1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Exploratory Study to Evaluate Effects of VX-661 in Combination With Ivacaftor on Lung and Extrapulmonary Systems in Subjects Aged 18 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

Vertex Study Number: VX14-661-111

[redacted]

Date of Protocol: 19 September 2016 (Version 4.0)
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2 PROTOCOL SYNOPSIS

Title A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Exploratory Study to Evaluate Effects of VX-661 in Combination With Ivacaftor on Lung and Extrapulmonary Systems in Subjects Aged 18 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

Clinical Phase and Clinical Study Type Phase 2, efficacy and safety

Objective To evaluate the clinical mechanisms of action in lung and extrapulmonary systems of VX-661 in combination with ivacaftor (IVA) (VX-661/IVA) in subjects with cystic fibrosis (CF) who are homozygous for the *F508del* mutation on the *CF transmembrane conductance regulator* (*CFTR*) gene.

Endpoints

Key Endpoints:

- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline at Day 28
- Absolute change in mucociliary clearance (MCC) from baseline at Day 28
- Absolute change in gastrointestinal pH from baseline at Day 29
- Absolute change in sweat chloride from baseline at Day 29

Other Endpoints:

- [redacted]
- [redacted]
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values (i.e., serum chemistry, vitamin levels, lipid panel, hematology, coagulation studies, and urinalysis), standard 12-lead electrocardiograms (ECGs), vital signs, and pulse oximetry

Number of Subjects A target of approximately 35 subjects and up to approximately 45 subjects

Study Population Male and female subjects aged 18 years and older with CF, homozygous for the *F508del-CFTR* mutation

Investigational Drug

Active substances: VX-661/IVA (fixed-dose combination [FDC] with VX-661 and IVA)

Activity: CFTR corrector (VX-661) and potentiator (IVA) (increased chloride ion [Cl−] secretion)

Strength and Route of Administration: 100-mg VX-661/150-mg IVA FDC film-coated tablet for oral administration

Dose Administered: 100-mg VX-661/150-mg IVA daily (qd) (1 × 100-mg/150-mg FDC tablet qd) in the morning

Active substance: IVA

Activity: CFTR potentiator (increased Cl^- secretion)

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

Dose Administered: 150-mg IVA qd (1 × 150-mg tablet qd) in the evening

VX-661/IVA FDC placebo and IVA placebo

Strength and Route of Administration: 0-mg, film-coated, matching placebo tablets for oral administration

Study Duration

Excluding the Screening Period (up to 28 days in duration), subjects will participate in this study for up to 57 ± 7 days.

During the Treatment Period, study drug (VX-661/IVA or placebo) will be administered for 29 ± 3 days. A Safety Follow-Up Visit is required for all subjects 28 ± 7 days after the last dose of study drug.

Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter, exploratory study in subjects with CF who are homozygous for the *F508del-CFTR* mutation.

This study includes a Screening Period, a Treatment Period, and a Safety Follow-up Visit.

Screening Period (Day −28 through Day −1):

The Screening Period will occur between 1 and 28 days before the first dose of study drug to confirm that the subjects meet the eligibility criteria.

During the Screening Period, a patency capsule and a wireless motility capsule (WMC) will be administered. The patency capsule will be administered at the Day -28 to Day -13 Clinic Visit. A telephone contact will occur 2 days after administration of the patency capsule to confirm the passage of the capsule in the stool (unless the subject confirms the passage of the capsule prior to the scheduled telephone contact). Subjects who are unable to successfully pass the patency capsule test will not be randomized.

The WMC will be administered at the Day -23 to Day -10 Clinic Visit after confirmation that the patency capsule has passed. A telephone contact will occur 5 days after administration of the WMC to confirm the passage of the capsule (unless the subject confirms the passage of the capsule prior to the scheduled telephone contact). The subject will not be randomized in the study until passage of the WMC has been confirmed by the central reader or X-ray, regardless of confirmation of passage by the subject at the telephone contact.

Treatment Period (Day 1 through Day 29 ± 3 days):

On Day 1, subjects will be randomized (4:1) to VX-661/IVA combination therapy (100-mg VX-661 qd/150-mg IVA every 12 hours [q12h]) or placebo

Safety Follow-up Visit (28 ± 7 days after the last dose of study drug)

The Safety Follow-up Visit is required for all subjects 28 ± 7 days after the last dose of study drug. Subjects who complete the Day 29 Visit and subsequently the Safety Follow-up Visit will be offered the opportunity to enroll into an extension study of VX-661/IVA combination therapy if they meet eligibility requirements for the extension study.

Assessments	**Efficacy:** spirometry, MCC, gastrointestinal pH, sweat chloride [redacted] **Safety**: AEs, clinical laboratory values (serum chemistry, vitamin levels, lipid panel, hematology, coagulation studies, and urinalysis), ECG, vital signs, pulse oximetry, and physical examinations **Pharmacokinetics:** VX-661, M1-661, IVA, and M1-IVA
Statistical Analyses	For all key endpoints, mean change from baseline within the VX-661/IVA group will be analyzed using a 2-sided, paired, *t*-test at a 5% level of significance. There will be no type I error multiplicity adjustment conducted for this analysis. A within-group estimate of the mean change from baseline for both the VX-661/IVA and placebo groups, with a 95% CI, will also be provided. [redacted] For the safety endpoints, only a descriptive analysis will be performed for each treatment group.

3 SCHEDULE OF ASSESSMENTS

Schedules of Assessments are shown in Table 3-1 (Screening Period) and Table 3-2 (Treatment Period through the Safety Follow-up Visit).

All visits are to be scheduled relative to the Day 1 Visit (first dose of study drug).

Table 3-1 Study VX14-661-111: Screening Period

Assessment	Screening Period Day -28 through Day -1			
	Screening Visit Day -28 to Day -13	**Telephone Contact 2 Days After Patency Capsule Administration**	**Clinic Visit Day -23 to -10[a]**	**Telephone Contact 5 Days After WMC Administration**
Clinic visit	X		X[b]	
Informed consent	X			
Inclusion/exclusion criteria review	Continuous from signing of informed consent form (ICF) before randomization[a]			
Demographics	X			
Medical history	X			
Ophthalmologic history	X			
CF genotype[c]	X			
Weight, height[d]	X			
Complete physical examination	X			
Ophthalmologic examination[e]	Between signing of ICF and randomization			
Standard 12-lead ECG[f]	X			
Vital signs[g]	X			

[a] Clinic Visit Day -23 through Day -10 will take place only if a subject passes the patency capsule test. Select baseline assessments are performed on Day -23 through Day -10 (Table 3-1), and the remaining are performed on Day 1 (Table 3-2). Before any baseline assessments are performed, eligibility for enrollment based on all available screening assessment results must be verified by the investigator.

[b] This visit may occur on 1 day or on 2 separate days (see Section 8.1.1).

[c] All subjects will be tested for *CFTR* genotype regardless of availability of a previous *CFTR* genotype laboratory report. Refer to the Laboratory Manual for specific instructions.

[d] Weight and height will be measured with shoes off.

[e] One ophthalmologic examination will be conducted by a licensed ophthalmologist during the Screening Period. The ophthalmologic examination does not need to be repeated if there is documentation of an examination that met the protocol criteria and that was conducted within 3 months before the Screening Period (see Section 11.7.7). Subjects with clinically significant cataracts, lens opacity, Y-suture, or lamellar rings will be excluded.

[f] A standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes. ECGs will be performed before vital signs, pulse oximetry, and any other procedures that may affect heart rate (e.g., blood sampling).

Table 3-1 Study VX14-661-111: Screening Period

Assessment	Screening Period Day -28 through Day -1			
	Screening Visit Day -28 to Day -13	**Telephone Contact 2 Days After Patency Capsule Administration**	**Clinic Visit Day -23 to -10[a]**	**Telephone Contact 5 Days After WMC Administration**
Pulse oximetry[g]	X			
Spirometry	X[h]		X[i]	
Urinalysis	X			
Serum FSH[j] (postmenopausal female subjects only)	X			
Pregnancy test[k]	Serum		Urine[l]	
Sweat chloride[m]	X			
Hematology	X			
Coagulation	X			
Serum chemistry	X			
Patency capsule	X[n]	Confirm passage[o]		
Meal or snack at site			X[p]	
WMC[q]			X[r]	confirm passage[s]

[g] Vital signs and pulse oximetry will be collected after the subject has been at rest (seated or supine) for 5 minutes. Vital signs will be performed after ECGs and before blood sampling.

[h] Spirometry may be performed pre- or postbronchodilator (see Section 11.4.1).

[i] Spirometry should be performed prebronchodilator, on the same day as the MCC assessment, and prior to both WMC and MCC if both are done on the same day. Spirometry values must be ≥30 percent predicted FEV1 before MCC (see Section 11.4.2).

[j] 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.

[k] Pregnancy tests will be performed for all female subjects of childbearing potential (see Section 11.7.5).

[l] Pregnancy test results will be obtained before administration of WMC and the MCC assessment. If the Clinic Visit Day -23 to -10 occurs on 2 separate days, pregnancy testing will occur before the procedures on each day.

[m] Sweat chloride test is not required if the subject has a documented sweat chloride test result in the medical records.

[n] All subjects will be administered a patency capsule test at the Day -28 to Day -13 Screening Visit after all other assessments have been completed. Subjects will stay under observation in the clinic for 2 hours after administration of the patency capsule.

[o] Telephone contact will occur 2 days after administration of the patency capsule to confirm passage of the patency capsule in the stool (unless the subject confirms passage of the capsule prior to the scheduled telephone contact [Section 11.4.3]). A subject must pass the patency capsule test to continue the Screening Period assessments. If passage of the patency capsule is not confirmed during the telephone contact, the medical monitor must be contacted immediately to confirm further course of action (see the Study Reference Manual for additional information).

