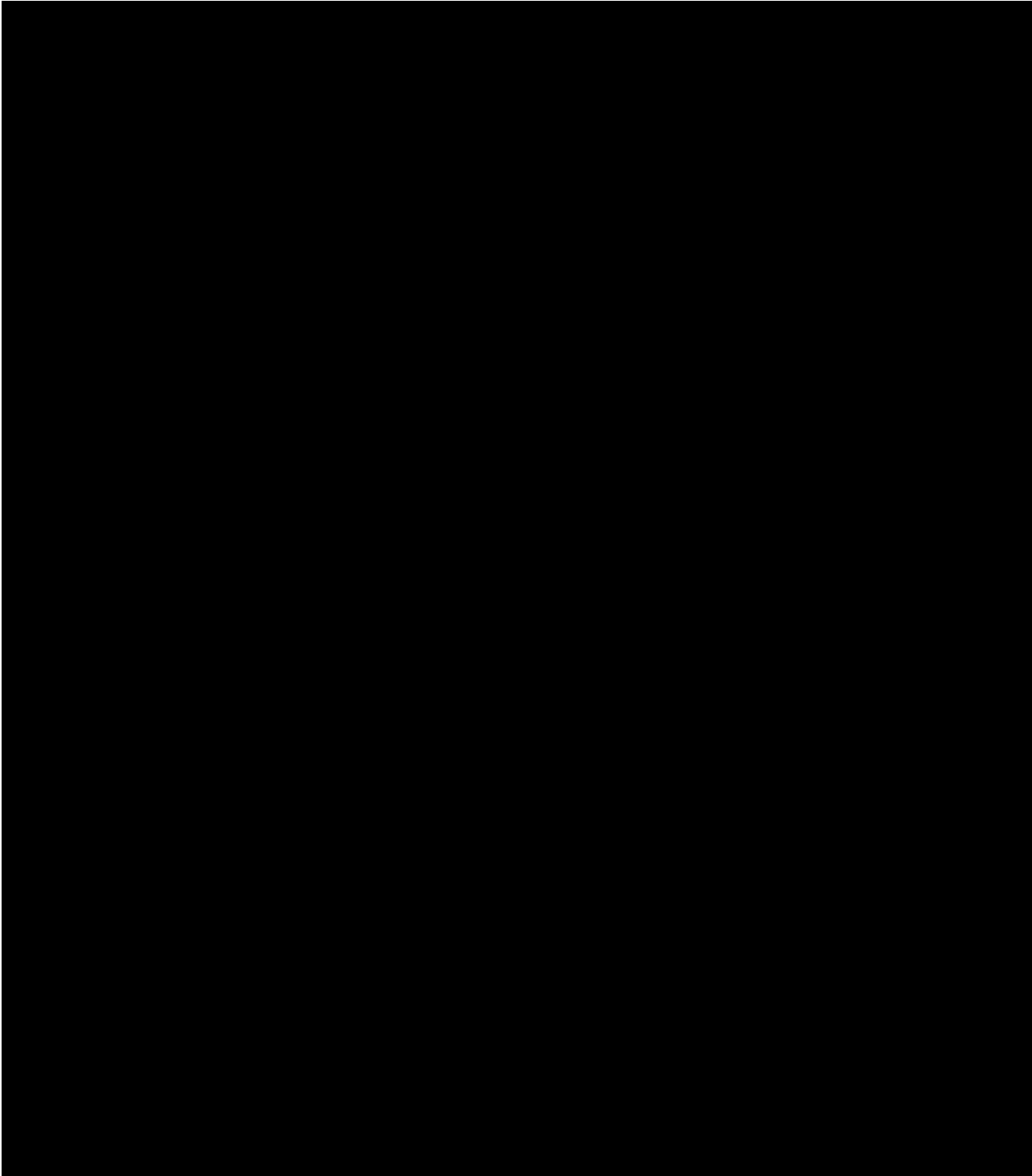
Chest imaging, as performed by LDCT [REDACTED] has the potential to reveal structural CF pulmonary disease even when a patient has normal spirometric function. As such, this study will explore the effect of VX-661/ivacaftor treatment on endpoints obtained through chest imaging.

11.5.1.1 Low-Dose Computed Tomography

Inspiratory and expiratory LDCT scans will be obtained at the time points noted in [Table 3-2](#), using a standard low-dose ionizing radiation protocol. CT scans will be obtained using a spirometry-controlled volumetric technique. Additional technique information specific to each manufacturer and model of CT scanner will be provided. Estimated dose for both inspiratory and expiratory scans will total <2.5 mSv combined. Dose calculations will be performed for each CT scanner.

Images will be reconstructed at 5 mm thickness and at <1 mm thickness (exact thickness will be specified for each manufacturer) using a high frequency reconstruction algorithm for 5 mm sections and standard reconstruction for <1 mm sections.

