1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3, Randomized, Double-Blind, Ivacaftor-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Heterozygous for the *F508del-CFTR* Mutation and a Second *CFTR* Allele With a Gating Defect That Is Clinically Demonstrated to be Ivacaftor Responsive

Vertex Study Number: VX14-661-109

[redacted]

EudraCT Number: 2014-004838-25

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2 PROTOCOL SYNOPSIS

Title

A Phase 3, Randomized, Double-Blind, Ivacaftor-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Heterozygous for the *F508del-CFTR* Mutation and a Second *CFTR* Allele With a Gating Defect That Is Clinically Demonstrated to be Ivacaftor Responsive

Clinical Phase and Clinical Study Type

3, efficacy and safety

Objectives

Primary

To evaluate the efficacy of VX-661 in combination with ivacaftor in subjects with cystic fibrosis (CF) who are heterozygous for the *F508del* mutation on the *CF transmembrane conductance regulator* (*CFTR*) gene and a second *CFTR* allele with a gating defect that is clinically demonstrated to be ivacaftor responsive.

Secondary

- To evaluate the safety of VX-661 in combination with ivacaftor
- To investigate the pharmacokinetics (PK) of VX-661 and its metabolite M1 (M1-661), and ivacaftor and its metabolite M1 (M1-ivacaftor)

Endpoints

Primary

Absolute change in percent predicted forced expiratory volume in 1 second (FEV_1) from baseline through Week 8 in the Active Comparator Treatment Period.

Key Secondary

- Relative change in percent predicted FEV_1 from baseline through Week 8 in the Active Comparator Treatment Period
- Absolute change in Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain score from baseline through Week 8 in the Active Comparator Treatment Period

Secondary

- Absolute change in sweat chloride from baseline through Week 8 in the Active Comparator Treatment Period
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values (hematology, serum chemistry, lipid panel, vitamin levels, coagulation studies, and urinalysis), standard digital electrocardiograms (ECGs), vital signs, pulse oximetry, and spirometry
- PK parameters of VX-661, M1-661, ivacaftor, and M1-ivacaftor

[redacted]

Number of Subjects

Approximately 160 subjects will be randomized (1:1) to the VX-661/ivacaftor combination therapy arm or ivacaftor monotherapy arm. Of the randomized subjects, approximately 15% will carry an *R117H* mutation on the second *CFTR* allele.

Study Population

Male and female subjects aged 12 years or older with CF who are heterozygous for the *F508del-CFTR* mutation and a second *CFTR* allele with a gating defect that is clinically demonstrated to be ivacaftor responsive

Investigational Drug

Active substances: VX-661 and ivacaftor

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

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

Active substance: ivacaftor

Activity: CF transmembrane potentiator (increased Cl^- secretion)

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

Active substance: not applicable

Activity: placebo

Strength and Route of Administration: 0-mg film-coated placebo tablets for oral administration visually matching the 100-mg VX-661/150-mg ivacaftor fixed-dose combination tablet and the 150-mg ivacaftor tablet.

Study Duration

Excluding the Screening Period (approximately 28 days in duration) and Ivacaftor Run-in Period (approximately 4 weeks in duration), subjects who complete the Active Comparator Treatment Period (including those who prematurely discontinue study treatment) will participate in this study for up to 13 weeks.

During the Active Comparator Treatment Period, study drug (VX-661/ivacaftor or ivacaftor only) will be administered up to 8 weeks.

A Safety Follow-up Visit will occur 28 days ± 7 days after the final dose of study drug. A Safety Follow-Up Visit is not required for subjects who have completed the Week 8 Visit and have enrolled in the extension study of VX-661 in combination with ivacaftor within 28 days after the last dose of study drug.

Study Design

This is a Phase 3, randomized, double-blind, ivacaftor-controlled, parallel-group, multicenter study in subjects aged 12 years and older with CF who are heterozygous for the *F508del-CFTR* mutation and a second *CFTR* allele with a gating defect that is clinically demonstrated to be ivacaftor responsive.

This study includes the following:

- Screening Period (Week -8 to Week -4)
- Ivacaftor Run-in Period where all subjects will receive ivacaftor (Week -4 to Day -1)
- Active Comparator Treatment Period (Day 1 through Week 8 ± 5 days)
- Safety Follow-up Visit (28 days ± 7 days after the final dose of study drug)

Subjects will be stratified by age at the Screening Visit (<18 versus ≥18 years of age), type of mutation on the second *CFTR* allele (*R117H* versus other allowed mutations), and percent predicted FEV_1 severity determined at the end of the Ivacaftor Run-in Period (<70 versus ≥70) and then randomized (1:1) to 1 of the following 2 treatment arms:

VX-661/ivacaftor combination therapy

- Morning dose: 1 tablet of fixed-dose combination of VX-661 100 mg/ivacaftor 150 mg and 1 tablet of placebo visually matched to ivacaftor
- Evening dose: 1 tablet of ivacaftor 150 mg

Ivacaftor monotherapy

- Morning dose: 1 tablet of placebo visually matched to the fixed-dose combination tablet and 1 tablet of ivacaftor 150 mg
- Evening dose: 1 tablet of ivacaftor 150 mg

Of the randomized subjects, approximately15% will carry an *R117H* mutation on the second *CFTR* allele.

Subjects who complete the Week 8 Visit of the Active Comparator Treatment Period, regardless of whether they have prematurely discontinued study drug treatment, will be offered the opportunity to enroll in an extension study, if they meet the eligibility criteria.

Schedule of Study Visits

Screening Period:

After obtaining consent and assent (where applicable), screening evaluations will be completed at any time during a period of 28 days (Weeks -8 through -4) before the first dose of study drug in the Ivacaftor Run-in Period.

Ivacaftor Run-in Period: The first dose of open-label ivacaftor will be administered at the Week -4 Visit. The last dose of open-label ivacaftor will be administered in the evening on Day -1 (1 day prior to the Day 1 Visit).

Subjects who prematurely discontinue study drug treatment during the Ivacaftor Run-in Period will not be randomized or participate in the Active Comparator Treatment Period. These subjects will complete an ETT and Safety Follow-up Visit. The Safety Follow-up Visit will be their last visit in the Study.

Active Comparator Treatment Period:

The first dose of the randomized study drug will be administered after randomization on Day 1.

Clinic visits will occur on Day 1, Week 2 (± 2 days), Week 4 (± 5 days), Week 8 (± 5 days), and Safety Follow-up Visit (28 days ± 7 days after the final dose of study drug).

Subjects who prematurely discontinue study drug treatment during the Active Comparator Treatment Period will continue to complete all other scheduled study visits for assessments of efficacy (spirometry, sweat chloride, and CFQ-R) [redacted]

Early Treatment Termination (ETT) Visit:

If the subject prematurely discontinues study treatment, an ETT Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 (± 7) days after their last dose of study drug. If the ETT Visit occurs 3 weeks or later following the last

dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

Safety Follow-up Visit:

The Safety Follow-up Visit is scheduled to occur 28 days (± 7 days) after the last dose of study drug. The Safety Follow-up Visit is not required for subjects who complete the Week 8 Visit and enroll in the extension study of VX-661 in combination with ivacaftor, within 28 days after the last dose of study drug. For subjects who prematurely discontinue study drug dosing, if the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

Assessments

Efficacy: spirometry, sweat chloride testing, and CFQ-R

[redacted]

Safety: AEs, clinical laboratory assessments (i.e., hematology, serum chemistry, lipid panel, vitamin levels, coagulation studies, and urinalysis), vital signs, physical examinations, ophthalmologic examinations, pulse oximetry, ECGs, and spirometry.

PK: VX-661, M1-661, ivacaftor, and M1-ivacaftor

[redacted]

Statistical Analyses

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

The null hypothesis to be tested is that the mean absolute change in percent predicted FEV_1 from baseline through Week 8 in the Active Comparator Treatment Period is the same for the 2 treatment arms. Assuming a common standard deviation (SD) of 7 percentage points and a 10% dropout rate, a sample size of 160 subjects will have at least 80% power to detect a treatment difference of 3.4 percentage points in absolute change in percent predicted FEV_1 between treatment groups at a 2-sided 0.05 significance level. A *P* value of 0.05 or less will be interpreted as sufficient evidence to reject the null hypothesis.

The primary analysis for the primary efficacy endpoint will be based on a mixed model for repeated measures (MMRM). The model will include absolute change in percent predicted FEV_1 from the Active Comparator Treatment Period baseline (including all measurements up to Week 8 [inclusive]) as the dependent variable; treatment, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect with adjustment for age group at screening (<18 versus ≥18 years old), type of mutation on the second *CFTR* allele (*R117H* versus all other allowed mutations), and percent predicted FEV_1 severity determined at the end of the Ivacaftor Run-in Period (<70 versus ≥70). The primary result obtained from the model will be the estimated treatment effect during the Active Comparator Treatment Period through Week 8. The estimated mean treatment effect, a 2-sided 95% confidence interval, and *P* value will be provided. Furthermore, the treatment effect at each postbaseline visit, obtained from the model, will also be provided.