[p] Subjects must adhere to study restrictions in Table 9-2 regarding meals. During the Clinic Visit(s) on Day -23 to Day -10, subjects will fast for 8 hours (water is permitted) before administration of a snack bar (in place of the morning meal), and for an additional 4 hours immediately following administration of the WMC.). If the Day -23 to – 10 Visit occurs on 2 separate days, a meal or snack bar will be provided at the clinic on both days.

Table 3-1 Study VX14-661-111: Screening Period

Assessment	Screening Period Day -28 through Day -1			
	Screening Visit Day -28 to Day -13	**Telephone Contact 2 Days After Patency Capsule Administration**	**Clinic Visit Day -23 to -10[a]**	**Telephone Contact 5 Days After WMC Administration**
MCC[t]			X	
[redacted]	[redacted]			
Prior and concomitant medications	Continuous from signing of ICF through Safety Follow-up Visit			
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit			

CF: cystic fibrosis; ECG: electrocardiogram; FSH: follicle-stimulating hormone; MCC: mucociliary clearance; WMC: wireless motility capsule

[q] If MCC and WMC administration occur on a single day, WMC administration should be completed before the MCC assessment.

[r] Subjects must pass the patency capsule test and adhere to WMC restrictions in Table 9-1 before administration of the WMC (see Section 11.4.3). Subjects will fast for 8 hours (water is permitted) before administration of a snack bar (in place of the morning meal) with the WMC, and will fast for an additional 4 hours immediately following administration of the WMC. All screening assessments, except for the ophthalmologic examination [redacted], must be completed before the WMC.

[s] Telephone contact will occur 5 days after the administration of the WMC to evaluate passage of the capsule (unless the subject confirms the passage of the capsule prior to the scheduled contact). If passage of the WMC is not confirmed during the telephone contact, the medical monitor must be contacted immediately to confirm further course of action. Subjects will not be randomized in the study until passage of the WMC has been confirmed by the central reader or X-ray, regardless of confirmation of passage by subject at telephone contact (see Section 11.4.3 and the Study Reference Manual for additional information).

[t] Bronchodilator usage is restricted for 12 hours before the MCC assessment. The first MCC scan will be immediately following radiolabeled aerosol inhalation, and the second scan 6 hours (± 30 minutes) after inhalation. Subjects will adhere to study restrictions in Table 9-1 related to MCC (see the Study Reference Manual for additional information).

[redacted]

Table 3-2 Study VX14-661-111: Treatment Period and Safety Follow-Up Visit

Event/Assessment[a]	Treatment Period				Telephone Contact 5 Days After WMC Administration	Early Treatment Termination[b] Visit	Safety Follow-up Visit 28 (± 7) Days After Last Dose of Study Drug
	Day 1	Day 14 (± 3 days)	Day 28 (± 3 days)[c]	Day 29 (± 3 days)			
Clinic visit	X		X[d]	X		X	X
Telephone contact		X[e]			X		
Inclusion and exclusion criteria review[f]	X						
Weight and Height[g]	X		X			X (weight)	X
Complete physical examination[h]	X						X
Standard 12-lead ECG[i]	X[j]			X[j]		X[j]	X[j]
Vital signs[k]	X		X	X		X	X
Pulse oximetry[k]	X		X	X		X	X
Spirometry[l]	X		X			X	X

[a] All assessments will be performed before administration of study drug unless noted otherwise.

[b] If the subject prematurely discontinues study treatment, an Early Treatment Termination (ETT) Visit should be scheduled as soon as possible after the last dose of study drug. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 (± 7) days after their last dose of study drug. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT will not be required (see Section 8.1.4).

[c] This visit may occur on 1 day or on 2 separate days (see Section 8.1.2). All assessments of the Day 28 Visit must be completed before the Day 29 Visit assessments.

[d] Subjects will be offered the option of an overnight stay in proximity to the clinic between Days 28 and 29.

[e] A telephone contact will occur on Day 14 to review adverse events (AEs) and concomitant medications.

[f] Confirmation of subject eligibility will occur before randomization.

[g] Weight and height will be measured before dosing with shoes off. Height will be collected only for subjects 21 years of age or younger at the Day 1, Day 28, and Safety Follow-up Visits.

[h] A complete physical examination will occur on Day 1 and at the Safety Follow-up Visit. Symptom-targeted physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.

[i] All ECGs will be performed before vital signs, pulse oximetry, and any other procedures that may affect heart rate (e.g., blood sampling). Subjects must be supine for at least 5 minutes before the start of the ECG.

[j] At the Day 1 and Day 29 Visits, ECGs will be collected before dosing and at 1.5 (approximately ± 15 minutes) and 3 hours (approximately ± 15 minutes) after the morning dose of study drug. ECGs collected on Day 1 before dosing will be performed in triplicate. If study drug is not administered on the Day of the visit (i.e., because of study drug interruption or permanent discontinuation of study drug), only 1 ECG will be collected.

[k] 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. Vital signs will be performed after ECGs and before blood sampling. In cases where Day 28 Visit assessments occur on 2 separate days, vital signs and pulse oximetry will be collected on both days.

[l] Spirometry will be performed before study drug dosing and should be performed prebronchodilator (see Section 11.4.1). At the Day 28 Visit, bronchodilator usage is restricted for 12 hours before the MCC assessment. If the Day 28 Visit assessments occur on 2 separate days, spirometry should be performed on the same day as and preceding the MCC assessment.

Table 3-2 Study VX14-661-111: Treatment Period and Safety Follow-Up Visit

Event/Assessment[a]	Treatment Period				Telephone Contact 5 Days After WMC Administration	Early Treatment Termination[b] Visit	Safety Follow-up Visit 28 (± 7) Days After Last Dose of Study Drug
	Day 1	Day 14 (± 3 days)	Day 28 (± 3 days)[c]	Day 29 (± 3 days)			
[redacted]	[redacted]		[redacted]				
Urinalysis	X			X		X	X
Sweat chloride[n]	X			X			
Pregnancy test[o]	Urine		Urine	Serum		Serum	X[p]
VX-661 and M1-661 PK[q]			X	X		X	X
IVA and M1-IVA PK[q]			X	X		X	X
Hematology	X			X		X	X
Coagulation	X			X		X	X
Serum chemistry	X			X		X	X
Lipid panel[r]	X			X		X	X
Vitamin levels	X			X		X	X
[redacted]	[redacted]						
[redacted]	[redacted]						

[redacted]

n Sweat collection will occur before the morning dose and no more than 1 hour before the predose PK sample collection. Sweat chloride assessments will not overlap with the collection of other assessments (see the Laboratory Manual for additional information).

o Pregnancy tests will be performed for all female subjects of childbearing potential. On Day 1, pregnancy test results must be obtained before randomization. On Day 28, pregnancy test results must be obtained before the MCC assessment.

p Serum pregnancy test must be performed at the ETT Visit for subjects who discontinue the study and at the Safety Follow-up Visit for subjects who complete the study and chose not to enroll in the extension study. Urine pregnancy test must be performed for subjects who complete Day 29 and choose to enroll in the extension study or for subjects who discontinue the study and complete both ETT and Safety Follow-up Visits.

q Single PK blood samples will be collected within 60 minutes before the morning dose of study drug at Day 28 and Day 29. If study drug is not administered at the visit (i.e., study drug interruption or permanent discontinuation of study drug), a PK blood sample will still be collected. At the ETT (as applicable) and the Safety Follow-up Visit, a single PK blood sample will also be collected.

r Blood samples for lipid panel tests will be collected after fasting for a minimum of 4 hours (see Section 11.7.2).

Table 3-2 Study VX14-661-111: Treatment Period and Safety Follow-Up Visit

Event/Assessment[a]	Treatment Period				Telephone Contact 5 Days After WMC Administration	Early Treatment Termination[b] Visit	Safety Follow-up Visit 28 (± 7) Days After Last Dose of Study Drug
	Day 1	Day 14 (± 3 days)	Day 28 (± 3 days)[c]	Day 29 (± 3 days)			
[redacted]	[redacted]		[redacted]			[redacted]	[redacted]
[redacted]	[redacted]		[redacted]				
Wireless motility capsule (WMC)				X[s]	Confirm passage[t]		
Mucociliary clearance assessment (MCC)[u]			X				
Adverse events and concomitant medications	Continuous from signing of ICF through Safety Follow-up Visit						
Randomization[v]	X						
Meal(s) or snack(s) at site[w]	X		X	X[x]			
Study drug dosing[y]	X						
Study drug count	X		X	X		X	X[z]

CF: cystic fibrosis; ECG: electrocardiogram; FSH: follicle-stimulating hormone; hCG: human chorionic gonadotropin; [redacted]; MCC: mucociliary clearance; PK: pharmacokinetics; WMC: wireless motility capsule

[s] Subjects will adhere to study restrictions in Table 9-1 related to WMC. During the Day 29 Visit, subjects will fast for 8 hours (water is permitted) before administration of a snack bar (in place of the morning meal) with the WMC and the morning dose of study drug , and will fast for an additional 4 hours immediately following administration of the WMC.

[t] Telephone contact will occur 5 days after the administration of the WMC to confirm passage of the capsule (unless the subject confirms passage of the capsule before the scheduled telephone contact). If passage of the WMC is not confirmed by the telephone contact, the medical monitor must be contacted immediately to confirm further course of action. Passage of the WMC must be confirmed by the central reader or X-ray, regardless of confirmation of passage by subject at telephone contact (see Section 11.4.3 and the Study Reference Manual for additional information).

[u] On Day 28, radiolabeled aerosol inhalation will occur after the dose of study drug. One MCC scan will occur immediately following radiolabeled aerosol inhalation and a second scan approximately 6 hours (± 30 minutes) after inhalation. Subjects will adhere to study restrictions in Table 9-1 related to MCC (see the Study Reference Manual for additional information). Refer to Section 8.1.2 for the Day 28 Visit assessments.

[v] Randomization must occur after all inclusion and exclusion criteria are met and before the first dose of study drug. Randomization may occur on Day -1.