CT scans involve exposure to ionizing radiation. The CT scans used in this research are optimized for low radiation dose and high image quality. While the range of radiation exposure is highly variable, Australians on average are exposed to 1.5 mSv each year from natural sources. No direct evidence of human health effects has been seen in ionizing radiation doses of up to 10 mSv.³⁵ The 2 CT scans used in this study will each use about 2 to 2.5 mSv.



11.5.1.3 Imaging Scoring

All CT [redacted] scans will be evaluated by centralized expert readers using the Brody/CF-CT scoring system.

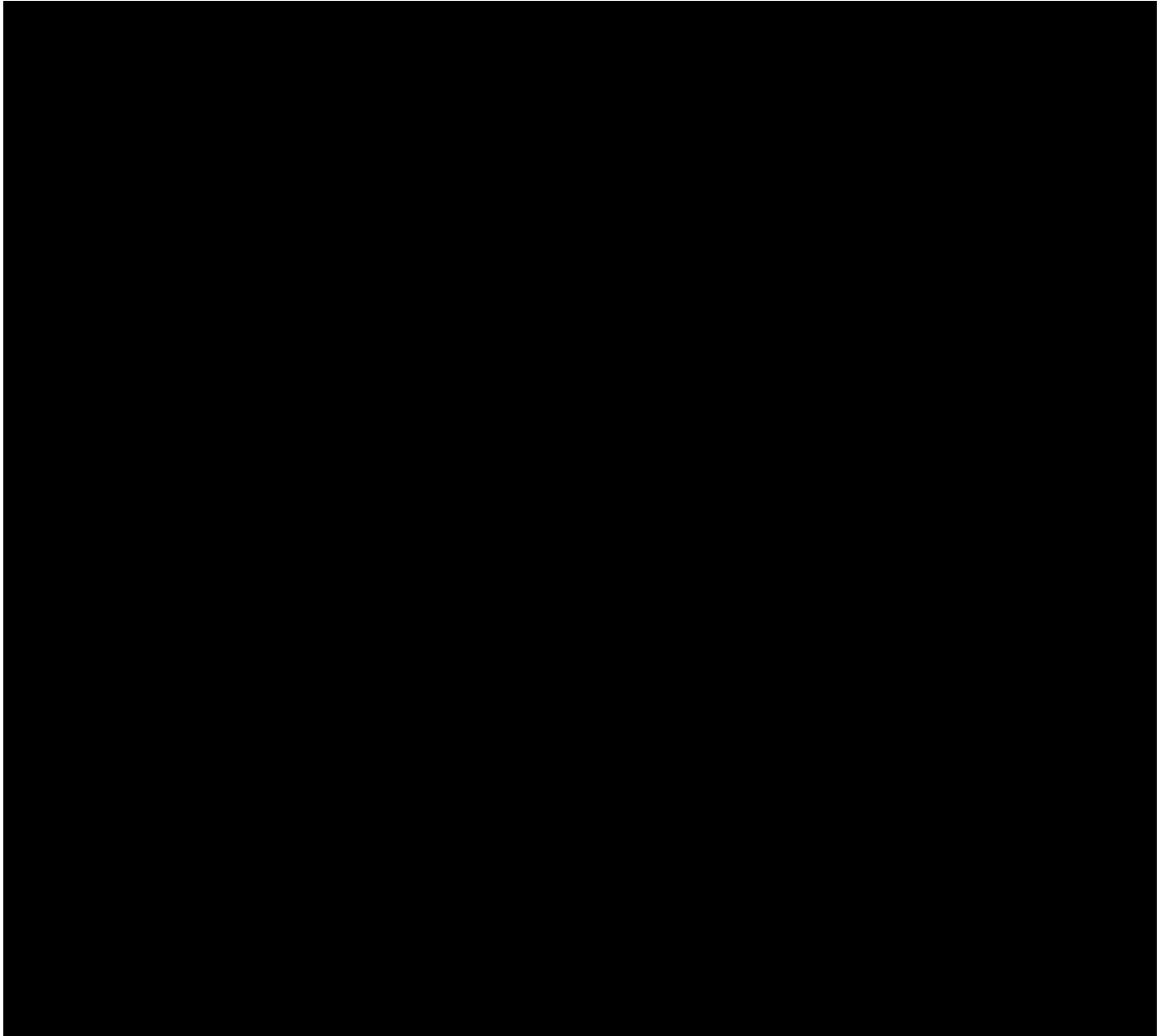
- The Brody/CF-CT scoring system semiquantitatively scores the degree of structural lung disease as shown on CT in patients with CF. It has been extensively tested and



validated (see [Section 8.2.3](#)). This score provides both localization and quantification of 5 abnormalities characteristic of CF lung disease: bronchiectasis, air trapping, mucous plugging, bronchial wall thickening, and parenchymal changes (includes parenchymal opacities, ground glass opacities, and cysts/bullae).