IDMC Safety Reviews

The Independent Data Monitoring Committee (IDMC) will conduct regular planned safety reviews of study data as outlined in the IDMC Charter.

3 SCHEDULE OF ASSESSMENTS

Table 3-1 and Table 3-2 provide the schedule of assessments during the study from the Screening Period through the Safety Follow-up Visit.

All visits are to be scheduled relative to the Day 1 Visit (first dose of randomized study drug). For example, the Week 8 (± 5 days) Visit would occur after 8 weeks of study drug administration in the Active Comparator Treatment Period has been completed (i.e., Day 57, first day of Week 9).

Table 3-1 Screening Period Assessments – Study VX14-661-109

Event/Assessment	Screening Period (Week -8 Through Week -4)
ICF and assent (when applicable)	X
Demographics	X
Medical history	X
Ophthalmological history	X
CFQ-R[a]	X
[redacted]	
CFTR genotype[b]	X
Height and weight[c]	X
Ophthalmologic examination[d]	X
Complete PE	X
FSH[e]	X
Serum pregnancy test (all females of childbearing potential)[f]	X
Standard digital ECG[g]	X
Vital signs[h]	X
Pulse oximetry[h]	X
Spirometry[i]	X

[a] The CFQ-R, [redacted] must be completed prior to the start of any other assessments scheduled at that visit.

[b] All subjects will be tested for *CFTR* genotype. The results of the confirmatory genotype sample obtained at the Screening Visit must be reviewed before enrollment. In subjects with confirmed *R117H* mutation, linkage to poly-T track polymorphisms will also be determined. Specific instructions will be provided in the Laboratory Manual.

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

[d] An ophthalmologic examination will be conducted on subjects of all ages by an ophthalmologist. The ophthalmologic examination does not need to be repeated if there is documentation of an examination that met the protocol criteria and that was conducted within 3 months before the Screening Period or if there is documentation of bilateral lens removal (Section 11.7.8). Subjects with clinically significant cataracts, lens opacity, Y-suture, or lamellar rings will be excluded from the study.

[e] FSH will be measured for any potentially postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be ≥40 mIU/mL to be considered postmenopausal.

[f] Any female subject who does not meet the criteria for non-childbearing potential is considered to be of childbearing potential and must have a serum pregnancy test.

[g] A standard digital ECG will be performed after the subject has been supine for at least 5 minutes.

[h] Vital signs and pulse oximetry will be collected after the subject has been at rest (seated or supine) for 5 minutes.

[i] Spirometry may be performed pre- or postbronchodilator (Section 11.6.1). Screening spirometry evaluation may be repeated, as specified in Section 8.1.1.1.

Table 3-1 Screening Period Assessments – Study VX14-661-109

Sweat chloride[j]	X
Urinalysis	X
Hematology	X
Coagulation	X
Serum chemistry	X
Inclusion/exclusion criteria review	X
Prior and concomitant medications	X
AEs and SAEs	Continuous from signing of ICF and assent (where applicable) through Safety Follow-up Visit[k]

AE: adverse event; CFTR: cystic fibrosis transmembrane conductance regulator; CFQ-R: Cystic Fibrosis Questionnaire-Revised; ECG: electrocardiogram; FSH: follicle-stimulating hormone; ICF: informed consent form; PE: physical examination; [redacted] SAE: serious adverse event; [redacted]

j A sweat chloride test must be performed at the Screening Visit if an eligible sweat chloride value is not available in the subject's medical records and the Screening Visit value is needed to establish eligibility. For subjects using sweat chloride values documented in their medical records to establish eligibility, the sweat chloride test at the Screening Visit is optional.

k For enrolled subjects who do not have a Safety Follow-up Visit, AEs and SAEs will be collected through the earliest of the following: 28 days after the last dose of study drug; the ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (Section 8.1.5); or prior to the first dose of study drug in the extension study.

Table 3-2 Ivacaftor Run-in Period, Active Comparator Treatment Period, ETT, and Safety Follow-up Visit Assessments – Study VX14-661-109

Event/Assessment[a]	Ivacaftor Run-in Period[b]		Active Comparator Treatment Period				ETT Visit[c]	Safety Follow-up Visit 28 days (± 7 Days) After Last Dose[d]
	Week -4 (Day -28 ± 2 Days)	Week -2 (Day -14) (± 2 Days)	Day 1	Week 2 (Day 15) (± 2 Days)	Week 4 (Day 29) (± 5 Days)	Week 8 (Day 57) (± 5 Days)		
Clinic visit	X	X	X	X	X	X	X	X
Inclusion and exclusion criteria review	X							
CFQ-R[e]	X	X	X		X	X	X	X
[redacted]								
Ophthalmologic examination[g]							X	X

[a] All assessments will be performed before dosing unless noted otherwise. Where repeats of the same assessment are required at a given visit, if study drug is not administered on the day of the visit (i.e., study drug interruption or premature discontinuation of study treatment), only 1 set of assessments will be collected. Subjects who prematurely discontinue study drug treatment in the Active Comparator Treatment Period will continue to complete all other scheduled study visits for assessments of efficacy (spirometry, sweat chloride, and CFQ-R) [redacted] as detailed in Section 8.1.5.

[b] Ivacaftor Run-in Period is from Week -4 to Day -1 (1 day prior to the Day 1 Visit).

[c] If the subject prematurely discontinues study treatment, an ETT Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 (± 7) days after their last dose of study drug. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required (Section 8.1.5).

[d] The Safety Follow-up Visit is not required for subjects who complete the Week 8 Visit and have enrolled in the extension study of VX-661 in combination with ivacaftor within 28 days after the last dose of study drug. For subjects who prematurely discontinue study drug dosing, if the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

[e] All questionnaires must be completed before the start of any other assessments scheduled at that visit. The CFQ-R must be completed first, followed by the [redacted] (Section 11.1). Subjects will need to complete a CFQ-R, [redacted] at the ETT Visit (Section 8.1.5).

[redacted]

[g] Subjects <18 years of age at the Screening Visit who discontinue treatment after receiving at least 1 dose of study drug treatment, and subjects <18 years of age at the Screening Visit who complete study drug treatment but do not enroll in a separate extension study of VX-661/ivacaftor within 28 days after the last dose of study drug will have an ophthalmologic examinations conducted by a licensed ophthalmologist at the ETT Visit or Safety Follow-up Visit. The examination may be completed at either the ETT Visit or Safety Follow-up Visit, but must be completed by the date of the Safety Follow-up Visit. Subjects who have documentation of bilateral lens removal are not required to complete the ophthalmologic examination at the ETT Visit or Safety Follow-up Visit. See Section 11.7.8 for further details on ophthalmologic examinations.

Table 3-2 Ivacaftor Run-in Period, Active Comparator Treatment Period, ETT, and Safety Follow-up Visit Assessments – Study VX14-661-109

Event/Assessment[a]	Ivacaftor Run-in Period[b]		Active Comparator Treatment Period				ETT Visit[c]	Safety Follow-up Visit 28 days (± 7 Days) After Last Dose[d]
	Week -4 (Day -28 ± 2 Days)	Week -2 (Day -14) (± 2 Days)	Day 1	Week 2 (Day 15) (± 2 Days)	Week 4 (Day 29) (± 5 Days)	Week 8 (Day 57) (± 5 Days)		
Complete PE[h]	X							
Pregnancy test[i]	X		X		X	X	X	X
Standard digital ECG[j]	X	X	X	X	X	X	X	X
Vital signs[k]	X	X	X	X	X	X	X	X
Pulse oximetry[k]	X	X	X	X	X	X	X	X
Spirometry[l]	X	X	X	X	X	X	X	X
Sweat chloride[m]	X		X		X	X	X	X
Urinalysis	X		X			X	X	X
Hematology	X		X		X	X	X	X
Coagulation	X		X			X	X	X
Serum chemistry	X[n]	X	X[n]	X	X	X	X	X
Lipid panel[o]			X			X	X	X

[h] Symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator.

[i] Pregnancy tests will be performed for all female subjects of childbearing potential. A urine β-hCG test will be performed at the Week -4 (before first dose of study drug), Day 1, and Week 4 Visits. A serum pregnancy test will be performed at the Week 8 Visit, at the ETT, and the Safety Follow-up Visit.

[j] All standard digital ECGs will be performed before dosing and after the subject has been supine for at least 5 minutes. At the Day 1 and Week 2 Visits, ECGs will be collected before dosing and at 1.5, 3, 4, and 6 hours after the morning dose. The ECG will be performed before the morning dose of study drug at Week -4, Week -2, and Week 4. Single ECGs will be performed at Week 8, ETT, and Safety Follow-up Visits. ECGs collected on Week -4 and Day 1 before dosing will be performed in triplicate. Where repeats of the same assessment are required at a given visit, if study drug is not administered on the day of the visit (i.e., 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 after the subject has been at rest (seated or supine) for at least 5 minutes.