[w] Fat-containing food such as a "standard CF" high-fat, high-calorie meal or snack will be provided at the site to subjects after all predose assessments have occurred (if the Day 28 assessments occur on 2 separate days, a meal or snack will be provided for each clinic visit.).

[x] Administration of a snack bar (in place of the morning meal).

[y] Study drug will be administered as described in Section 10.2. On Day 1 through the morning of the Day 29 Clinic Visit, study drug will be administered within 30 minutes of starting a meal with fat-containing food such as a "standard CF" high-fat, high-calorie meal or snack. At the Day 29 Visit, subjects will receive a snack bar in place of the morning meal. On days of scheduled visits, the morning dose of study drug will be administered at the site after the last predose assessment has been completed.

[z] Study drug count will occur at the Safety Follow-up Visit for all subjects who discontinue the study and for whom the Safety Follow-up Visit replaces the ETT.

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5 INTRODUCTION

Cystic fibrosis (CF) is an orphan disease[1,2] that affects an estimated 70,000 children and adults worldwide,[3] and is the most common fatal genetic disease in persons of European descent.[4] Despite progress in the treatment of CF with antibiotics and mucolytics, the predicted median age of survival for a person with CF is in the mid-30s.[4,5] Although most morbidity and mortality are caused by progressive loss of lung function, the disease affects multiple organs.[6]

CF is an autosomal recessive genetic disease caused by defects in the gene encoding the CF transmembrane conductance regulator (CFTR), an epithelial chloride ion 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.[4] This function is defective in patients with CF due to a loss of either cell surface expression and/or function.

The most prevalent mutation is an in-frame deletion in the *CFTR* gene resulting in a loss of phenylalanine at position 508 in the CFTR protein (F508del-CFTR). The proportion of patients with CF who are homozygous for the F508del-CFTR mutation is similar across geographic regions: approximately 47% in the US,[7] 44% in the European Union (EU),[8] 49% in Canada,[9] and 52% in Australia.[10]

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 chloride and bicarbonate transport,[11,12,13] which impairs fluid regulation and promotes accumulation of thick, sticky mucus in the airway. The mucus build-up obstructs the airways and interferes with the activity of defensins, which contributes to dysbiosis and predisposes the patient to chronic lung infections.[14,15]

In addition to pulmonary disease, multiple other organ systems are impacted in patients with CF. One key extrapulmonary manifestation of CF is pancreatic disease, which results in pathophysiologic changes in both endocrine and exocrine pancreatic function. CFTR-mediated transport of both chloride and bicarbonate ions plays an important role in maintaining optimal solubility of intraluminal fluid and facilitating flow of alkaline fluid from acinar cells into the pancreatic and bile ducts. Alkaline fluid enters the duodenum of the small intestine and rapidly neutralizes the acidic pH of chyme entering the small intestine from the stomach, thus creating an optimal pH for digestive enzyme activity and micelle formation. Decreased CFTR function results in pancreatic duct blockages and decreased secretion of bicarbonate-rich fluids and enzymes from the exocrine pancreas into the small intestine.[16] The role of CFTR as a bicarbonate channel will be explored in this study by examining the change in pH from the stomach to the proximal small intestine.

Two complementary approaches to increase CFTR-mediated chloride secretion in the airway epithelia have been studied.[17] One approach is to treat with a compound (CFTR "correctors") that will modify the cellular processing and trafficking of the CFTR protein to increase the amount of functional CFTR at the cell surface. Another approach is to treat with compounds ("potentiators") that increase the channel gating activity of protein kinase A-activated CFTR at the cell surface to enhance ion transport. 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 chloride secretion through the action of a

potentiator and/or corrector could prevent the hyperabsorption of water across the apical surface of epithelial cells, allowing proper maintenance of airway hydration. Restoration of adequate airway hydration could alleviate the cycle of mucus plugging, infection, and inflammation, which 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 to the cell surface.[18] When added for more than 24 hours to human bronchial epithelial (HBE) cells isolated and cultured from lung explants obtained from donors with CF (CF-HBE cells) who are homozygous for the *F508del-CFTR* mutation, a concentration-dependent increase in levels of mature (i.e., plasma membrane) F508del-CFTR was observed. The increased trafficking of F508del-CFTR to the cell surface resulted in a substantial increase in Cl^- secretion.[18] VX-661 did not correct the processing and localization of other misfolded or normally folded proteins other than CFTR, suggesting that the mechanism of VX-661 action is selective for CFTR (CFTR corrector).[19]

Ivacaftor (IVA, VX-770; Kalydeco [150-mg tablets]) is a compound developed by Vertex that has been shown to have CFTR potentiator properties. Proof of concept that pharmacologic modulation of CFTR function can result in clinical benefit in patients with CF was observed in subjects with CF and the *G551D-CFTR* mutation who had robust clinical improvement following administration of IVA.[20] Kalydeco is currently indicated for treatment of CF in a subset of patients with Class III or "gating" CFTR mutations, including the *G551D-CFTR* mutation.

Details about the VX-661 and IVA development programs can be found in the Investigator's Brochures.[21,22]

6 STUDY OBJECTIVE

To evaluate the clinical mechanisms of action in lung function and extrapulmonary systems of VX-661 in combination with IVA (VX-661/IVA) in subjects with CF who are homozygous for the *F508del-CFTR* mutation

7 STUDY ENDPOINTS

7.1 Key Endpoints

- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline at Day 28
- Absolute change in mucociliary clearance (MCC) from baseline at Day 28
- Absolute change in gastrointestinal pH from baseline at Day 29
- Absolute change in sweat chloride from baseline at Day 29

7.2 Other Endpoints

[redacted]

- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values (i.e., serum chemistry, vitamin levels, lipid panel, hematology, coagulation studies, and urinalysis), standard 12-lead electrocardiograms (ECGs), vital signs, and pulse oximetry

8 STUDY DESIGN

8.1 Overview of Study Design

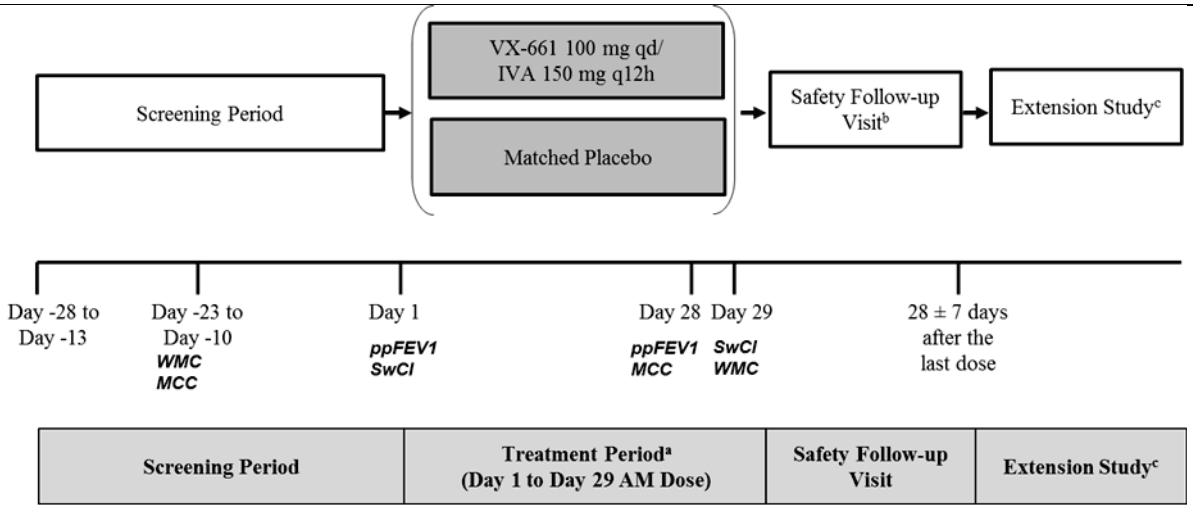
This is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter, exploratory study in subjects with CF who are homozygous for the *F508del-CFTR* mutation. This study is designed to evaluate the lung function and extrapulmonary responses of subjects receiving VX-661/IVA combination therapy.

This study includes a Screening Period, Treatment Period, and a Safety Follow-up Visit. The study plans to randomize approximately 35 subjects and up to approximately 45 subjects. Subjects will be randomized (4:1) to VX-661/IVA or placebo, respectively, as shown in Figure 8-1.

Subjects who prematurely discontinue study drug treatment will be asked to complete assessments as described in Section 8.1.4.

Subjects who complete the Treatment Period and are eligible and elect to roll into an extension study will be required to have a Safety Follow-up visit 28 ± 7 days after the last dose of study drug.

Figure 8-1 Schematic of the Study Design



MCC: mucociliary clearance; ppFEV1: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; WMC: wireless motility capsule.
Note: Only key assessments are included in the figure.
[a] Study drug will be administered for 29 day (± 3 days) and the last dose of study drug will be administered at the Day 29 Visit.
[b] The Safety Follow-up Visit is scheduled to occur 28 (± 7) days after the last dose of study drug for all subjects.
[c] Subjects who complete the Day 29 Visit and subsequently the Safety Follow-up Visit will be offered the opportunity to enroll in an extension study of VX-661/IVA combination therapy if they meet eligibility requirements for the extension study.

8.1.1 Screening

Screening assessments are shown in Table 3-1. All visits should occur within the windows specified. Subjects will be outpatients during the Screening Period.

The Screening Period will occur between 1 and 28 days before the first dose of study drug to confirm that the subjects meet the eligibility criteria. The investigator (or an appropriate authorized designee) will obtain informed consent from each subject before beginning any study assessments. To prepare for study participation, subjects will be instructed on the study restrictions (Section 9.3).