- Scores from other scoring algorithms for measuring the features of the Brody CF-CT scoring systems, as well as other features associated with structural lung disease, may be assessed.



11.6 Safety

Safety evaluations will include AEs, clinical laboratory assessments, and clinical evaluation of vital signs, pulse oximetry, ECGs, and PEs.

11.6.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (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 case report form (CRF) completion guidelines for investigators as well as training will be provided.

11.6.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory, except for urine pregnancy tests, which will be analyzed at the site. Fasting is not required at any time point. On Day 1, blood samples will be collected before the first dose of the study drug. At all other scheduled visits, these samples will be collected in the order specified in [Section 11.1](#).

Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see [Section 13.1](#)).

The safety laboratory test panels are shown in [Table 11-1](#).

Table 11-1 Safety Laboratory Test Panels

Serum Chemistry	Hematology	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	
Creatine kinase	International Normalized Ratio	
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.

Pregnancy (β-human chorionic gonadotropin) Tests for Females of Childbearing Potential: Serum samples will be obtained as specified in [Table 3-1](#) and [Table 3-2](#) and analyzed at the central laboratory. Urine pregnancy test kits will be provided by the central laboratory and performed and analyzed at the site as specified in [Table 3-2](#). The urine pregnancy test may be performed on Day 1 and must be negative before the randomization. Tests must also be reviewed and confirmed as negative before each LDCT scan.

Follicle-stimulating Hormone (FSH; Screening Period only): Blood sample for FSH will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be ≥40 mIU/mL to be considered postmenopausal.

CF Genotype (Screening Period only): CF genotyping will be performed on all subjects to confirm the genotype documented in the subject’s medical record. CF genotyping may be waived if the subject has a documented result from a previous Vertex study. Specific instructions will be provided in the Laboratory Manual.



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.

11.6.3 Liver Function Test Parameters

Liver Function Testing

Liver function testing (ALT, AST, GGT, ALP, direct bilirubin, and total bilirubin) must be performed as noted in [Table 3-2](#) for serum chemistry, while subjects are receiving study drug treatment and at 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 $>3 \times \text{ULN}$ 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 $>5 \times \text{ULN}$, 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 (before confirmatory testing), and the medical monitor must be notified, if any of the following criteria is met:

- ALT or AST $>8 \times$ ULN
- ALT or AST $>5 \times$ ULN for more than 2 weeks
- ALT or AST $>3 \times$ ULN, in association with total bilirubin $>2 \times$ 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 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 $\leq 2 \times$ 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.

11.6.4 Physical Examinations and Vital Signs

A PE of all body systems and vital signs assessment will be performed at screening and select study visits (see [Table 3-1](#) and [Table 3-2](#)). Symptom-targeted PEs and symptom-targeted vital sign assessments will occur at any other time during the study if triggered by AEs or if deemed necessary by the investigator.

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. After screening, any clinically significant abnormal findings in PEs will be reported as AEs.

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

11.6.5 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout according to the Schedule of Assessments ([Table 3-1](#) and [Table 3-2](#)). Additional standard 12-lead ECGs will

be performed at any other time if clinically indicated. The performance of all ECGs will adhere to the following guidelines:

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

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.

11.6.6 Contraception and Pregnancy

11.6.6.1 Contraception

The effects of VX-661 monotherapy or in combination with ivacaftor on conception, pregnancy, and lactation in humans are not known. Neither VX-661 nor ivacaftor showed any genotoxic potential in a standard battery of in vitro (Ames test, Chinese hamster ovary cell chromosomal aberration) and in vivo (mouse micronucleus) studies. VX-661 and ivacaftor were each found to be nonteratogenic in reproductive toxicology studies in rats and rabbits (see VX-661 and VX-770 Investigator's Brochures). Subjects should follow the contraception requirements outlined in this study protocol. The effects of VX-661 monotherapy or in combination with ivacaftor on the pharmacokinetics (PK) of hormonal contraceptives are not known. Thus, hormonal contraception is not an acceptable method of contraception for female subjects though it is acceptable for the female partners of male subjects.

At this stage in the development of VX-661 in combination with ivacaftor, participation in this study requires a commitment from the research subject and his/her partner to use at least

1 effective method of birth control. Acceptable methods of contraception for participants of this study and their partners are listed below. Methods of contraception should be in successful use from signing of consent, approximately 28 days before the first dose of study drug (unless otherwise noted), and until 90 days following the last dose of study drug.