[l] At all visits, spirometry will be performed for all subjects pre-bronchodilator and before dosing (Section 11.6.1). On Days 1 and 15, subjects <18 years of age at the Screening Visit will have additional spirometry assessments performed at 2 and 4 hours postdose. If more than 1 spirometry assessment is required at a visit, bronchodilators will be withheld until the last scheduled spirometry assessment is completed.

[m] The sweat chloride collection on dosing days should occur before the morning dose of the study drugs. At each time point, 2 samples will be collected, 1 from each arm (left and right). Collection of sweat chloride will not overlap with any other study assessments.

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

[o] Subjects will require 4 hours of fasting before the blood sample for the lipid panel is obtained.

Table 3-2 Ivacaftor Run-in Period, Active Comparator Treatment Period, ETT, and Safety Follow-up Visit Assessments – Study VX14-661-109

Event/Assessment[a]	Ivacaftor Run-in Period[b]		Active Comparator Treatment Period				ETT Visit[c]	Safety Follow-up Visit 28 days (± 7 Days) After Last Dose[d]
	Week -4 (Day -28 ± 2 Days)	Week -2 (Day -14) (± 2 Days)	Day 1	Week 2 (Day 15) (± 2 Days)	Week 4 (Day 29) (± 5 Days)	Week 8 (Day 57) (± 5 Days)		
Vitamin levels			X			X	X	X
PK sampling[p]		X		X			X	X
[redacted]								
Randomization[r]			X					
Meal(s) or snack(s) at site[s]	X	X	X	X	X			
Ivacaftor dosing[t]	X							
Randomized treatment dosing[u]			X	X	X			
Study drug count		X	X	X	X	X	X	
Concomitant medications[v]	X	X	X	X	X	X	X	X

[p] PK blood samples will be collected at Week -2 (before the morning dose and at 2 and 6 hours after the morning dose) and Week 2 (before the morning dose and at 3 and 8 hours after the morning dose). If study drug is not administered at the Week -2 Visit or Week 2 Visit (i.e., study drug interruption or permanent discontinuation of study drug), a single PK blood sample will still be collected. At the ETT and the Safety Follow-up Visits (as applicable), a PK blood sample will also be collected.

[redacted]

Randomization must occur after all inclusion and exclusion criteria are met, after the 4 weeks Ivacaftor Run-in Period, and before the first dose of study drug on Day 1 of the Active Comparator Treatment Period. Randomization will be done through IWRS.

[s] 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 been completed.

[t] Subjects will receive ivacaftor 150 mg q12h from the Week -4 Visit through the evening of Day -1 (1 day prior to the Day 1 Visit). The study drug should be administered every 12 hours (± 2 hours) within 30 minutes after starting a meal with fat-containing food such as a "standard CF" high-fat, high-calorie meal or snack. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed.

[u] Subjects will receive randomized study treatment from randomization through the evening of the day before the Week 8 Visit. The study drug should be administered every 12 hours (± 2 hours) within 30 minutes after starting a meal with fat-containing food such as a "standard CF" high-fat, high-calorie meal or snack. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed.

[v] Information on concomitant medications is collected through the Safety Follow-up Visit for all subjects. For subjects who discontinue treatment and are followed for certain efficacy assessments after the ETT Visit (see Section 8.1.5), information on concomitant antibiotic therapy for "sinopulmonary signs/symptoms" are collected through the Week 8 Visit, as described in Section 11.6.4.1.1

Table 3-2 Ivacaftor Run-in Period, Active Comparator Treatment Period, ETT, and Safety Follow-up Visit Assessments – Study VX14-661-109

Event/Assessment[a]	Ivacaftor Run-in Period[b]		Active Comparator Treatment Period				ETT Visit[c]	Safety Follow-up Visit 28 days (± 7 Days) After Last Dose[d]
	Week -4 (Day -28 ± 2 Days)	Week -2 (Day -14) (± 2 Days)	Day 1	Week 2 (Day 15) (± 2 Days)	Week 4 (Day 29) (± 5 Days)	Week 8 (Day 57) (± 5 Days)		
Concomitant treatments and procedures	X	X	X	X	X	X	X	X
AEs and SAEs	Continuous from signing of ICF and assent (where applicable) through Safety Follow-up Visit[w]							

AE: adverse event; β-hCG: beta-human chorionic gonadotropin; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire–Revised; ECG: electrocardiogram; ETT: Early Treatment Termination; IWRS: interactive web response system; PE: physical examination; PK: pharmacokinetic; [redacted]; SAE: serious adverse event; [redacted]

[w] For enrolled subjects who do not have a Safety Follow-up Visit, AEs and SAEs will be collected through the earliest of the following: 28 days after the last dose of study drug; the ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (Section 8.1.5); or prior to the first dose of study drug in the extension study.

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5 INTRODUCTION

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

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

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

CFTR gene mutations associated with minimal CFTR function include

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

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

Two complementary approaches to increase CFTR-mediated Cl^- secretion in the airway epithelia have been studied.[9] One approach is to treat with a compound that will modify the cellular processing and trafficking of the CFTR protein to increase the amount of functional CFTR at the cell surface. This kind of compound has been termed a CFTR corrector. Another approach is to treat with a compound that increases the channel gating activity of protein kinase A-activated CFTR at the cell surface to enhance ion transport. This kind of compound has been termed a potentiator. Depending on the amount of residual CFTR channel activity in the membrane and the pathophysiology of that activity (reflecting the CFTR genotype of the patient and possibly other factors), both approaches may be required to ameliorate lung disease in patients with CF. A modest restoration of Cl^- secretion through the action of a potentiator and/or corrector could prevent the hyperabsorption of water across the apical surface of epithelial cells, allowing proper maintenance of airway hydration. Adequate airway hydration could alleviate the cycle of 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 the F508del-CFTR protein during its biogenesis and processing in the endoplasmic reticulum, allowing it to exit the endoplasmic reticulum and traffic the cell surface.[16] When added for more than 24 hours to human bronchial epithelial (HBE) cells isolated and cultured from lung explants obtained from donors with CF (CF-HBE cells) who are homozygous for the *F508del-CFTR* mutation, a concentration-dependent increase in levels of mature (i.e., plasma membrane) F508del-CFTR was observed. The increased trafficking of F508del-CFTR to the cell surface resulted in a significant increase in Cl^- secretion.[16] VX-661 did not correct the processing and localization of other misfolded or normally folded proteins other than CFTR, suggesting that the mechanism of VX-661 action is selective for CFTR (CFTR corrector).[17]

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

Kalydeco (ivacaftor) is indicated for the treatment of CF in patients as young as 2 years of age who have 1 of the following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R*, or *R117H*. Please refer to the ivacaftor IB and local prescribing information or summary of product characteristics for your region for the current approved use of Kalydeco.

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

6 STUDY OBJECTIVES

6.1 Primary Objective

To evaluate the efficacy of VX-661 in combination with ivacaftor in subjects with CF who are heterozygous for the *F508del* mutation on the *CFTR* gene and a second *CFTR* allele with a gating defect that is clinically demonstrated to be ivacaftor responsive

6.2 Secondary Objectives

- To evaluate the safety of VX-661 in combination with ivacaftor
- To investigate the pharmacokinetics (PK) of VX-661 and its metabolite M1 (M1-661), and ivacaftor and its metabolite M1 (M1-ivacaftor)

7 STUDY ENDPOINTS

The Ivacaftor Run-in Period is designed to establish a reliable on-treatment baseline for all subjects. The true baseline for evaluating the efficacy of VX-661/ivacaftor combination therapy over ivacaftor monotherapy is prior to dosing during the Active Comparator Treatment Period (Day 1).

7.1 Primary Endpoints

Absolute change in percent predicted forced expiratory volume in 1 second (FEV_1) from baseline through Week 8 in the Active Comparator Treatment Period

7.2 Key Secondary Endpoints

- Relative change in percent predicted FEV_1 from baseline through Week 8 in the Active Comparator Treatment Period
- Absolute change in Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain score from baseline through Week 8 in the Active Comparator Treatment Period

7.3 Secondary Endpoints

- Absolute change in sweat chloride from baseline through Week 8 in the Active Comparator Treatment Period
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values (hematology, serum chemistry, lipid panel, vitamin levels, coagulation studies, and urinalysis), standard digital electrocardiograms (ECGs), vital signs, pulse oximetry, and spirometry.
- PK parameters of VX-661, M1-661, ivacaftor, and M1-ivacaftor

[redacted]

8 STUDY DESIGN

8.1 Overview of Study Design

This is a Phase 3, randomized, double-blind, ivacaftor-controlled, parallel-group, multicenter study in subjects aged 12 years and older with CF who are heterozygous for the *F508del-CFTR* mutation and a second *CFTR* allele with a gating defect that is clinically demonstrated to be ivacaftor responsive (Section 16).