During the Screening Period, a patency capsule and a wireless motility capsule (WMC) will be administered. The patency capsule will be administered at the Day -28 to Day -13 Clinic Visit. A telephone contact will occur 2 days after administration of the patency capsule to confirm the passage of the capsule in the stool (unless the subject confirms passage of the capsule prior to the scheduled telephone contact). If passage of the patency capsule is not confirmed by the telephone contact, the medical monitor must be contacted immediately to confirm further course of action. Subjects who are unable to successfully pass the patency capsule test will not be randomized (see the Study Reference Manual for additional information).
A telephone contact will occur 5 days after administration of the WMC to confirm the passage of the capsule (unless the subject confirms passage of the capsule prior to the scheduled telephone contact). If passage of the WMC is not confirmed by the telephone contact, the medical monitor must be contacted immediately to confirm further course of action. Final confirmation of passage will be obtained by the central reader following review of the data. If the WMC data review is

inconclusive, an X-ray will be required to confirm the WMC passage. The subject will not be randomized in the study until passage of the WMC has been confirmed by the central reader or X-ray, regardless of confirmation of passage by the subject at the telephone contact (see the Study Reference Manual for additional information).

To allow flexibility, the Clinic Visit Day -23 to Day -10 may occur on 1 day or on 2 separate days as follows (see Table 3-1):

- Spirometry and MCC should be performed on the same day and spirometry should precede MCC.
- If WMC administration and MCC occur on a single day, spirometry should occur before WMC administration, and WMC administration should occur before MCC.
- A urine pregnancy test will be completed before WMC administration and the MCC; if WMC administration and MCC occur on 2 separate days, pregnancy testing will occur before the procedures on each day.
- If assessments occur on 2 separate days, a meal or snack bar will be provided at the clinic on both days.
- Fasting will occur only on the day of WMC administration.

Subjects will be outpatients during the Screening Period.

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,[23] repeat spirometry evaluation may be performed once, after discussion with the medical monitor.

If repeat values of the individual assessment(s) described above are within the eligibility criteria and completed within the screening window, then the subject will be eligible for the study, provided they meet all eligibility criteria.

8.1.1.2 Rescreening

Subjects may only be rescreened with the approval of the medical monitor. If a subject is rescreened, all Screening Visit (Day -28 to Day -13) assessments will be repeated **except** for the following:

- Patency capsule assessment
- Ophthalmology examination (if performed within the last 3 months)
- CF genotyping

- Follicle stimulating hormone (FSH) test (if serum FSH level was ≥40 mIU/mL during prior screening)
- Sweat chloride test
- [redacted]

If a subject is rescreened, the screening window will restart once the first rescreening assessment has been initiated. Clinic Visit (Day -23 to Day -10) assessments do not need to be repeated when subjects are rescreened.

8.1.1.3 Extension of Screening Period Window

A subject may have the Screening Period window extended by 2 weeks 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
- Scheduling of ophthalmologic examinations (Section 11.7.7)

8.1.2 Treatment Period

Study visits during the Treatment Period will occur as shown in Table 3-2. All visits should occur within the windows specified.

To allow flexibility, the Day 28 Visit may occur on 1 day or on 2 separate days as follows:

- Spirometry and urine HCG will occur on the same day as and preceding the MCC assessment.
- [redacted]
- If the Day 28 Visit occurs on 2 separate days, vital signs and pulse oximetry will occur on both days.
- If the Day 28 Visit occurs on 2 separate days, a meal or snack will be provided at the clinic on both days.

The Treatment Period will last 29 ± 3 days. Subjects will be randomized 4:1 to the VX-661/IVA group or the placebo group. The dosing regimen for each treatment arm is shown in Figure 8-1 and is as follows:

- VX-661/IVA: 100-mg VX-661/150-mg IVA fixed-dose combination (FDC), film-coated tablet for oral administration (morning dose); 150-mg IVA film-coated tablet for oral administration (evening dose)
- Placebo: film-coated matching placebo tablets for oral administration

The first dose of the study drug will be administered on Day 1. Dosing details are given in Section 10.2.

8.1.3 Safety Follow-up Visit

The Safety Follow-up Visit assessments are listed in Table 3-2. The Safety Follow-up Visit will occur approximately 28 (± 7) days after the last dose of study drug for all subjects, including subjects who discontinue treatment (see Section 8.1.4).

Subjects who complete the Day 29 Visit and subsequently the Safety Follow-up Visit will be offered the opportunity to enroll into an extension study of VX-661/IVA combination therapy if they meet eligibility requirements for the extension study.

8.1.4 Early Treatment Termination

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

If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the Safety Follow-up Visit will be completed in place of the ETT.

8.2 Rationale for Study Design and Study Drug Regimens

8.2.1 Study Design

A randomized, double-blind, placebo-controlled study design will avoid measurement bias by the investigator and will reduce reporting bias of symptoms or outcomes by subject.

This study is designed to observe the effects of VX-661 (100 mg daily [qd]) and IVA (150 mg every 12 hours [q12h]) combination therapy on lung function (measured by ppFEV$_1$ and MCC), gastrointestinal pH, and CFTR modulation (sweat chloride). These data will be informative for understanding the underlying clinical mechanisms of physiological improvements derived from CFTR modulation.

8.2.2 Study Drug Dose and Duration

The dose regimen of VX-661 for this study is equivalent to the dose evaluating VX-661/IVA combination therapy in a Phase 2 study, Study VX11-661-101 (Study 101), and is the same dose selected for the Phase 3 studies.[21] The dose regimen of 100-mg VX-661 qd/ 150 mg IVA q12h provided clinically meaningful and statistically significant improvements in ppFEV$_1$ in Study 101 with 28 days of treatment in subjects homozygous for the *F508del-CFTR* mutation. In addition, a trend of decreased sweat chloride levels was observed with VX-661/IVA combination therapy at multiple dose levels investigated in Study 101 in subjects heterozygous and homozygous for the *F508del-CFTR* mutation.[21]Finally, in a separate study evaluating IVA monotherapy in patients with the G551D-CFTR mutation, improvements were observed within 1 month in both ppFEV1 and MCC, as well as in gastrointestinal pH as measured by WMC.[24] Based on the timing of these treatment effects in those studies, a 4-week placebo-controlled duration was considered adequate.

8.2.3 Rationale for Study Population

The study population will be subjects with CF who are 18 years of age and older and are homozygous for the *F508del-CFTR* mutation. The *F508del-CFTR* mutation interferes with the processing and trafficking of the CFTR protein, resulting in decreased chloride transport.[18,19] In

Study 101, subjects homozygous for *F508del-CFTR* who were treated with VX-661/IVA combination therapy had statistically significant and clinically meaningful improvements in $ppFEV_1$, supporting the further development of VX-661/IVA combination therapy.[21] The baseline characteristics of the population to be enrolled in this study are anticipated to be similar to the subset of subjects aged 18 years and older in the Phase 3 study (Study VX14-661-106) of VX-661/IVA combination therapy in subjects homozygous for *F508del-CFTR*.

8.2.4 Rationale for Study Assessments

The rationale for all efficacy assessments, including those related to lung function (ppFEV1), MCC, gastrointestinal pH, and sweat chloride, is provided below. Given the complexity and duration required to complete these assessments, clinical visits have been extended over multiple days within the screening and treatment periods. The safety assessments are standard parameters for clinical studies in drug development. The pharmacokinetics (PK) assessment (Section 11.3) is included to assess exposure to study drug.

Spirometry

To study the effect of VX-661/IVA combination therapy on lung function, $ppFEV_1$ will be assessed as a measure of air flow in the lungs. Since lung disease is the major cause of morbidity and mortality for patients with CF, CF lung disease is the desired primary target of VX-661/IVA combination therapy. Spirometry is the most widely implemented standardized assessment to evaluate lung function.

MCC

Mucus clearance is an innate airway defense mechanism for clearing bacteria and viruses, which is dependent on adequate airway surface hydration. It is hypothesized that patients with CF have defects in airway hydration, which in turn slows mucus clearance and promotes airway obstruction and subsequent infection. In a study evaluating IVA monotherapy in patients with the *G551D-CFTR* mutation, improvements were observed in both $ppFEV_1$ and MCC. These results provide evidence for the underlying mechanism of action of IVA monotherapy and the observed clinical benefit in these patients.[24] Therefore, the effect of VX-661/IVA combination therapy on MCC will also be assessed in this study using an imaging technique that enables the tracking of mucus within the airways.

Gastrointestinal pH

In addition to studying effects in the pulmonary system, and given that CFTR transports bicarbonate and chloride, the effect of VX-661/IVA combination therapy on gastrointestinal pH will be assessed. Efficient neutralization of gastric acid in the proximal portion of the small intestine is an important factor in optimal nutrient absorption and digestion. Patients with CF have reduced bicarbonate secretion from the pancreas and gastrointestinal mucosa,[25, 26,27] and a more acidic small intestinal milieu as compared with healthy controls,[28] resulting in increased mucus viscosity, inefficient pancreatic enzyme activity and malnutrition. In a study evaluating IVA monotherapy in patients with the *G551D-CFTR* mutation, IVA treatment results in improvement in the pH of the small bowel, as measured using an ingested capsule device (a WMC).[24] Therefore, the effect of VX-661/IVA combination therapy on bicarbonate secretion will also be assessed in this study using gastrointestinal pH as determined by a WMC.

Sweat Chloride Testing:

The relationship between CFTR modulation and physiological improvement in the lungs and gastrointestinal tract will be explored via assessment of sweat chloride levels. In patients with CF, the underlying ion-transport defect in CFTR results in elevated sweat electrolyte levels.[29,30] The sweat chloride test (quantitative pilocarpine iontophoresis) is the most common diagnostic tool for CF. A sweat chloride concentration of ≥60 mmol/L is considered to indicate CF, whereas <40 mmol/L is considered normal. The sweat chloride test is included in this study as a pharmacodynamic (PD) measure of the effect of VX-661/IVA combination therapy on CFTR chloride transport function.

[redacted]

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.