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, and 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 or medical record before the first dose of the study drug.
- If the female is of non-childbearing potential, per the following:
 - Postmenopausal: spontaneous amenorrhea for at least 12 consecutive months and serum FSH level ≥ 40 mIU/mL at Screening
 - Documented hysterectomy or a bilateral oophorectomy/salpingo-oophorectomy
 - Has not achieved menarche (has not had her first menstrual period). Females who fall into this category are considered not to be of childbearing potential only as long as they have not had their first menstrual period. If a female achieves menarche during the study, she will need to provide consent for compliance (proper method of contraception or abstinence).
 - NOTE: All other female subjects who have had their first menstrual period will be considered to be of childbearing potential.

Acceptable contraceptive methods:

Acceptable contraceptive methods for **male subjects** or **male partners** of female subjects include the following:

- Vasectomy 6 months or more previously, with a documented negative postvasectomy semen analysis for sperm
- Condom and spermicide
 - In countries where spermicide is not available, condom without spermicide will be considered acceptable.
- Local regulations may require use of an additional acceptable method of contraception.

Acceptable contraceptive methods for **female subjects** include the following:

- Bilateral tubal ligation performed at least 6 months previously



- Continuous use of an intrauterine device (nonhormone-releasing) for at least 90 days before the first dose of study drug
- Barrier contraception (such as diaphragm, cervical cap, or female condom) and spermicide
 - In countries where spermicide is not available, barrier contraception without spermicide will be considered acceptable.
- Local regulations may require use of an additional acceptable method of contraception.
 - NOTE: Hormonal contraceptives will not be considered as an effective method; however, female subjects are not required to discontinue hormonal contraceptives.

Acceptable contraceptive methods for **female partners** of male subjects:

- Bilateral tubal ligation performed at least 6 months previously
- Continuous use of an intrauterine device for at least 90 days before first dose of study drug
- Barrier contraception (such as diaphragm, cervical cap, or female condom) and spermicide
 - In countries where spermicide is not available, condom without spermicide will be considered acceptable.
- Local regulations may require use of an additional acceptable method of contraception.
- Hormonal contraceptives, if successfully used for at least 60 days before first dose of study drug

Additional notes:

- Acceptable methods of contraception listed above are examples. Local requirements may prohibit the use of some of these examples. Please contact the medical monitor with any questions.
- A female condom cannot be used with male condom (as a double method of contraception) due to risk of tearing.
- 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 with a partner of the opposite sex.
- If applicable, additional contraception requirements may need to be followed according to local regulations and/or requirements.
- 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.
- Male subjects whose female partner becomes pregnant through well-documented in vitro fertilization (donated sperm) or banked sperm (collected before the subject received study drug) must be compliant with the contraception requirements. In this scenario, the male subject and his female partner must commit to using barrier methods of contraception (to ensure there is no exposure of the fetus to study drug) for the duration of the study and until 90 days after 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.
- Unique situations that may not fall within the above specifications should be discussed with the medical monitor.

11.6.6.2 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 11.6.6.1](#)). 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 is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

11.6.7 Pulse Oximetry

Arterial oxygen saturation by pulse oximetry will be measured at visits noted in [Table 3-1](#) and [Table 3-2](#). This will be assessed following a 5-minute rest (seated or supine) and before administration of study drug. 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.

11.6.8 Ophthalmologic Examination

At Screening, subjects who have documentation of bilateral lens removal are not required to complete any ophthalmologic examinations.

All other subjects will undergo an ophthalmologic examination performed by a licensed ophthalmologist at Screening, 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 screening ophthalmologic examination must be completed and the results reviewed before randomization. This examination does not have to be repeated if there is documentation of an examination that met protocol criteria and that was within 3 months before the start of the Screening Period or if there is documentation of a medical history of bilateral lens removal.

If a cataract, lens opacity, Y-suture, or lamellar rings are identified and determined to be clinically significant by the ophthalmologist at the Screening examination, the subject is ineligible for study entry (see [Section 9.2](#)).

If a cataract or lens opacity is identified and determined to be clinically significant by the ophthalmologist after dosing, the subject and Vertex medical monitor will be notified. After discussion with the principal investigator, who collaborates with the Vertex medical monitor, the subject may elect to continue or discontinue study drug treatment. If the subject discontinues study drug treatment, the subject should complete the ETT (see [Section 8.1.4](#)) and Safety Follow-up Visits (see [Section 8.1.3](#)). If the subject continues study drug treatment, more frequent ophthalmologic monitoring should be considered.

In addition to the screening examination, subjects <18 years of age at the Screening Visit will have an ophthalmologic examination conducted by a licensed ophthalmologist at Week 72. This exam may be completed within 4 weeks before the Week 72 Visit, but must be completed by the end of the Week 72 Visit.