This study is designed to compare active treatment of VX-661 (100 mg daily [qd]) and ivacaftor (150 mg every 12 hours [q12h]) combination therapy with ivacaftor monotherapy (150 mg q12h).

The treatment regimens will be as follows:

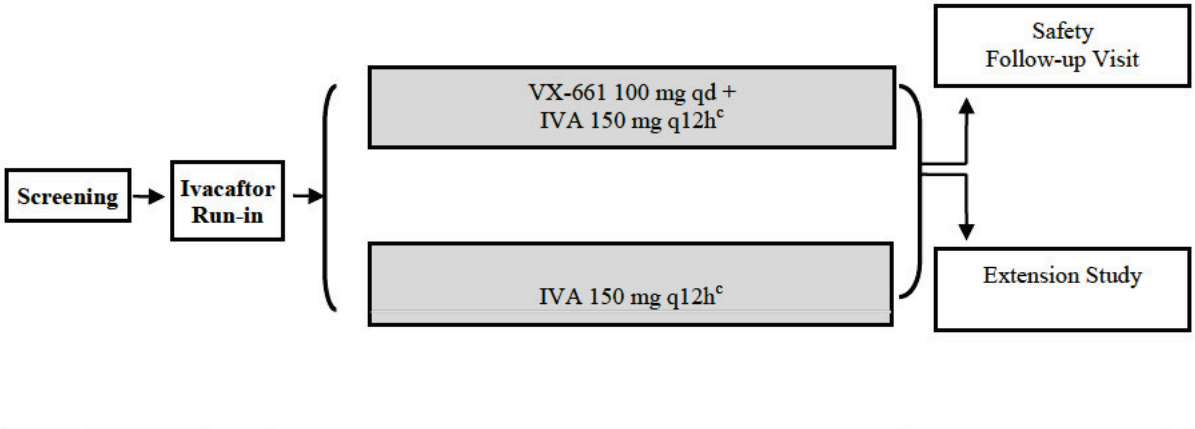
- VX-661/ivacaftor combination therapy
  - Morning dose: 1 tablet of fixed-dose combination of VX-661 100 mg/ivacaftor 150 mg and 1 tablet of placebo visually matched to ivacaftor
  - Evening dose: 1 tablet of ivacaftor 150 mg
- Ivacaftor monotherapy
  - Morning dose: 1 tablet of placebo visually matched to the fixed-dose combination tablet and 1 tablet of ivacaftor 150 mg
  - Evening dose: 1 tablet of ivacaftor 150 mg

This study includes a Screening Period (approximately 28 days), an Ivacaftor Run-in Period (approximately 4 weeks), an Active Comparator Treatment Period (up to 8 weeks), and a Safety Follow-up Visit (approximately 28 days after last dose). Following the Ivacaftor Run-in Period, approximately 160 subjects will be randomized in a ratio of 1:1 to receive either VX-661/ivacaftor combination therapy or ivacaftor monotherapy for 8 weeks during the Active Comparator Treatment Period. The randomization will be stratified by age at the Screening Visit (<18 versus ≥18 years of age), type of mutation on the second *CFTR* allele (*R117H* versus other allowed mutations; Section 16), and percent predicted FEV_1 severity determined at the end of the Ivacaftor Run-in Period (<70 versus ≥70; see Figure 8-1). Of the randomized subjects, approximately 15% will carry an *R117H* mutation on the second *CFTR* allele (Section 16). Week 8 is the conclusion of the Active Comparator Treatment Period of the study.

Subjects who complete the Week 8 Visit, regardless of whether they have prematurely discontinued study drug treatment, will be offered the opportunity to enroll in an extension study, if they meet the eligibility criteria.

All subjects randomized in the Active Comparator Treatment Period will be required to complete study assessments for all scheduled visits through Week 8, regardless of whether they have prematurely discontinued study treatment (Section 8.1.5).

Figure 8-1 Schematic View of the Study Design



FEV_1: forced expiratory volume in 1 second; IVA: ivacaftor; q12h: every 12 hours; qd: once daily.

[a] Approximately 160 subjects will be stratified by age at the Screening Visit (<18 versus ≥18 years of age), type of mutation on the second *CFTR* allele (*R117H* versus all other allowed mutations), and percent predicted FEV_1 severity determined at the end of the Ivacaftor Run-in Period (<70 versus ≥70) and will be randomized (1:1) before the first dose of study drug at Day 1.

[b] The Ivacaftor Run-in Period has a total duration of approximately 4 weeks and is designed to establish a reliable on-treatment (ivacaftor monotherapy) baseline.

[c] Subjects will receive the same number of tablets each day to maintain the blind during the Active Comparator Treatment Period. Subjects in the VX-661/Ivacaftor Arm will receive 100 mg VX-661 + 150 mg ivacaftor (fixed-dose combination tablet) and a placebo tablet (visually matched to the IVA 150 mg tablet) for the morning dose, and an IVA 150 mg tablet for the evening dose. Subjects in the Ivacaftor Monotherapy Arm will receive placebo tablet (visually matched to the VX-661 100 mg + ivacaftor 150 mg fixed-dose combination tablet) and 150 mg ivacaftor for the morning dose, and 150 mg ivacaftor for the evening dose.

[d] The Safety Follow-up Visit is scheduled to occur 28 (± 7) days after the last dose of study drug. The Safety Follow-up Visit is not required for subjects who complete the Week 8 Visit and have enrolled in the extension study of VX-661 in combination with ivacaftor within 28 days after the last dose of study drug.

8.1.1 Screening

The Screening Period will occur within 28 days before the first dose of study drug in the Ivacaftor Run-in Period to confirm that the subjects meet the selection criteria for the study. The assessments to be conducted are shown in Table 3-1. The investigator (or an appropriate authorized designee) will obtain informed consent and assent, if applicable, from each subject.

The ophthalmologic examination does not need to be repeated if there is documentation of an examination that met protocol criteria and that was conducted within 3 months before the Screening Period or if there is documentation of bilateral lens removal (Section 11.7.8).

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 (ATS)/European Respiratory Society (ERS) guidelines,[20] repeat spirometry evaluation may be performed once.

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

8.1.1.2 Rescreening

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

8.1.1.3 Extension of the Screening Period Window

A subject may have the Screening Period window extended by 2 weeks for the following reasons:

- Unexpected operational or logistic delays, or to meet the eligibility criteria
- Repetition of the Screening Period assessments (Section 8.1.1.1)
- Additional time to conduct ophthalmologic examinations (Section 11.7.8)

8.1.2 Ivacaftor Run-in Period (4 Weeks)

The Ivacaftor Run-in Period will have a total duration of 4 weeks and is designed to establish a reliable on-treatment (ivacaftor monotherapy) baseline for the Active Comparator Treatment Period. The first dose of open-label ivacaftor will be administered at the Week -4 Visit. The last dose of open-label ivacaftor will be administered in the evening on Day -1 (1 day prior to the Day 1 Visit). With prior approval of the medical monitor, the Ivacaftor Run-in Period may be extended if the subject does not meet criteria for entry into the Active Comparator Treatment Period (Section 8.1.3).

Study visits during the Ivacaftor Run-in Period will occur as shown in Table 3-2. Subjects will be outpatients during the Ivacaftor Run-in Period. All visits should occur within the windows specified.

Subjects who prematurely discontinue study drug treatment during the Ivacaftor Run-in Period will not be randomized or participate in the Active Comparator Treatment Period. These subjects will complete an ETT Visit and Safety Follow-up Visit. The Safety Follow-up Visit will be their last visit in the study.

8.1.3 Active Comparator Treatment Period (8 Weeks)

The Active Comparator Treatment Period will last approximately 8 weeks. Subjects will be randomized to 1 of 2 treatment arms (VX-661/ivacaftor or ivacaftor alone) as shown in Figure 8-1.

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

In order to continue into the Active Comparator Treatment Period, subjects must have stable CF disease (as judged by the investigator) and have remained on a stable CF medication regimen during the run-in period. If these criteria are not met (for example, if the subject has an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy [including antibiotics] for pulmonary disease within 28 days before the Day 1 Visit [first dose of study drugs in the Active Comparator Treatment Period]), possible extension of the Ivacaftor Run-in Period should be discussed with the medical monitor.

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

Subjects who prematurely discontinue study treatment during the Active Comparator Treatment Period will remain in the study from the time of discontinuation of study treatment through the Week 8 Visit and complete assessments for all study visits, as described in Section 8.1.5.

8.1.4 Safety Follow-up

The Safety Follow-up Visit assessments are listed in Table 3-2. There will be an outpatient Safety Follow-up Visit 28 days ± 7 days after the last dose of study drug for subjects who complete study drug dosing and for subjects who prematurely discontinue study drug dosing. If the Early Treatment Termination (ETT) Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

The Safety Follow-up Visit is not required for subjects who complete the Week 8 Visit and have enrolled in the extension study of VX-661 in combination with ivacaftor within 28 days after the last dose of study drug.