1. Subject will sign and date an informed consent form (ICF).
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Male and female subjects will be ages 18 years or older on the date of informed consent Homozygous for the *F508del-CFTR* mutation. 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.*

4. Confirmed diagnosis of CF[32] defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis (as documented in the subject's medical record OR from sweat chloride test result obtained during screening, if subject does not have a sweat chloride test result in the medical record).
5. FEV_1 ≥40% and ≤90% of predicted normal for age, sex, and height (equation of Hankinson et al.)[33] during the Day -28 to Day -13 Screening Visit (Section 11.4.1). Spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria[23] for acceptability and repeatability (Section 8.1.1.1).
6. Stable CF disease as judged by the investigator.
7. Willing to remain on a stable CF medication regimen as described in Section 9.4 from screening through the Safety Follow-up Visit.
8. All subjects must agree to undergo a patency capsule test and WMC assessment during screening. Subjects will not be randomized if they have not passed the patency capsule and WMC.

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: ≥3 × upper limit of normal (ULN) aspartate aminotransferase (AST), ≥3 × ULN alanine aminotransferase (ALT), ≥3 × ULN gamma-glutamyl transpeptidase (GGT), ≥3 × ULN alkaline phosphatase (ALP), or ≥2 × ULN total bilirubin
   - Abnormal liver function defined as any increase of ≥5 × ULN AST or ALT
   - Abnormal renal function defined as glomerular filtration rate ≤50 mL/min/1.73 m^2 (calculated by the Modification of Diet in Renal Disease Study Equation)[34,35]

3. 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)
4. A standard 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 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 (Section 11.7.7).
6. History of solid organ or hematological transplantation
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 or prior participation in an investigational drug study as follows:
    - A washout period of 5 terminal half-lives of the previous investigational study drug (i.e., non-CFTR modulators) or **30** days, whichever is longer, must elapse before screening. The duration of the elapsed time may be longer if required by local regulations.
    - Subjects with previous participation in an investigational study of VX-661, lumacaftor, or another CFTR modulator within **90** days of screening or a washout period of 5 terminal half-lives of the previous investigational drug, whichever is longer, are not eligible. Eligibility of subjects enrolled in previous CFTR modulator studies must be confirmed by the medical monitor.
    - Ongoing participation in any observational (noninterventional) study, including 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 and before specific assessments as defined in Section 9.3.
10. Pregnant or nursing females (females of childbearing potential must have negative pregnancy test in the Screening Period and at the Day 1 Visit)
11. Sexually active subjects of reproductive potential who are not willing to follow the contraception requirements outlined in Section 11.7.5.1
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
    - 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. Subjects who have had radiation exposure within 1 year before the first MCC procedure that would cause them to exceed federal regulations by participating in this study (whole body exposure >5 Rem [50 mSv] for adults)
15. In the opinion of the investigator, unable to adequately perform inhalation maneuvers needed for isotope deposition during the MCC procedures
16. Additional exclusion criteria related to administration of WMCs include:

- History of any intraperitoneal abdominal or pelvic surgery (cesarean section, cholecystectomy and appendectomy are permitted if performed >3 months before the patency assessment during screening) or surgery involving the luminal gastrointestinal tract. The Vertex medical monitor should be contacted in case of questions.

  (Note: A percutaneous endoscopic gastrostomy [PEG] tube in the past or present or an extraperitoneal abdominal surgery, such as an inguinal hernia or umbilical hernia repair, are not exclusionary.)
- Clinical or radiographic evidence of bowel obstruction or stricture within the last 12 months
- Prior intestinal resection
- Previous history of bezoars (the presence of retained liquid, bile, or small amounts of poorly organized food residue is permitted)
- Presence or history of extensive intestinal diverticulosis, diverticular stricture, and other intestinal strictures
- History of inflammatory bowel disease, with or without strictures
- Presence or history of fibrosing colonopathy
- Dysphagia to solid food or pills (unable to swallow a 13 mm × 26 mm capsule)
- Use of cardiac medical devices such as pacemakers and defibrillators (gastric stimulators, bladder stimulators, spinal stimulators, medication infusion devices, insulin pumps, and continuous glucose monitors are permitted)

9.3 Study Restrictions

Study restrictions related to the biomarker assessments are summarized in Table 9-1.

Table 9-1 Study Restrictions

Restricted Medication/Food/Activity [a]	Timing of Restriction
MCC	
No hypertonic saline, bronchodilator, or dornase alfa usage	12 hours before MCC procedures
WMC	
Food or drink (water permitted)	8 hours before WMC administration AND for 4 hours immediately after WMC administration with a snack bar
Proton-pump inhibitors[b]	1 week before WMC administration until capsule has passed
Calcium, aluminum, or magnesium antacids[b]	24 hours before WMC administration until capsule has passed
Histamine 2 blockers[b]	48 hours before WMC administration until capsule has passed
Narcotic medications[b]	48 hours before WMC administration until capsule has passed
Chronic laxatives changes	From Screening until the last WMC has passed
Tobacco	8 hours before WMC administration and for 6 hours immediately after WMC administration
Alcohol	24 hours before WMC administration until capsule has passed
Rigorous exercise	From WMC administration until capsule has passed
MRI	No MRI from patency capsule or WMC administration until capsule has passed

MCC: mucociliary clearance; MRI: magnetic resonance imaging; WMC: wireless motility capsule

[a] See Section 9.4 for guidance for concomitant medications.

[b] A nonexhaustive list of medications is included in the Study Reference Manual. For questions, contact the Vertex medical monitor.

9.3.1 Additional Dietary Restrictions/Prohibited Medications

Prohibited medications and certain foods are not allowed in this study (Screening Period through Safety Follow-up Visit) (Table 9-2). Known CYP3A4 inducers and inhibitors are restricted because VX-661 and IVA are metabolized at least in part via the hepatic enzymatic pathway using CYP3A4.

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

Table 9-2 Additional Study Restrictions

	Study Period	
Restricted Medication/Food	**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, lumacaftor)	None allowed during Screening Period	None allowed through the Safety Follow-up Visit

CYP: cytochrome P450; IVA: ivacaftor.
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 at least 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 at least 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. 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 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 of up to 10 mg/day (chronically) or prednisone 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 and MCC assessments performed according to the guidelines provided in Section 11.4.1. and Section 11.4.2.
- Concomitant use of medications known to prolong the QT interval should be used with caution during the study, as the effect of VX-661/IVA combination therapy on the QT interval has not been evaluated in a thorough QT study. Consideration should be given to

obtaining an ECG when concomitant medication known to prolong the QT interval is administered.

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 has been withdrawn from study drug treatment, the subject should continue to be followed, provided the subject has not withdrawn consent. Subjects will be continued to be followed for safety for 28 days ± 7 days after the last dose of study drug (see Table 3-2).

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a Safety Follow-up Visit, if applicable (Section 8.1.4), 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.

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

Subjects must return all unused study drug.

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 11.7.8.
- A subject has an increase in QTc according to evaluations and management described in Section 11.7.4.1.
- A subject develops a cataract or lens opacity.

Subjects who discontinue study treatment early should complete the assessments of the ETT and/or Safety Follow-up Visit, as noted in Section 8.1.4.

Subjects who are randomized and whose screening *CFTR* genotype results do not confirm study eligibility must be discontinued from study drug treatment, will undergo ETT and/or Safety Follow-up Visits per Section 8.1.3 and Section 8.1.4, and will then 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 Treatment Period may be replaced in order to have approximately 35 subjects completing the study.

10 STUDY DRUG ADMINISTRATION AND MANAGEMENT

Study drug refers to VX-661/IVA, IVA, and their matching placebos.

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 during the Treatment Period as shown in 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/IVA	AM	100-mg VX-661 / 150-mg IVA FDC tablet, oral
	PM	150-mg IVA tablet, oral
Placebo	AM	VX-661/IVA-matching placebo FDC tablet, oral
	PM	IVA-matching placebo tablet, oral

AM: morning; FDC: fixed dose combination; IVA: ivacaftor; PM: evening.

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

1. 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 (± 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 WMC administration, subjects will fast overnight and will ingest a snack bar provided at the site in place of the morning high-fat meal immediately before ingesting the WMC. Subjects will fast for 4 hours after the capsule is taken and snack bar is consumed.

4. At the Day 1 Visit, all subjects will be observed for 6 hours after the morning dose of the study drug.
5. The date, amount taken, and time of study drug administration, including whether food was taken with each dose, will be recorded for 2 days before PK sample collection and on the days of PK sample collection.
6. 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.
7. 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 their morning dose of study drug and the morning dose will be administered in the clinic.
    - If the dose in the clinic will be more than 6 hours after the subject's scheduled morning dose, the subject should take the morning dose at home and the evening dose will be administered in the clinic. In this event, all assessments will be collected relative to the evening dose.
8. For visits after the Day 1 Visit, subjects will be instructed to bring all used and unused study drug to the site.

10.3 Method of Assigning Subjects to Treatment Groups

A target of approximately 35 subjects, with up to approximately 45, who meet the eligibility criteria will be randomized in a ratio of 4:1 (active study drug:placebo). An interactive web response system (IWRS) will be used to assign subjects to treatment. Detailed instructions for randomization will be provided separately.

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

10.5 Dose Modification for Toxicity

The dosage of VX-661 or ivacaftor cannot be altered, but the investigator can stop treatment (Section 9.5).

10.6 Packaging and Labeling

Vertex will supply the 100-mg VX-661 / 150-mg IVA FDC tablets, VX661/IVA-matching placebo FDC tablets, 150-mg IVA tablets, and IVA-matching placebo tablets. Study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing for the study drugs will be included in the Pharmacy Manual.

10.7 Study Drug Supply, Storage, and Handling

The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for as detailed in Section 10.8 or via the drug accountability forms as instructed by Vertex.