For subjects <18 years of age at the Screening Visit who discontinue treatment after receiving at least 1 dose of study drug, an ophthalmologic examination will be performed by a licensed ophthalmologist at the Safety Follow-up Visit or ETT Visit. This examination may be completed at either the ETT or Safety Follow-up Visit, but must be completed by the end of the Safety Follow-up Visit. Subjects <18 years of age at the Screening Visit are required to complete only 1 ophthalmologic exam at the end of treatment (Week 72 Visit, ETT Visit, or Safety Follow-Up Visit), as described in [Table 3-2](#).

For all subjects, additional ophthalmologic examinations may be conducted at the discretion of the investigator. The medical monitor should be notified of any additional ophthalmologic examinations.

Lastly, at Screening, the following history will be obtained for all subjects:

- 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

12 STATISTICAL AND ANALYTICAL PLANS

Analysis of all data will be performed by Vertex or its designee. The results of all parts of the study will be reported in the clinical study report. A detailed analysis plan for the analysis of safety and efficacy data will be presented in a statistical analysis plan (SAP) before the database is locked for analysis.

12.1 Sample Size and Power

The primary endpoint is the absolute change from baseline of Total Brody/CF-CT score measured by the Brody/CF-CT score system at Week 72 using LDCT. The difference between the VX-661/ivacaftor group and the placebo group in the mean change from baseline in Total Brody/CF-CT score at Week 72 will be estimated.

This is an exploratory, Phase 2 study; the sample size is not based on statistical power. With 40 subjects (20 per arm), the study is aimed to explore changes in the Total Brody score over a 72 week period and for VX-661/ivacaftor versus placebo, based on the published literature.^{19,20}

12.2 Analysis Sets

The following analysis sets are defined: All Subjects Set, Full Analysis Set (FAS), and Safety Set.

The **All Subjects Set** is defined as all subjects who have been randomized or have received at least 1 dose of study drug. This analysis set will be used in subject listings and disposition summary table, unless otherwise specified.

The **Full Analysis Set (FAS)** is defined as all randomized subjects who have received at least 1 dose of study drug. The FAS is to be used in efficacy analyses in which subjects will be analyzed according to their randomized treatment group.

The **Safety Set** is defined as all subjects who received at least 1 dose of study drug. The Safety Set is to be used for all safety analyses in which subjects will be analyzed according to the treatment they received.

12.3 Statistical Analysis

This section presents a summary of the planned statistical analyses of efficacy and safety for this study. Statistical analysis details will be provided in the SAP for this study, which will be finalized before clinical database lock.

12.3.1 General Considerations

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

Categorical variables will be summarized using counts and percentages.

Baseline value, unless otherwise specified, is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of study drug. For ECGs, the baseline will be defined as the average of the 3 pretreatment measurements (triplicate) on Day 1.

Change (Absolute Change) from baseline will be calculated as Postbaseline value - Baseline value.

Relative change from baseline will be calculated and expressed in percentage as $100\% \times \frac{\text{Postbaseline value} - \text{Baseline value}}{\text{Baseline value}}$

Treatment-emergent (TE) Period will include the time from the first dose 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. The TE period will be used for safety analyses unless otherwise specified.

12.3.2 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. All summaries will be based on the FAS unless otherwise specified in the SAP for the study. No statistical hypothesis testing will be performed on background characteristics.

12.3.2.1 Subject Disposition

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

- All Subjects Set
- Randomized
- Dosed (Safety Set)
- Randomized and dosed (FAS)
- Completed study drug treatment
- Prematurely discontinued the study treatment and the reasons for discontinuation
- Completed study/Safety Follow-up
- Prematurely discontinued the study/Safety Follow-up and the reasons for discontinuation

12.3.2.2 Demographics and Baseline Characteristics

Demographic, background (e.g., medical history) and baseline characteristics will be summarized.

The following demographics and baseline characteristics will be summarized by dose group for the FAS: sex, race, ethnicity, age, weight, height, [REDACTED] baseline ppFEV₁, baseline medications, [REDACTED] and baseline Brody/CF-CT scores: total [REDACTED] by LDCT.

12.3.2.3 Prior and Concomitant Medications

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 initial dosing of study drug, regardless of when it ended
- **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 after 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 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.

Prior medications and concomitant medications will be summarized descriptively based on the FAS. Post-treatment medications will be listed for each subject.

12.3.2.4 Study Drug Exposure and Compliance

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 study drug plus 1.

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

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

12.3.3 Efficacy Analysis

Assessment of efficacy of VX-661/ivacaftor is the primary objective of this study.