8.1.5 Early Treatment Termination

If the subject prematurely discontinues study treatment, an ETT Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. 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 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 ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

Subjects who prematurely discontinue study drug treatment during the Ivacaftor Run-in Period will not be randomized or participate in the Active Comparator Treatment Period. These subjects will complete an ETT Visit and Safety Follow-up Visit. The Safety Follow-up Visit will be their last visit in the study.

Subjects who prematurely discontinue study drug treatment during the Active Comparator Treatment Period will continue to complete all other scheduled study visits for assessments of efficacy (spirometry, sweat chloride, and CFQ-R) [redacted] as detailed in the Schedules of Assessments (Section 3).

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

8.1.6 Independent Data Monitoring Committee

The safety of administration of VX-661 in combination with ivacaftor will be monitored by an external independent data monitoring committee (IDMC), which will conduct periodic reviews of safety data. Procedural details of the IDMC structure and function, frequency of meetings, and data planned for review will be included in the IDMC charter. The IDMC charter will be finalized before the first subject is screened.

8.2 Rationale for Study Design and Study Drug Regimens

8.2.1 Study Design

The present study is 1 of 4 pivotal Phase 3 clinical studies designed to demonstrate the clinical efficacy and safety of VX-661 in combination with ivacaftor in subjects with CF. A randomized, double-blind study design will avoid observer bias and reduce symptoms or outcomes arising from the subjects' knowledge of treatment. The study will evaluate the efficacy of 1 dose level of VX-661 (100 mg qd) in combination with ivacaftor (150 mg q12h) compared with ivacaftor alone (150 mg q12h).

The study population will be subjects with CF who are 12 years of age or older and who are heterozygous for the *F508del-CFTR* mutation and a second *CFTR* allele with a gating defect that is clinically demonstrated to be ivacaftor responsive (Section 16). This population was selected based on a "Proof-of-Concept" study (Study VX11-661-101 [Study 101]). Results from the Study 101, Group 7, in subjects heterozygous for *F508del-CFTR* and *G551D-CFTR*, suggest that clinically meaningful improvement in percent predicted FEV_1 can be achieved with the combination of VX-661 and ivacaftor compared with ivacaftor alone.

An 8-week period was selected as the duration for the Active Comparator Treatment Period. A significant response in percent predicted FEV_1 is anticipated to be observed after 2 to 4 weeks of treatment with VX-661 in combination with ivacaftor. The 8-week primary

endpoint was selected in order to obtain a more robust assessment of the durability of response that is less affected by short-term variability in FEV_1. The Week 8 Visit is the conclusion of the Active Comparator Treatment Period in this study.

8.2.2 Study Drug Dose and Duration

The dose regimen of VX-661 chosen for continued development in Phase 3 was studied in Study 101 in 2 CF populations: *F508del-CFTR* homozygous subjects (Group 4) and *F508del-CFTR* heterozygous subjects who had *G551D-CFTR* on the other allele (Group 7). The dose regimen of VX-661 100 mg qd in combination with ivacaftor 150 mg q12h provided clinically meaningful and statistically significant improvements in percent predicted FEV_1 in both populations, as well as a signal of CFTR modulation as assessed by the change in sweat chloride.

The dose regimen of ivacaftor planned for this study (150 mg q12h) is the current approved dose regimen for patients with CF with gating mutations who are aged 6 years and older.

8.2.3 Rationale for Study Population

The study population will be subjects with CF 12 years of age and older who are heterozygous for the *F508del-CFTR* mutation and a second *CFTR* allele with a gating defect that is clinically demonstrated to be ivacaftor responsive. Based on the results from Study 101 (Section 8.2.1), subjects with the *F508del-CFTR* mutation on only 1 allele may respond to VX-661/ivacaftor combination therapy when the second allele is also responsive to potentiator modulation.

Patients with CF who have *CFTR* alleles that qualify them for inclusion in this study may live in a region where ivacaftor (Kalydeco) is already approved for patients with their mutations and is available for use by prescription. Because of this, it is anticipated that this study will enroll both subjects who have been exposed to ivacaftor within 28 days prior to the Screening Visit and subjects who have not. The intent of this study is to determine if VX-661/ivacaftor combination therapy has additional benefit over ivacaftor monotherapy in this population. Subjects who have been exposed to ivacaftor within 28 days prior to the Screening Visit must have an FEV_1 ≥40% and ≤90% of predicted normal for age, sex, and height at the Screening Visit. Those who have not been exposed to ivacaftor within 28 days prior to the Screening Visit must have an FEV_1 ≥40% and ≤75% of predicted normal for age, sex, and height at the Screening Visit.

The inclusion of subjects with CF who are 12 to 17 years of age is justified based on severity of disease and allometric scaling. The overall disease status for the adolescent and adult populations to be enrolled in this study is anticipated to be similar based on the identical enrollment criteria, particularly the FEV_1 and the requirement for clinical stability. Both VX-661 and ivacaftor are predominantly eliminated by metabolism via the cytochrome P450 (CYP) 3A4 enzymatic pathway. The maturity of the CYP enzymes in adolescents is expected to be similar to adults.[21] Therefore, the low likelihood of differences in PK of VX-661 and ivacaftor between adolescents and adults further supports the inclusion of adolescents in this study. The dose regimen of ivacaftor planned for this study (150 mg q12h) is the current labeled dose regimen for patients with CF with gating mutations who are aged 6 years and older. Based on the historical data from the ivacaftor Phase 3 program and the US CF

Foundation Registry on weight as a function of age in patients with CF, weights in the adolescent population are expected to be only slightly lower than those of the adult CF population.

8.2.4 Rationale for Study Assessments

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

Spirometry: 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/ivacaftor combination therapy. Spirometry (as measured by FEV_1) is the most widely implemented standardized assessment to evaluate lung function. Spirometry assessments will be performed predose in all subjects according to Section 11.6.1. To meet a request from a regulatory authority, subjects <18 years of age at the Screening Visit will have additional spirometry assessments performed after dosing at the time points noted in Table 3-2.

Sweat Chloride Testing: In patients with CF, the underlying ion-transport defect in CFTR results in elevated sweat electrolyte levels.[22,23] 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. Based on the mechanisms of action of VX-661 and ivacaftor, the sweat chloride test was included in this study as a measure of the effect of ivacaftor and VX-661 in combination with ivacaftor on CFTR activity.

CFQ-R: The CFQ-R is a frequently used CF-specific instrument that measures the health-related quality of life of patients with CF.[24,25,26] As both ivacaftor and VX-661 in combination with ivacaftor are systemic therapies, they have the potential to improve respiratory symptoms as well as other extrapulmonary manifestations of CF. These improvements can be captured by the non-respiratory symptoms domains of the CFQ-R. Linguistically validated versions of the CFQ-R[27,28] are available, thereby allowing consistent interpretation of the results in this global study. The CFQ-R will be used to capture and evaluate the impact of ivacaftor and VX-661 in combination with ivacaftor on patient report of respiratory symptoms and other aspects of health-related quality of life.

[redacted]

[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 (or their legally appointed and authorized representative) will sign and date an informed consent form (ICF) and, where appropriate, assent form.
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Subjects (male and female) will be aged 12 years or older on the date of ICF or, where appropriate, date of assent.
4. Heterozygous for *F508del-CFTR* mutation and a second *CFTR* allele with a gating defect that is clinically demonstrated to be ivacaftor-responsive (Section 16). The results of the confirmatory genotype sample obtained at the Screening Visit must be reviewed before enrollment.
5. For subjects exposed to ivacaftor within 28 days prior to the Screening Visit, an FEV_1 ≥40% and ≤90% of predicted normal for age, sex, and height (equations of Hankinson et al. or Wang et al.)[29,30] during screening (Section 11.6.1).

   For subjects who have not been exposed to ivacaftor within 28 days prior to the Screening Visit, an FEV_1 ≥40% and ≤75% of predicted normal for age, sex, and height (equations of Hankinson et al. or Wang et al.)[29, 30] during screening (Section 11.6.1).

   Spirometry measurements must meet ATS/ERS criteria[20] for acceptability and repeatability (Section 8.1.1.1).

Subjects must meet either inclusion criterion 6 or 7.

6. Sweat chloride value ≥60 mmol/L from test results obtained during screening OR as documented in the subject's medical record (may be collected prior to Kalydeco use).
7. If the sweat chloride value is <60 mmol/L, there must be documented evidence of chronic sinopulmonary disease[31] manifested by at least 1 of the following:
   - Persistent colonization/infection with typical CF pathogens, including *Staphylococcus aureus*, *Haemophilus influenzae*, and mucoid and nonmucoid *Pseudomonas aeruginosa*

- Chronic cough and sputum production
- Persistent chest radiograph abnormalities (e.g., bronchiectasis, atelectasis, infiltrates, hyperinflation)
- Nasal polyps, chronic sinusitis; radiographic or computed tomographic abnormalities of the paranasal sinuses

If it is unclear whether a subject meets this criterion, please consult with the medical monitor prior to enrollment.