Table 10-2 Identity of Study Drugs, Dosage, and Storage

Drug Name	Strength/Formulation/Route	Dosage	Storage Condition
VX-661/IVA FDC tablet	100 mg/150 mg tablet; oral	100 mg/150 mg, 1 tablet morning dose	≤25°C (77°F) with excursions to 30°C (86°F)
IVA	150 mg tablet, oral	150 mg, 1 tablet evening dose	≤25°C (77°F) with excursions to 30°C (86°F)
VX-661/IVA FDC-matching placebo	0 mg/0 mg tablet; oral	0 mg/0 mg, 1 tablet morning dose	≤25°C (77°F) with excursions to 30°C (86°F)
IVA-matching placebo	0 mg tablet, oral	0 mg, 1 tablet evening dose	≤25°C (77°F) with excursions to 30°C (86°F)

FDC: fixed dose combination; IVA: ivacaftor

10.8 Drug Accountability

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

10.9 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.

10.10 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.

10.11 Blinding and Unblinding

This is a double-blind study.

10.11.1 Blinding

Blinding of treatment codes and applicable study data will be maintained until the database is locked for the final analysis.

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
- Vendor analyzing PK samples
- Vertex medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time

Vertex Drug Metabolism and Pharmacokinetics laboratory personnel will not be involved in the conduct of the study and will be unblinded to the bioanalysis results but will remain blinded to subject number and treatment assignment.

Spirometry Data Blinding

Despite treatment blinding, knowledge of the spirometry 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 spirometry results data. The vendor for central reading of the spirometry data will only send the blinded spirometry files (blinded treatment group, with real values for screening and baseline, but with dummy values for all the spirometry results data 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 spirometry results during the Treatment Period regardless of whether the subject has prematurely discontinued treatment.

Sweat Chloride Data Blinding

Despite treatment blinding, knowledge of the sweat chloride data 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 not have access to the sweat chloride data; dummy data will be used to develop statistical programs. During the process of locking the clinical database, after all study visits have been completed, access to treatment-blinded sweat chloride data will be provided to a small group of individuals who are not part of the Vertex study team. This group, which will consist of a biostatistician, a statistical programmer, a validation statistical programmer, and a clinical reviewer, will review the sweat chloride data to ensure there are no significant data issues and will use the blinded data set to refine the statistical programs.

MCC Blinding

Despite treatment blinding, knowledge of the MCC data 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 MCC data. Results data will be submitted to a central reader. These individuals, including site staff performing the MCC assessment, will otherwise not be involved in any other aspects of study conduct or subject interaction.

WMC Blinding

Despite treatment blinding, knowledge of the WMC data 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 WMC data, except confirmation that the WMC has passed. Results data will be submitted to the central reader, who will otherwise not be involved in any other aspects of study conduct or subject interaction.

10.11.2 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.

In addition, the Vertex Medical Information Call Center (MICC) [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. Contact information for the Vertex medical monitor and MICC will be provided in the Study Reference Manual.

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 Vertex, the 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.

All ECGs will be performed before vital signs, pulse oximetry, and any other procedures that may affect heart rate (e.g., blood sampling). On visits when urine pregnancy tests are performed, the urine pregnancy test will be completed before the WMC administration, MCC assessment, and the first dose of study drug. If WMC administration and MCC assessment occur on the same day, spirometry should be performed before both. [redacted] (See Section 8.1.1).

All assessments will be performed predose with the following exceptions:

- On Day 28, MCC will be performed after the morning dose of study drug.
- On Day 29, the WMC will be administered with the morning dose of study drug and the snack bar in place of a meal.

11.2 Subject and Disease Characteristics

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

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 body systems, past medical and surgical histories, and any allergies.

11.3 Pharmacokinetics

11.3.1 Blood Sampling

Blood samples will be collected as shown in Table 3-2.

At each of the visits and time points indicated in Table 3-2, single blood samples will be collected for the determination of the concentrations of VX-661, M1-661, IVA, and M1-IVA. Blood samples collected before dosing on Days 28 and 29 must be collected within 60 minutes before dosing.

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

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

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

11.3.2 Processing and Handling of Pharmacokinetic Samples

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

11.3.3 Bioanalysis

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

If appropriate, these samples may also be used for evaluations of metabolites of VX-661 and IVA during treatment. These samples may also be used for further evaluation of the bioanalytical method and for analyses that provide information on the metabolic pathways used or impacted by VX-661 and IVA. These data will be used for exploratory purposes and may not be included in the clinical study report.

11.4 Key Efficacy Assessments

11.4.1 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines[23] at the time points noted in Table 3-1 and Table 3-2 according to the additional guidelines that follow.

Prebronchodilator spirometry is defined as spirometry testing performed for subjects who have:

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

During the Screening Visit, spirometry assessments may be performed pre- or postbronchodilators. At all other visits (including the Clinic Visit on Day -23 to Day -10), all spirometry assessments should be performed prebronchodilator. During the Treatment Period, spirometry assessments must be performed before administration of study drug.

In the event that a subject forgets to withhold bronchodilator(s), spirometry should be performed according to the following:

- If a subject's Clinic Visit Day -23 to -10 spirometry is prebronchodilator, but, on a subsequent visit, the subject forgets to withhold bronchodilator use, a postbronchodilator spirometry will be obtained for that visit only, and the visit will not be rescheduled.
- If, on Clinic Visit Day -23 to -10, the subject forgets to withhold his/her dose of bronchodilator, then spirometry and MCC should be performed post-bronchodilator, and all subsequent spirometric measurements (according to the schedule of assessments detailed in Table 3-2), and the MCC assessment at Day 28, should be performed post-bronchodilator.
- Each spirometry assessment will be recorded in the source documents as prebronchodilator or postbronchodilator.

If more than 1 spirometry assessment is required at a visit, bronchodilators will be withheld until completion of the last scheduled spirometry assessment is completed.

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

Subjects should not be informed of their study-related spirometry results during the Treatment Period.

The following parameters will be determined as part of the spirometry assessment:

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

11.4.2 Mucociliary Clearance

MCC will be assessed as indicated in Table 3-1 and Table 3-2.

All bronchodilators usage is restricted for 12 hours before the MCC assessments at the Day -23 to Day -10 Visit and the Day 28 Visit.

On Day 28, MCC will occur after the dose of study drug. MCC assessments will be performed according to an SOP in the Study Manual.

Subjects with less than 30 percent predicted FEV_1 on day of MCC, or with acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 14 days before scheduled MCC procedures, should not have the assessment performed.

Sites that perform MCC assessments will be expected to procure the MCC equipment as described in the SOP. During the MCC assessment, a series of images will be collected immediately following inhalation of a radiolabeled aerosol and again approximately 6 hours later. Specific instructions for the conduct of MCC testing and submission of results to the central reading center are provided in the Study Reference Manual.

Subjects will not be informed of their MCC results.

11.4.3 Gastrointestinal pH

Gastrointestinal pH will be assessed as indicated in Table 3-1 and Table 3-2 using a WMC device. Before the WMC can be administered, all subjects must be evaluated using a patency capsule at the Day -28 to Day -13 Visit.

The patency capsule will be administered between Day -28 and Day -13. A telephone contact will occur 2 days after administration of the patency capsule to confirm the passage of the capsule in the stool (unless the subject confirms passage of the capsule prior to the scheduled telephone contact). If passage of the patency capsule is not confirmed by the telephone contact, the subject must return to the clinic and the medical monitor must be contacted immediately. Subjects who are unable to successfully pass the patency capsule test will not be randomized (See Study Reference Manual for additional information).

The WMC will be administered at the Day -23 to Day -10 (after a successful patency capsule test) and the Day 29 Visits. On Day 29, the WMC will be administered with the morning dose of study drug and the snack bar in place of a meal. During the WMC assessments, subjects will wear a receiver either on their belt or around their neck from the moment the WMC is administered until the receiver indicates the WMC passage, or until telephone contact within 5 days after the WMC administration. If passage of the WMC is not confirmed, the medical monitor must be contacted immediately to confirm further course of action. Final confirmation of passage will be obtained by the central reader following review of the data. If the WMC data review is inconclusive, an X-ray will be required to confirm the WMC passage, regardless of confirmation of passage by the subject at the telephone contact.

Specific instructions for the conduct of WMC testing and submission of results to the central reader are provided in the Study Reference Manual.

11.4.4 Sweat Chloride

The sweat chloride test is a standard diagnostic tool for CF, serving as a biomarker of CFTR activity. Sweat chloride will be assessed through review of the medical history during the Screening Visit (Table 3-1) and the test will be performed at visits specified in Table 3-2, using an approved collection device. Sweat samples will be sent to a central laboratory for testing and interpretation of results. Individual sweat chloride test results will not be disclosed to the study sites. Specific instructions for collection, handling, processing, and shipping of sweat chloride samples to the central laboratory will be provided in the Laboratory Manual.

The sweat chloride collection before the morning dose on Day 29 should occur within 60 minutes before the PK sample collection and before the morning dose of the study drugs. Collection of sweat chloride will not overlap with any other study assessments.

[redacted]

[redacted]

11.7 Safety

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

11.7.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with ICH GCP guidelines. Section 13.1 outlines the definitions, collection periods, criteria, and procedures for

documenting, grading, and reporting AEs. A separate document that details AE case report form (CRF) completion guidelines for investigators as well as training will be provided.

11.7.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory. Blood samples requiring a 4-hour fast will be collected predose on Day 1 and Day 29, and at the ETT and Safety Follow-Up Visit. Fasting is not required at other time points unless specified in Table 3-1 and Table 3-2.

Blood and urine samples for clinical laboratory assessments will be collected as shown in Table 3-1 and Table 3-2. 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 International Normalized Ratio	
Creatine kinase		
Amylase		
Lipase		
Vitamin Levels		
Vitamins A, D, E, K, and B12		
Lipid Panel		
Total cholesterol, triglycerides		
Low-density lipoprotein (LDL)		
High-density lipoprotein (HDL)		

Note: Day 1, Day 29, ETT, and Safety Follow-up blood draws will be done after a minimum 4-hour fast. All other blood draws do not require fasting.

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

Additional tests at screening: The following additional tests will be performed during screening to assess eligibility:

Clinical laboratory assessments from screening will have no clinically significant findings that preclude participation in the study, as judged by the investigator, for a subject to receive study drug on Day 1.