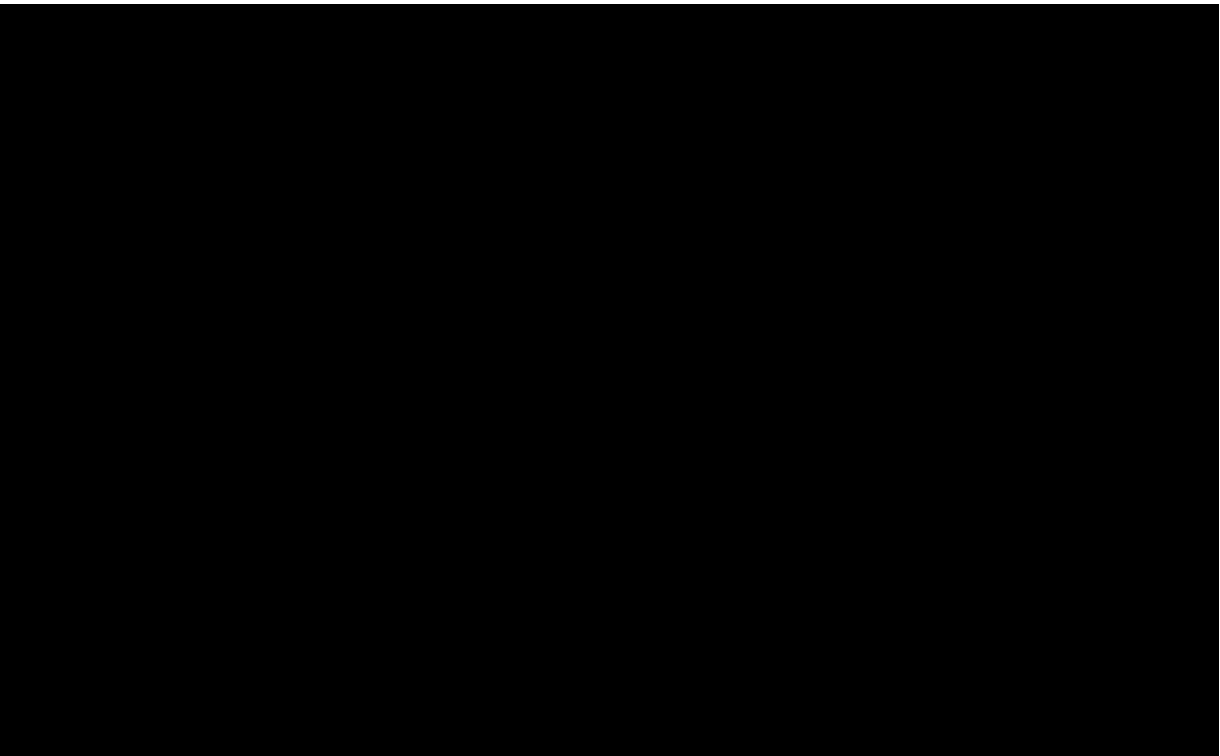
12.3.3.1 Analysis of Primary Endpoint

The primary endpoint is the absolute change from baseline of Total Brody/CF-CT score at Week 72 using LDCT. The primary analysis will be based on an analysis of covariance

(ANCOVA) model with the change from baseline of Total Brody/CF-CT score at Week 72 as dependent variable, treatment, sex (male versus female), and age as covariates. LDCT images will be scored by 2 central reader(s) blinded to treatment group and visit time point, as described in [Section 11.5.1.3](#). The difference between the VX-661/ivacaftor group and the placebo group in mean change from baseline in Total Brody/CF-CT score at Week 72 will be estimated.

The primary result obtained from the model will be the estimated treatment effect in each treatment group (with a 95% confidence interval), the estimated between-group difference in treatment effects, and a 95% confidence interval (CI) for the difference. For missing data, no imputation will be performed.

Methodological details will be provided in the study SAP.



12.3.4 Safety Analysis

All safety analyses will be based on the set of data associated with the TE period for subjects in the Safety Set.

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

- Incidence of treatment-emergent adverse event (TEAEs)
- Clinical laboratory values (i.e., hematology, serum chemistry, lipid and vitamin levels, coagulation studies, and urinalysis)
- ECGs

- Vital signs
- Pulse oximetry

All safety data will also be presented in individual subject data listings.

12.3.4.1 Adverse Events

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

- **Pretreatment AE:** any AE that started before initial dosing of study drug
- **TEAE:** any AE that increased in severity or that was newly developed at or after initial dosing of study drug through the end of TE period
- **Post-treatment AE:** any AE that increased in severity or that was newly developed 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.

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

- All TEAEs
- TEAEs by relationship
- TEAEs by maximal severity
- TEAEs leading to treatment discontinuation
- Serious TEAEs
- TEAEs leading to death

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 will be presented in the relationship summaries. An AE overview table will be provided. A separate table will summarize all TEAEs when each 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.

12.3.4.2 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 by treatment group at each scheduled time point. In addition, mean value at each visit will be plotted by treatment groups for each of the liver function parameters.