8. Stable CF disease as judged by the investigator.
9. Willing to remain on a stable CF medication regimen from Week -4 through the last day of dosing (Week 8) or, if applicable, the Safety Follow-up Visit.
10. Willing to discontinue use of physician-prescribed ivacaftor (Kalydeco) from Week -4 to the last day of dosing (Week 8). Beginning Week -4, subjects will receive ivacaftor (Kalydeco) as the study drug.

9.2 Exclusion Criteria

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

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, a
   - history of cirrhosis with portal hypertension and/or
   - history of risk factors for Torsades 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, or intracranial trauma], and autonomic neuropathy).
2. Any of the following abnormal laboratory values at the Screening Visit:
   - 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, 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)[32,33] for

subjects ≥18 years of age and ≤45 mL/min/1.73 m^2 (calculated by the Counahan-Barratt equation)[34] for subjects aged 12 to 17 years (inclusive).

3. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before Week -4 (first dose of study drug for the Ivacaftor Run-in Period).
4. A 12-lead ECG demonstrating QTc >450 msec at the Screening Visit. If QTc exceeds 450 msec for the screening ECG, the ECG should be repeated 2 more times during the Screening Period, and the average of the 3 QTc values should be used to determine the subject's eligibility.
5. History of solid organ or hematological transplantation.
6. History or evidence of cataract, lens opacity, Y-suture, or lamellar rings determined to be clinically significant by the ophthalmologist during the ophthalmologic examination during the Screening Period. The ophthalmologic examination does not need to be repeated if there is documentation of an examination meeting protocol criteria that was conducted within 3 months before the Screening Period or if there is documentation of bilateral lens removal (Section 11.7.8).
7. History of alcohol or drug abuse, as deemed by the investigator, in the past year, including but not limited to cannabis, cocaine, and opiates
8. Ongoing or prior participation in an investigational study drug (including studies investigating lumacaftor [VX-809] or VX-661) within 30 days of the Screening Visit.
   - A washout period of 5 terminal half-lives of the previous investigational study drug or 30 days, whichever is longer, must elapse before the Screening Visit. The duration of the elapsed time may be longer if required by local regulations.
   - Subjects enrolled in open-label extension studies of ivacaftor are not excluded from enrollment.
   - Ongoing participation in a noninterventional study (including observational studies and studies requiring assessments without administration of study drug) is permitted.
9. Use of restricted medications or foods within the specified window before the first dose of study drug as defined in Table 9-1.
10. Pregnant and nursing females (females of childbearing potential must have a negative pregnancy test at Screening and Week -4 Visits).
11. 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 enrolled 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.

12. 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.

9.3 Study Restrictions

9.3.1 Dietary Restrictions/Prohibited Medications

Prohibited medications and certain foods are not allowed in this study (Screening Period through Safety Follow-up Visit) while subjects are receiving study drug (Table 9-1). Both ivacaftor and VX-661 are metabolized predominantly via the hepatic enzymatic pathway utilizing CYP3A4. Therefore, the use of known inducers and inhibitors of CYP3A, which have the potential to significantly alter the exposure of VX-661 and ivacaftor, will be restricted in this study.

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

Table 9-1 Study Restrictions

	Study Period	
Restricted Medication/Food	**Screening Period**	**Ivacaftor Run-in and Active Comparator Treatment Period**
Certain fruits and fruit juices (Grapefruit, grapefruit juice, Seville oranges, marmalade)	None allowed within 14 days before the first dose of the study drug (Week -4)	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 (Week -4)	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 (Week -4)	None allowed through the Safety Follow-up Visit
Commercially available ivacaftor (Kalydeco)	Permitted during the Screening Period but none allowed after the first dose of the study drug (Week -4)	None allowed through the Safety Follow-up Visit
Commercially available CFTR modulators other than ivacaftor (Kalydeco)	None allowed within 30 days before the Screening Visit.	None allowed through the Safety Follow-up Visit

CYP: cytochrome P450.
Note: The use of restricted medication by subjects with medical needs will be addressed on a case-by-case basis with the medical monitor.

9.4 Prior and Concomitant Medications

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

- Subjects must remain on a stable medication (and supplement) regimen for their CF from 28 days before Week -4 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 Week -4. Subjects must not initiate long-term treatment with new medication from 28 days before Week -4 through the Safety Follow-up Visit unless it is discussed and approved by the Vertex medical monitor. Guidelines for stable medication regimens for CF are as follows:
    - Subjects who are taking daily inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.
    - Subjects who are on inhaled cycling antibiotics should continue on their prior schedule. The timing of the first dose of study drug should be synchronized as closely as possible to the first day of inhaled cycling antibiotics in the cycle.

  - Subjects who alternate 2 different antibiotics monthly should remain on the same schedule during the study. The timing of the first dose of study drug should be synchronized as closely as possible to the first day of 1 of the inhaled alternating antibiotics.

- 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 assessments performed according to the guidelines provided in Section 11.6.1.
- Concomitant use of medications known to prolong the QT interval should be used with caution during the study, as the effect of VX-661 in combination with ivacaftor 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 as outlined in Section 8.1.5, provided the subject has not withdrawn consent.

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 and return for all scheduled visits.

A subject will be withdrawn from study 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 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 adverse event (SAE) that places him/her at immediate risk, and discontinuation of study treatment 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 11.7.7.
- A subject has an increase in QTc according to evaluations and management described in Section 11.7.4.
- A subject develops a cataract or lens opacity.

Subjects who discontinue study treatment early should continue to return for assessments, as described in Section 8.1.5.

9.6 Replacement of Subjects

Subjects who withdraw or are withdrawn for nonsafety reasons during the study drug treatment periods (Ivacaftor Run-in Period and Active Comparator Treatment Period) may be replaced at Vertex's discretion.

10 STUDY DRUG ADMINISTRATION AND MANAGEMENT

Study drug refers to VX-661/ivacaftor, ivacaftor, and placebo tablets visually matching the VX-661/ivacaftor and ivacaftor tablets.

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 Ivacaftor Run-in Period, subjects will receive ivacaftor 150 mg q12h from the Week -4 Visit through the evening of Day -1 (1 day prior to the Day 1 Visit) (Table 10-1). During the Active Comparator Treatment Period, subjects will receive randomized study treatment from randomization through the evening of the day before the Week 8 Visit. Subjects will receive the same number of tablets each day to maintain the blind during the Active Comparator Treatment Period (Table 10-2).

Table 10-1 Study Drug Administration – Ivacaftor Run-in Period

Treatment Arm	Time	Drug(s) and Dose(s) Administered Route of Administration
ivacaftor	AM	IVA 150-mg tablet oral
	PM	IVA 150-mg tablet oral

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

Table 10-2 Study Drug Administration - Active Comparator Treatment Period

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

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

Study drug should be administered within 30 minutes before 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 Ivacaftor Run-in Period and the Active Treatment Comparator 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. At the Week -4 Visit, all subjects will be observed for 1 hour after the morning dose of study drug. At the Day 1 Visit, all subjects will be observed for 6 hours after the morning dose of study drug.
4. 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.
5. 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.
6. 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.

7. For visits after the Week -4 Visit, subjects will be instructed to bring all used and unused study drug to the site; study drug will be dispensed at each visit, as appropriate.
8. At the Week 8 Visit, the morning dose of study drug will NOT be administered. The last dose of study drug will be the evening dose administered the day before the Week 8 Visit.

10.3 Method of Assigning Subjects to Treatment Groups

Approximately 160 subjects will be stratified by age at the Screening Visit (<18 versus ≥18 years of age), type of mutation on the second *CFTR* allele (*R117H* versus other allowed mutations; Section 16), and percent predicted FEV_1 severity determined at the end of the Ivacaftor Run-in Period (<70 versus ≥70), and then randomized (1:1) to receive either the VX-661/ivacaftor combination therapy or ivacaftor monotherapy during the Active Comparator Treatment Period.

An interactive web response system (IWRS) will be used to assign subjects to study treatment, as well as to ensure randomization of approximately 15% of subjects with an *R117H* mutation on the second *CFTR* allele. Detailed instructions for randomization will be provided separately.

10.4 Dose Modification for Toxicity

Neither the dosage of individual study drugs nor the combination therapy can be altered, but the investigator can interrupt or stop treatment with all study drugs.

10.5 Study Drug Interruption

If study drug dosing must be interrupted for more than 72 hours, the medical monitor must be notified. In these instances, study drug dosing may only resume after approval by the medical monitor. Specific instructions for interruption for elevated LFT levels and elevated QTc levels are provided in Section 11.7.7 and Section 11.7.4, respectively.