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 tests will be performed at the site as specified in Table 3-1 and Table 3-2.

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): *CFTR* genotyping will be performed on all subjects to confirm the genotype documented in the subject's medical record (if available). Refer to the Laboratory Manual for details.

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.

11.7.3 Physical Examinations and Vital Signs

A physical examination (PE) of all body systems and vital signs assessment will be performed at visits noted in Table 3-1 and Table 3-2. At other visits, symptom-directed PEs and symptom-directed vital sign assessments can be performed at the discretion of the investigator or healthcare provider.

A PE includes a review of the following systems: head/neck/thyroid; eyes/ears/nose/throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. After screening, any clinically significant abnormal findings in PEs will be reported as AEs.

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

11.7.4 Electrocardiograms

11.7.4.1 Standard 12-Lead 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). A window of approximately ± 15 minutes will be allowed around the nominal times for all ECG assessments. 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 and Safety Follow-up Visits. A printout of the ECG traces will be made for safety review by the investigator and maintained with source documentation. Clinically significant ECG abnormalities occurring during the study through the Safety Follow-up Visit will be recorded as AEs.

To ensure safety of the subjects, a qualified individual at the study site will make comparisons to baseline measurements. If the QTcF is increased by >45 msec from the baseline or an absolute QTcF value is ≥500 msec for any scheduled ECG, 2 additional ECGs will be performed approximately 2 to 4 minutes apart to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (>45 msec from baseline or ≥500 msec), a single ECG will be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If the QTc 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 QTc, 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.

11.7.5 Contraception and Pregnancy

11.7.5.1 Contraception

The effects of VX-661 monotherapy or in combination with IVA on conception, pregnancy, and lactation in humans are not known. Neither VX-661 nor IVA 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 IVA were each found to be nonteratogenic in reproductive toxicology studies in rats and rabbits.[21,22] Subjects should follow the contraception requirements outlined in this study protocol. The effects of VX-661 monotherapy or in combination with IVA on the 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/IVA combination therapy, 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 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, postovulation methods) and withdrawal are not acceptable methods of contraception.
- The male subject 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
- 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 (non-hormone-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 <u>not</u> 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.

11.7.5.2 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 study drug(s).

If a female subject or the female partner of a male subject becomes pregnant while participating in the study, study drug will 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 11.7.5.1). 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 active 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.

11.7.6 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 study drug dosing. At visits when study drug is taken at the site, pulse oximetry will be collected before the morning dose. This is a noninvasive measure of oxygen delivery to the tissues and has been correlated with clinical status and lung function.

11.7.7 Ophthalmologic Examination

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)
- 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.

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).

Additional ophthalmologic examinations may be conducted at the discretion of the investigator. The medical monitor should be notified of any additional ophthalmologic examinations.

In addition, 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

11.7.8 Liver Function Test Parameters

Liver function testing (ALT, AST, GGT, ALP, and total bilirubin) must be performed as noted in Table 3-2. These blood samples should be processed and shipped immediately per the Laboratory Manual.

Subjects with new treatment-emergent ALT or AST elevations of >3 × ULN and clinical symptoms must be followed closely, including repeat confirmatory testing performed by the central laboratory within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT and AST levels, as clinically indicated. In addition, if ALT or AST is >5 × ULN, 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 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 × ULN
- ALT or AST >5 × ULN for more than 2 weeks
- ALT or AST >3 × ULN, in association with total bilirubin >2 × ULN and/or clinical jaundice

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

If no convincing alternative etiology (e.g., acetaminophen use, viral hepatitis, or alcohol ingestion) for the confirmed elevated transaminases is identified, regardless of whether ALT or AST levels have improved, study drug treatment must be permanently discontinued if repeat testing within 48 to 72 hours confirms the initial elevation. Subjects in whom treatment is discontinued for elevated transaminases should have their transaminases monitored closely until levels normalize or return to baseline.

Resumption of Study Drug

If an alternative, reversible cause of transaminase elevation has been identified, study drug may be resumed once transaminases return to baseline or are ≤2 × ULN, whichever is higher. Approval of the medical monitor is required before resumption of study drug. Upon resumption of study drug, transaminases should be assessed weekly while the subject remains on study drug and during the followup. If a protocol-defined transaminase elevation occurs within 4 weeks of

rechallenge with the study drug, then the study drug must be permanently discontinued, regardless of the presumed etiology.

12 STATISTICAL AND ANALYTICAL PLANS

This study is planned as an exploratory study. No type I error control for hypothesis testing will be applied, and each of the key endpoints will be assessed individually using a significance level α of 0.05.

Analysis of all data will be performed by Vertex or its designee(s). Before the database is locked for analysis, a detailed plan for the analysis of efficacy and safety data will be presented in a statistical analysis plan (SAP), and a detailed plan for PK analysis will be presented in a clinical pharmacology analysis plan (CPAP).

12.1 Sample Size and Power

A target of approximately 35 subjects, with up to approximately 45, who meet the eligibility criteria will be randomized in a ratio of 4:1 to active study drug or placebo to maximize power across the endpoints.

The objective of the study is to evaluate the clinical mechanisms of VX-661/IVA combination therapy in both lung function and extrapulmonary systems in subjects with CF who are homozygous for the *F508del* mutation on the *CFTR* gene. For a subset of the key endpoints (specifically, MCC and gastrointestinal pH, as captured in Table 12-2 and Table 12-3), no data are available for the *F508del* homozygous population. Therefore, data for both gastrointestinal pH and MCC were compiled from a study evaluating IVA monotherapy in patients with the *G551D-CFTR* mutation for the purpose of sample size calculation.[24] Mean changes from baseline for gastrointestinal pH and MCC endpoints in the combination group were derived assuming approximately 50% of those observed for the active group in the observational study. Standard deviations were assumed to be similar to those observed in the reference studies. For $ppFEV_1$ and sweat chloride endpoints, sample size assumptions were based on observed data from the VX11-661-101 study.[23]

Based on these assumptions, a sample size of 36 subjects in the combination group (based on 45 subjects randomized 4:1) will provide adequate power to detect a statistically significant difference from baseline at Day 28 or 29 for the key endpoints, even after assuming that 10 to 30% subjects may not have complete data through Day 29 (depending on the endpoint).

Table 12-1 through Table 12-4 display power estimates to detect an expected mean change from baseline (Δ) for key endpoint measures in the VX-661/IVA combination therapy based on a sample size of 36 subjects in the VX-661/IVA group using a 2-sided paired *t*-test at a significance level of $\alpha = 0.05$. More specifically, the endpoint measures include $ppFEV_1$ at Day 28 (Table 12-1), percent whole lung mucus clearance through 60 minutes at Day 28 (Table 12-2), small bowel area under the curve (AUC) over 1-minute mean pH increments through 30 minutes after gastric emptying at Day 29 (Table 12-3), and sweat chloride at Day 29 (Table 12-4). Further, a sample size of 28 subjects in the VX661/IVA group (resulting in a total of 35 subjects including 7 subjects in the placebo group) will provide at least 80% power to detect the expected mean change from baseline with the expected standard deviation. Sample size calculations were performed using PASS 11 software, Version 11.0.2. Given the exploratory

nature of this study, no multiplicity adjustment of type I error will be conducted for the analysis of key endpoints.

Table 12-1 Power for Within-Group Comparison (100 mg VX-661 qd + 150 mg IVA q12h) for ppFEV$_1$ With N = 36 and Δ = 4.5%

Standard deviation	σ = 7% (expected)	σ = 8%	σ = 9%	σ = 10%
Power	96%	91%	83%	75%
Power (10% missing data)	95%	88%	80%	71%
N for 80% power	21	27	34	41

ppFEV1: percent predicted forced expiratory volume in 1 second; IVA: ivacaftor

Table 12-2 Power for Within-Group Comparison (100 mg VX-661 qd + 150 mg IVA q12h) for Average % Whole Lung Clearance Through 60 Minutes With N = 36 and Δ = 6%

Standard deviation	σ = 6%	σ = 8% (expected)	σ = 10%	σ = 12%
Power	>99%	99%	94%	83%
Power (20% missing data)	>99%	97%	88%	74%
N for 80% power	10	16	24	34

ppFEV1: percent predicted forced expiratory volume in 1 second; IVA: ivacaftor

Table 12-3 Power for Within-Group Comparison (100 mg VX-661 qd + 150 mg IVA q12h) for Small Bowel AUC Over 1-minute Mean pH Increments Through 30 Minutes After Gastric Emptying With N = 36 and Δ = 22 pH Minutes (or Equivalently, 0.73 pH)

Standard deviation (pH mins)	σ = 20	σ = 24 (expected)	σ = 28	σ = 32
Power	>99%	>99%	>99%	98%
Power (30% missing data)	>99%	>99%	97%	92%
N for 80% power	9	12	15	19

ppFEV1: percent predicted forced expiratory volume in 1 second; IVA: ivacaftor

Table 12-4 Power for Within-Group Comparison (100 mg VX-661 qd + 150 mg IVA q12h) for Sweat Chloride With N = 36 and Δ = -5 mmol/L

Standard deviation (mmol/L)	σ = 5	σ = 6	σ = 7 (expected)	σ = 8
Power	>99%	>99%	99%	95%
Power (10% missing data)	>99%	>99%	98%	94%
N for 80% power	10	14	18	23

ppFEV1: percent predicted forced expiratory volume in 1 second; IVA: ivacaftor

12.2 Analysis Sets

The **All Subjects Set** will include all subjects who were randomized or received at least 1 dose of study drug. This analysis set will be used for all individual subject data listings and the disposition summary table, unless otherwise specified.

The **Full Analysis Set (FAS)** will include all randomized subjects who were *F508del* homozygous and received at least 1 dose of study drug. The FAS will be used for all efficacy analyses.

The **Safety Set** will include all subjects who received at least 1 dose of study drug. The Safety Set will be used for all safety analyses.