The number and percentage of subjects with at least 1 potentially clinically significant (PCS) event during the TE period will be summarized by treatment group. The PCS (postbaseline) shift from baseline will also be summarized for selected laboratory parameters. The PCS criteria and the parameter selection criteria will be provided in the SAP.

Results of urinalysis and the serum pregnancy test will be listed in individual subject data listings only. In addition, a listing containing individual subject laboratory assessment values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

12.3.4.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of raw values and change from baseline values will be provided by treatment group at each scheduled time point for the following standard 12-lead ECG measurements: PR, QT, and QTc for HR intervals (QTcF), QRS duration, and HR. In addition, the mean value at each visit will be plotted by treatment groups for QTc.

Additional ECG analyses will be described in the SAP.

12.3.4.4 Vital Signs

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

Additional vital sign analyses will be described in the SAP.

12.3.4.5 Physical Examination

PE findings will be presented as a data listing only. Clinically relevant results identified after screening will be reported as AEs.

12.3.4.6 Other Safety Analysis

12.3.4.6.1 Pulse Oximetry

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

12.3.5 Interim and IDMC Analyses

12.3.5.1 Interim Analysis

No interim analysis will be done.

12.3.5.2 IDMC Analysis

An IDMC will be formed before study initiation. The IDMC's objectives and operational details will be defined in a separate document (IDMC Charter), which will be finalized before the first subject is screened in the study. The IDMC will conduct regular planned safety reviews of study data as outlined in the IDMC Charter.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

An AE is considered serious if it meets the definition in [Section 13.1.2.1](#).

13.1.1.2 Clinically Significant Assessments

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

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

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

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

A laboratory value that is Grade 4 will not automatically be an SAE. A Grade 4 laboratory value will be an SAE if the 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 until the following time points:

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit, the **earliest** of
 - 28 days after the last dose of study drug,
 - the ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (see [Section 8.1.4](#)), or
 - before the first dose of study drug in another study (if applicable).

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

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

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed June 2015). 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

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**.

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 SAE Form, relationship to study drug(s) will be assessed only as related (includes possibly related) or not related (includes unlikely related), and severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the event to resolution and report to Vertex the outcome of the event using the SAE Form.

13.1.2.3 Reporting Serious Adverse Events

The investigator is responsible for notifying the sponsor within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational study drug. The SAE Form will be completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via:

Email: [REDACTED] (Preferred Choice)

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 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 form 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 subjects. Vertex will submit all protocol modifications to the required regulatory authorities.

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

13.2.4 Access to Records

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

13.2.5 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all CRFs, study reports, and communications relating to the study will identify subjects by assigned subject numbers and access to subject names linked to such numbers shall be limited to the site and the study physician and shall not be disclosed to Vertex. As required by applicable laws and regulations in the countries in which the study is being conducted, the investigator will allow Vertex and/or its representatives access to all pertinent medical records to allow for the verification of data gathered in the CRFs/SAE forms and the review of the data collection process. The FDA and regulatory authorities in other jurisdictions, including the IRB/EC, 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 (HIPAA) and associated regulations, an executed HIPAA authorization shall be obtained by the site from each subject (or the legal representative of the subject) before research activities may begin. Each HIPAA authorization shall comply with all HIPAA requirements including authorization allowing the site access to and use of the subject's personally identifiable health information, authorization for the site to disclose such information to Vertex, the FDA, and other parties requiring access under the protocol, and statements as to the purpose for which such information may be used and for how long.

13.2.6 Record Retention

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

13.2.7 Study Termination

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

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

- Subject or investigator noncompliance

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

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

13.3 Data Quality Assurance

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

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data for each enrolled subject will be entered into a CRF by study site personnel using a secure, validated, web-based electronic data capture (EDC) application. Vertex will have read-only access to site-entered clinical data in the EDC application.