10.6 Missed Doses

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

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

10.7 Packaging and Labeling

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

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

10.8 Study Drug Supply, Storage, and Handling

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

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

Blister cards must be stored at room temperature according to Table 10-3 and to the instructions provided in the Pharmacy Manual. While at the clinical site, the investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended study conditions, and in accordance with applicable regulatory requirement. To ensure adequate records, all study drugs will be accounted for as detailed in Section 10.9.

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

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

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

10.9 Drug Accountability

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

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

Subjects will be instructed to return all used, partially used, and full study drug blister cards to the site. These materials will be retained at the site according to instructions provided by Vertex or its designee until inventoried by the study monitor. The study monitor will verify study drug records and inventory throughout the study.

10.10 Disposal, Return, or Retention of Unused Drug

The site staff or pharmacy personnel will retain all materials returned by the subjects until the site 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.

Procedures for destruction or return of the study drug will be detailed in the Pharmacy Manual.

10.11 Compliance

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

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

10.12 Blinding and Unblinding

This is a double-blind study.

10.12.1 Blinding

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 their fetus in the event of a pregnancy
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy SAE processing and reporting regulations
- Unblinded statistician preparing the final (production) randomization list who is not part of the study team
- Vertex Clinical Operations IWRS management
- Vertex Clinical Supply Chain

- IDMC
- Vendor preparing the unblinded analysis for the IDMC
- Vendor analyzing PK samples
- Vertex personnel or vendor conducting the population PK analysis
- 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 corresponding active control. Therefore, during the conduct of the study, the Vertex study team will not have access to the postdose spirometry data during the Active Comparator Treatment Period. The vendor for central reading of the spirometry data will only send the blinded spirometry files (blinded treatment group with dummy values for all the spirometry assessment after baseline in the Active Comparator Treatment Period) to Vertex to be used for developing the statistical programs. Furthermore, subjects and their caregivers should not be informed of their study-related spirometry results during the Active Comparator 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 treatment or corresponding active control. Therefore, during the conduct of the study, the Vertex study team will not have access to the postdose sweat chloride data; dummy data will be used to develop statistical programs. During the process of locking the clinical database and after all study visits have been completed, treatment-blinded access to the sweat chloride data will be provided to a small group of individuals who are not involved in the study. 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.

10.12.2 Unblinding

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

Unblinding of the individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, investigators should 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 that it is 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 should use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding without having successfully reached and discussed the situation with the medical monitor.

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

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

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

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

11 ASSESSMENTS

11.1 Timing of Assessments

The timing of assessments is shown in Table 3-1 and Table 3-2.

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

[redacted]

3. standard 12-lead ECG recordings
4. vital signs and pulse oximetry
5. spirometry
6. sweat chloride
7. safety laboratory assessments (including blood draws)
8. PK sampling

Note: where repeats of the same assessment are required at a given visit, if study drug is not administered on the day of the visit (for any reason, including study drug interruption or premature discontinuation of study drug), only 1 set of assessments will be collected (Table 3-2).

11.1.1 Informed Consent/Assent

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

11.1.2 Assigning Subject Number

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

11.2 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history, height, and 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 systems, past medical and surgical histories, and any allergies.

11.3 Total Blood Volume

Total blood volume will be outlined in the laboratory manual.

11.4 Pharmacokinetics

11.4.1 Blood Sampling

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

At the visits and time points indicated in Table 3-2, blood samples will be collected for the determination of the concentrations of VX-661, M1-661, ivacaftor, and M1-ivacaftor. Blood samples collected before dosing must be collected within 60 minutes before dosing. The acceptable windows for PK sampling time points are detailed in Table 11-1.

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

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

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

Table 11-1 Acceptable PK Sampling Windows

Sampling Time	Time From Sampling Schedule Allowed
Predose	Within 60 minutes before study drug dose on PK sampling days
2, 3, 6, and 8 hours after study drug dosing	± 30 minutes

PK: pharmacokinetic.

11.4.2 Processing and Handling of Pharmacokinetic Samples

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

11.4.3 Bioanalysis

Samples will be analyzed using a validated analytical method in compliance with Vertex or designee standard operating procedures. A description of the assay methods 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 ivacaftor 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 ivacaftor. These data will be used for exploratory purposes and may not be included in the clinical study report.

11.6 Efficacy

11.6.1 Spirometry

Spirometry will be performed according to the ATS/ERS guidelines[20] 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., ipratropium bromide [Atrovent®]) for more than 4 hours before the spirometry assessment;
- withheld their long-acting bronchodilator (e.g., salmeterol) for more than 12 hours before the spirometry assessment; and
- withheld their once-daily, long-acting bronchodilator (e.g., tiotropium bromide [Spiriva®]) for more than 24 hours before the spirometry assessment.

During the treatment periods (both Ivacaftor Run-in Period and the Active Comparator Treatment Period), spirometry assessments must be performed before dosing. In adolescent subjects (<18 years of age at the Screening Visit) additional postdose spirometry assessments on Day 1 and Day 15 will be performed at 2 and 4 hours after the morning dose as a safety assessment. A window for ± 15 minutes will be allowed around the nominal times for all postdose spirometry assessments.

During the Screening Period, spirometry assessments may be performed pre- or postbronchodilators. At all other visits, all spirometry assessments should be performed "prebronchodilator."

In the event that a subject does not withhold his/her bronchodilator(s), spirometry should be performed according to the following:

<u>During the Ivacaftor Run-in Period</u>

- If a subject's Week -4 spirometry is prebronchodilator, but, on a subsequent visit during the Ivacaftor Run-in Period, the subject does not withhold bronchodilator use, a postbronchodilator spirometry will be obtained for that visit only, and the visit will not be rescheduled.
- If, on Week -4, the subject does not withhold his/her dose of bronchodilator, spirometry should be performed postbronchodilator, and subsequent spirometric measurements during the Ivacaftor Run-in Period (according to the schedule of assessments detailed in Table 3-2) should be performed postbronchodilator.

<u>During the Active Comparator Treatment Period</u>

- If a subject's Day 1 spirometry is prebronchodilator, but, on a subsequent visit during the Active Comparator Treatment Period, the subject does not withhold bronchodilator use, a postbronchodilator spirometry will be obtained for that visit only, and the visit will not be rescheduled.

- If, on Day 1, the subject does not withhold his/her dose of bronchodilator, spirometry should be performed postbronchodilator, and all subsequent spirometric measurements during the Active Comparator Treatment Period (according to the schedule of assessments detailed in Table 3-2) should be performed postbronchodilator.
- Spirometry assessments that occur after dosing (postdose) on Day 1 and Day 15 (for subjects <18 years of age at the Screening Visit) should be performed prebronchodilator. If Day 1 and/or Day 15 predose spirometry is performed postbronchodilator, the subject should withhold any further bronchodilator use until after completion of the 4-hour postdose spirometry assessment on that day.
- For both Ivacaftor Run-in Period and the Active Comparator Treatment Period, each spirometry assessment will be recorded in the source documents as pre- or postbronchodilator.

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

Subjects and their parent/caregiver should not be informed of their study-related spirometry results during the Active Comparator Treatment Period (Day 1 through Week 8), regardless of whether the subject prematurely discontinues treatment.

The parameters listed below will be normalized using the standards of Wang et al[30] (for female subjects aged 12 to 15 years [inclusive] and male subjects aged 12 to 17 years [inclusive]) or Hankinson et al[29] (for female subjects aged 16 years and older and male subjects aged 18 years and older).

- FEV_1 (L)
- Forced vital capacity (FVC) (L)
- FEV_1/FVC (ratio)
- Forced expiratory flow (L/s)

11.6.2 Sweat Chloride Testing

The sweat chloride test is a standard diagnostic tool for CF, serving as a biomarker of CFTR activity. Collection of sweat samples will be performed at visits specified in Table 3-1 and 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 separately.

The sweat chloride collection on dosing days should occur before the morning dose of the study drugs. At each time point, 2 samples will be collected, 1 from each arm (left and right). Additionally, sweat chloride collection will be performed at the Screening Visit and the ETT Visit. For subjects using sweat chloride values documented in their medical records to establish eligibility, the sweat chloride test at the Screening Visit is optional. Collection of sweat chloride will not overlap with any other study assessments.

11.6.3 Cystic Fibrosis Questionnaire-Revised

Subjects will be asked to complete the CFQ-R in their native language.[26,35] The CFQ-R will be completed before the start of any other assessments, as noted in Table 3-1 and Table 3-2. At all visits, subjects who are 12 and 13 years of age at Week -4 will complete the CFQ-R Child version themselves, and their parents/caregivers will complete the CFQ-R Parent version, regardless of whether the subject subsequently turns 14 years of age during the study. Subjects 14 years of age and older at Week -4 will complete the Adolescent/Adult version of the questionnaire themselves at all visits. The questionnaires provide information about demographics; general quality of life, school, work, or daily activities; and symptom difficulties (pertaining to CF). Copies of the CFQ-R used in this study will be provided in the Study Reference Manual. Validated translations[27,28] of the CFQ-R will be provided for participating centers in non-English-speaking countries.