12.3 Statistical Analysis

This section presents a summary of the planned statistical analyses of efficacy and safety. Analysis details will be provided in the SAP.

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). The precision of the measurement for each continuous variable will be specified in the SAP. Unless otherwise specified, minimum and maximum values will be reported with the same precision as the units of the raw data. The mean and median will be reported to 1 additional decimal place, and the SD and SE will be reported to 2 additional decimal places. Any values that require a transformation to standard units (metric or International System [SI]) will be converted with the appropriate precision.

Categorical variables will be summarized using counts and percentages. Percentages will be presented to 1 decimal place.

Baseline value, unless otherwise specified, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug. For ECG, the baseline will be defined as the average of the most recent triplicate pretreatment measurements before the first dose of study drug.

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

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

The 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 did not complete the Safety Follow-up Visit.

Rules for handling missing data will be described in the SAP.

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

The number and percentage of subjects in each disposition category (e.g., randomized, dosed, included in the FAS, included in the Safety Set, completed Treatment Period, completed study/Safety Follow-up Visit, and discontinued treatment or study with a breakdown of the reasons for discontinuation for treatment or study, respectively) will be summarized overall and by treatment group.

12.3.2.2 Demographics and Baseline Characteristics

Demographic, background (e.g., medical history), and baseline characteristics will be summarized using descriptive summary statistics. Protocol deviations/violations will be provided in an individual subject data listings.

The following demographics and baseline characteristics will be summarized overall and by treatment group for the FAS and will include (but are not limited to): sex, race, age, baseline weight, baseline height, baseline body mass index (BMI), baseline ppFEV$_1$, baseline whole lung mucus clearance through 60 minutes, and baseline small bowel AUC over 1-minute mean pH increments through 30 minutes after gastric emptying.

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

12.3.2.3 Prior and Concomitant Medications

Medications used in this study will be coded 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 during the TE period
- Post-treatment medication: medication continued or newly received after the TE period

A given medication may 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 partially missing start/end date or time and if it cannot be determined whether it was taken before the first dose of study drug, concomitantly during the TE period, or after the TE period, it will be considered in all 3 categories of prior, concomitant, and post-treatment medication.

Prior medications and concomitant medications will be summarized descriptively based on the FAS. Post-treatment medications will be provided separately in an individual subject data listing.

12.3.2.4 Study Drug Exposure and Compliance

Exposure to study drug 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 will be derived as 100 × [(total number of pills dispensed) – (total number of pills returned)]/(total number of pills planned to be taken per day × duration of study drug exposure in days).

12.4 Efficacy Analysis

12.4.1 Analysis of Key Efficacy Variables

The variables for key efficacy endpoints are:

- Absolute change in $ppFEV_1$ from baseline at Day 28,
- Absolute change in average percent whole lung clearance through 60 minutes from baseline at Day 28,
- Absolute change in small bowel AUC over 1-minute mean pH increments through 30 minutes after gastric emptying from baseline at Day 29,
- Absolute change in sweat chloride from baseline at Day 29, and

The analysis for each of these endpoints will be performed for the VX-661/IVA combination group based on a 2-sided paired-*t* test performed at $\alpha = 0.05$ to test a null hypothesis of a zero mean change from baseline, using the Day 28 or Day 29 changes from baseline. The results from these analyses will include the observed mean change from baseline, a 95% CI, and a 2-sided *P* value. A sensitivity analysis based on the Wilcoxon signed rank test will be described in the SAP.

A descriptive analysis that includes the observed mean change from baseline at Day 28 or Day 29 and 95% CI will also be presented for the placebo group.

Further, a descriptive analysis of observed values and change from baseline values at each scheduled time point will be presented by treatment group.

[redacted]

[redacted]

12.4.3 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 based on the following safety and tolerability endpoints:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (i.e., hematology, serum chemistry, vitamin levels, lipid panel, coagulation, and urinalysis)
- ECGs
- Vital signs
- Pulse oximetry

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

12.4.3.1 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 the first dose of study drug
- TEAE: any AE that increased in severity or that was newly developed at or after the first dose of study drug through the end of the 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 drug treatment, then the AEs will be classified as TEAEs.

AE summary tables will be presented for TEAEs only, overall and by treatment group, and will include the following:

- All TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- Serious TEAEs
- TEAEs leading to death
- Frequently reported TEAEs

Summaries will be presented by MedDRA system organ class and preferred term using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once, only the maximum severity level will be presented in the severity summaries, and the strongest relationship level in the relationship summaries. In addition, a listing containing individual subject level 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.

12.4.3.2 Clinical Laboratory Assessments

For the treatment-emergent laboratory measurements, the observed values and change from baseline values of the continuous hematology and chemistry results will be summarized in SI units overall and by treatment group at each scheduled time point.

The number and percentage of subjects with at least 1 potentially clinically significant (PCS) event during the TE period will be summarized overall and 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 hematology, chemistry, and coagulation values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

12.4.3.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided overall and by treatment group at each scheduled time point for the following ECG measurements: RR, PR, QT, and QT corrected for HR intervals (QTcF), QRS duration, and HR.

The number and percentage of subjects with at least 1 PCS event during the TE period will be summarized overall and by treatment group. The PCS (postbaseline) shift from baseline will also be summarized. The PCS criteria will be provided in the SAP.

Additional ECG analyses will be described in the SAP.

12.4.3.4 Vital Signs

For the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized overall and by treatment group at each scheduled time point.

The following vital signs parameters will be summarized: systolic and diastolic blood pressure (mm Hg), body temperature (°C), HR (beats per minute), and respiratory rate (breaths per minute).

The number and percentage of subjects with at least 1 PCS event during the TE period will be summarized overall and by treatment group. The PCS (postbaseline) shift from baseline will also be summarized. The PCS criteria will be provided in the SAP.

Additional vital sign analyses will be described in the SAP.

12.4.3.5 Pulse Oximetry

For the treatment-emergent pulse oximetry measurements, a summary of observed values and change from baseline values will be provided overall and by treatment group at each scheduled time point for the percent of oxygen saturation by pulse oximetry.

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 summarized overall and by treatment group.

12.4.3.6 Physical Examination

PE findings will be presented in an individual subject data listing only.

12.4.3.7 Other Safety Analysis

Not applicable.

12.4.4 Interim and IDMC Analyses

Not applicable.

12.5 Clinical Pharmacology Analysis

12.5.1 Pharmacokinetic Analysis

A detailed description of the clinical pharmacology analyses will be provided in a CPAP. Listings of plasma concentration data of VX-661, IVA, and their metabolites (M1-661 and M1-IVA) will be provided in the clinical study report. A population approach may be used to analyze the time-versus-plasma concentration data of VX-661, IVA, and their metabolites. The PK/PD relationship between concentrations of VX-661 and IVA and (their metabolites as appropriate) and efficacy and safety measurements may be investigated. The results of the PK and PK/PD analyses using a population approach will be presented in a separate report.

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 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 the 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: through the Safety Follow-up Visit

All subjects will be queried, using non-leading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms will be identified as 1 overall event or diagnosis. All AEs for enrolled subjects will be recorded in the electronic CRF (eCRF) 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 “non-serious”
- 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
- Indication of dose limiting toxicity

13.1.1.4 Adverse Event Severity

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

AE: adverse event.

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).

AE: adverse event.

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.

AE: adverse event.

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)

AE: adverse event.

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 should 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) should not be considered to indicate an SAE.

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

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

13.1.2.3 Reporting Serious Adverse Events

The investigator is responsible for notifying the sponsor within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational study drug. The Vertex Clinical Trial SAE Form will be completed for new/initial events as well as to report follow-up

information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via
Email: [redacted] (preferred choice)
Or via fax: [redacted]
Contact telephone: [redacted]

13.1.2.4 Expedited Reporting and Investigator Safety Letters

Vertex, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities and participating investigators in accordance with ICH guidelines and/or local regulatory requirements, as applicable.

It is the responsibility of the investigator or designee to promptly notify the local institutional review board (IRB) 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 IRBwill 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 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 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), before study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

13.2.3 Investigator Compliance

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

When circumstances require an immediate departure from procedures set forth in the protocol, the investigator will contact Vertex to discuss the planned course of action. If possible, contact

will be made before the implementation of any changes. Any departures from protocol will be fully documented in the source documentation and in a protocol deviation log.

13.2.4 Access to Records

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

13.2.5 Subject Privacy

To maintain subject confidentiality, all eCRFs, study reports, and communications relating to the study will identify subjects by assigned subject numbers. As required by federal regulations, the investigator will allow Vertex and/or its representatives access to all pertinent medical records to allow for the verification of data gathered in the eCRFs/SAE Forms and the review of the data collection process. The FDA (or other regulatory authority) may also request access to all study records, including source documentation, for inspection.

As applicable, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated privacy regulations, a subject authorization to use personally identifiable health information may be required from each subject before research activities begin. This authorization document will clearly specify which parties will have access to a subject's personal health information, for what purpose, 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 may terminate the study at their center.

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

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

- Decision by the FDA or other regulatory authority

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

13.3 Data Quality Assurance

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

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

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

13.4 Monitoring

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

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

13.5 Electronic Data Capture

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

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

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

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

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

[redacted]

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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX14-661-111	Version #: 4.0	Version Date 19 Sep 2016
Study Title: A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Exploratory Study to Evaluate Effects of VX-661 in Combination With Ivacaftor on Lung and Extrapulmonary Systems in Subjects Aged 18 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation		

This clinical study protocol has been reviewed and approved by the sponsor.

[redacted]

CF Medical Director

[redacted]

15.2 Investigator Signature Page

Protocol #: VX14-661-111	Version #: 4.0	Version Date 19 Sep 2016
Study Title: A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Exploratory Study to Evaluate Effects of VX-661 in Combination With Ivacaftor on Lung and Extrapulmonary Systems in Subjects Aged 18 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation		

I have read Protocol VX14-661-111, Version 4.0 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 (Vertex) is confidential.

Printed Name

Signature Date