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

13.4 Monitoring

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

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

13.5 Electronic Data Capture

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

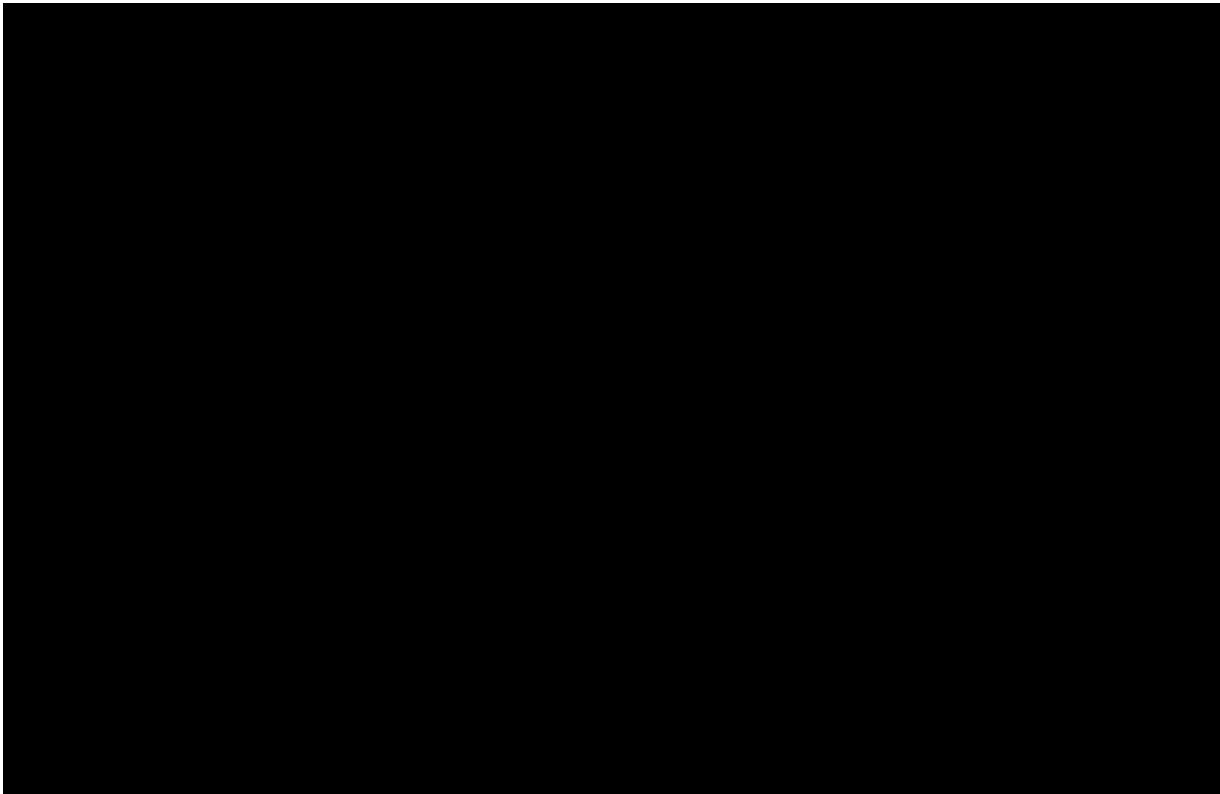
A CRF will be completed for each enrolled study subject. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data will indicate the subject's participation in the study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

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

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

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

13.6 Publications and Clinical Study Report



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.



14 REFERENCES

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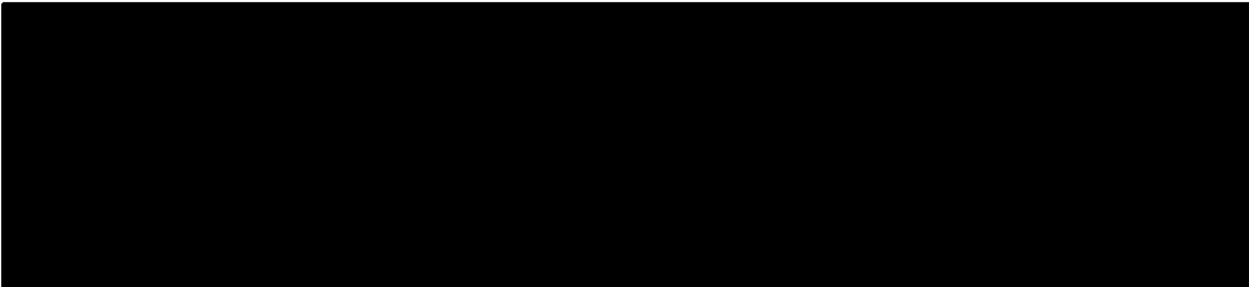
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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #:	VX15-661-112	Version #:	5.0	Version Date	26 February 2018
Study Title: A Phase 2, Randomized, Placebo-Controlled, Double-blind Study to Evaluate the Effect of VX-661 in Combination With Ivacaftor on Chest Imaging Endpoints in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the <i>F508del CFTR</i> Mutation					

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



15.2 Investigator Signature Page

Protocol #:	VX15-661-112	Version #:	5.0	Version Date	26 February 2018
Study Title: A Phase 2, Randomized, Placebo-Controlled, Double-blind Study to Evaluate the Effect of VX-661 in Combination With Ivacaftor on Chest Imaging Endpoints in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the <i>F508del CFTR</i> Mutation					

I have read Protocol VX15-661-112, Version 5.0 and agree to conduct the study according to its terms. I understand that all information concerning VX-661, ivacaftor, and this protocol supplied to me by Vertex Pharmaceuticals Incorporated is confidential.

Printed Name

Signature

Date