[redacted]

11.7 Safety

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

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 electronic case report form 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, with the exception of urine pregnancy tests, which are performed and analyzed at the site. Blood samples requiring a 4-hour fast will be collected on Day 1, Week 8, the ETT, and the Safety Follow-up Visit. Fasting is not required at other time points unless specified in the assessment table. At the Week -4 and Day 1 Visits, blood samples will be collected before the first dose of the study

drug. At all other scheduled visits, these samples will be collected at any time during the visit, relative to the order of assessments indicated in Section 11.1and according to the schedule of assessments 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 (Section 13.1.1).

The safety laboratory test panels are shown in Table 11-2.

Table 11-2 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		
Vitamin levels A, D, E, K, B12		
Lipid Panel		
Total cholesterol, triglycerides		
Low-density lipoprotein		
High-density lipoprotein		

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

Pregnancy (β-human chorionic gonadotropin) Tests for Females of Childbearing Potential: Serum samples will be obtained as specified in Table 3-1 and Table 3-2 and analyzed at the central laboratory. Urine pregnancy tests will be performed at the site as specified in Table 3-2. The urine pregnancy test at the Week -4 Visit must be negative before the first dose of study drug.

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

CFTR Genotype (Screening Period only): CF genotyping will be performed on all subjects to confirm the genotype documented in the subject's medical record. The results of the confirmatory genotype sample obtained at the Screening Visit must be reviewed before enrollment. In patients with confirmed *R117H* mutation, linkage to poly-T track polymorphisms will also be determined. Specific instructions will be provided in the Laboratory Manual.

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

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

11.7.3 Physical Examinations and Vital Signs

A PE of all body systems and vital signs assessment will be performed at the Screening and Week -4 Visits (see 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; 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 (oral), pulse rate, and respiration rate. These will be assessed following a 5-minute rest in the seated or supine position.

11.7.4 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 ± 15 minutes will be allowed around the nominal times for all postdose 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 QTcF value remains above the threshold value (>45 msec from the average of the 3 predose values on Day 1 or ≥500 msec) on repeated measurement or is noted on >2 occasions with no identified alternative etiology for the increased QTcF study drug, then discontinuation from study treatment may be required after discussion with the medical monitor.

Subjects who discontinue treatment 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 ivacaftor on conception, pregnancy, and lactation in humans are not known. Neither VX-661 nor ivacaftor showed any genotoxic potential in a standard battery of in vitro (Ames test, Chinese hamster ovary cell chromosomal aberration) and in vivo (mouse micronucleus) studies. VX-661 and ivacaftor were each found to be nonteratogenic in reproductive toxicology studies in rats and rabbits.[18,19] Subjects should follow the contraception requirements outlined in this study protocol. The effects of VX-661 monotherapy or in combination with ivacaftor 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 in combination with ivacaftor, participation in this study requires a commitment from the research subject and his/her partner to use at least 1 effective method of birth control. Acceptable methods of contraception for participants of this study and their partners are listed below. Methods of contraception should be in successful use from signing of consent, approximately 28 days, before the first dose of study drug (unless otherwise noted), and until 90 days following the last dose of study drug.

Contraception for the couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and postovulation methods) and withdrawal are not acceptable methods of contraception.
- If the male is infertile (e.g., bilateral orchiectomy). Infertility may be documented through examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound or medical record before the first dose of study drug.
- If the female is of non-childbearing potential, per the following:
    - Postmenopausal: spontaneous amenorrhea for at least 12 consecutive months and serum FSH level ≥40 mIU/mL at Screening
    - Documented hysterectomy or a bilateral oophorectomy/salpingo-oophorectomy
    - Has not achieved menarche (has not had her first menstrual period). Females who fall into this category are considered not to be of childbearing potential only as long as they have not had their first menstrual period. If a female achieves menarche during the study, she will need to provide consent for compliance (proper method of contraception or abstinence).
- NOTE: All other female subjects who have had their first menstrual period will be considered to be of childbearing potential.

Acceptable contraceptive methods:

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

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

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

- Bilateral tubal ligation performed at least 6 months previously
- Continuous use of an intrauterine device (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 not be considered as an effective method; however, female subjects are not required to discontinue hormonal contraceptives.

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

- Bilateral tubal ligation performed at least 6 months previously
- Continuous use of an intrauterine device for at least 90 days before 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, 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 the 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.

If a female subject or the female partner of a male subject becomes pregnant while participating in the study, study drug must be permanently discontinued immediately. For male subjects, study drug does not need to be permanently discontinued if the female partner's pregnancy resulted from donated sperm or sperm banked before study drug exposure (Section 11.7.5.1). 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 study drug, the subject or partner will be followed until the end of the pregnancy and the infant will be followed for 1 year after the birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

11.7.6 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 Liver Function Test Parameters

Liver Function Testing

Liver function testing (ALT, AST, GGT, ALP, direct bilirubin, and total bilirubin) must be performed as noted in Table 3-2 for serum chemistry, while subjects are receiving study drug treatment and at the Safety Follow-up Visit. These blood samples should be processed and shipped immediately per the Laboratory Manual.

Subjects with new treatment-emergent ALT or AST elevations of >3 × ULN and clinical symptoms must be followed closely, including repeat confirmatory testing performed by the central laboratory within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT and AST levels, as clinically indicated. In addition, if ALT or AST is >5 × ULN, repeat follow-up levels must be obtained within 7 ± 2 days.

If a subject cannot return to the site for liver function testing, a local laboratory may be used. Elevations in LFTs at the local laboratory must be reported immediately to the medical monitor, and the subject must have the tests repeated and sent to the central laboratory as soon as possible (ideally within 48 to 72 hours).

Study Drug Interruption

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

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

Resumption of Study Drug

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

11.7.8 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); and
- pharmacologically dilated examination of the lens with a slit lamp.

The screening ophthalmologic examination must be completed and the results reviewed before enrollment. This examination does not have to be repeated if there is documentation of an examination that met protocol criteria and that was within 3 months before the start of the Screening Period or if there is documentation of bilateral lens removal.

If a cataract, lens opacity, Y-suture, or lamellar rings are identified and determined to be clinically significant by the ophthalmologist at the Screening examination, the subject is ineligible for study entry (Section 9.2). If a cataract or lens opacity is identified and determined to be clinically significant by the ophthalmologist after dosing, the subject and Vertex medical monitor will be notified. After discussion with the principal investigator, who collaborates with the Vertex medical monitor, the subject may elect to continue or discontinue study drug treatment. If the subject discontinues study drug treatment, the subject should complete the ETT Visit, all subsequent scheduled visits per Table 3-2, and the Safety Follow-up Visit (see Sections 8.1.4 and 8.1.5). If the subject continues study drug treatment, more frequent ophthalmologic monitoring should be considered.

In addition to the Screening Visit, an ophthalmologic examination will be performed by a licensed ophthalmologist at the Safety Follow-up Visit or ETT Visit for the following subjects:

- subjects <18 years of age at the Screening Visit who discontinue study drug treatment after receiving at least 1 dose of study drug,
- subjects <18 years of age at the Screening Visit who complete study drug treatment but do not enroll in a separate extension study of VX-661/ivacaftor within 28 days after the last dose of study drug.

This examination may be completed at either the ETT Visit or Safety Follow-up Visit, but must be completed by the date of the Safety Follow-up Visit.

Subjects ≥18 years of age at the Screening Visit are not required to complete ophthalmologic examinations at the ETT Visit or Safety Follow-Up Visit.

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

Subjects who have documentation of bilateral lens removal are not required to complete the ophthalmologic examination at the Safety Follow-up Visit or ETT Visit.

In addition, at the Screening Visit, the following history will be obtained for all subjects:

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

12 STATISTICAL AND ANALYTICAL PLANS

This section presents a summary of the planned analyses for this protocol. Statistical analysis details will be provided in the Statistical Analysis Plan (SAP), and clinical pharmacologic analysis details will be provided in the Clinical Pharmacology Analysis Plan (CPAP), both of which will be finalized before the clinical data lock for the study and treatment unblinding.

12.1 Sample Size and Power

The primary efficacy endpoint is the absolute change in percent predicted FEV_1 from baseline through Week 8 in the Active Comparator Treatment Period.

The null hypothesis to be tested is that the mean absolute change in percent predicted FEV_1 from baseline through Week 8 in the Active Comparator Treatment Period is the same for the VX-661/ivacaftor combination therapy and the ivacaftor monotherapy. Assuming a common standard deviation (SD) of 7 percentage points and a 10% dropout rate, a sample size of 160 subjects will have at least 80% power to detect a treatment difference of 3.4 percentage points between treatment arms in absolute change in percent predicted FEV_1 at a 2-sided 0.05 significance level. A *P* value of 0.05 or less will be interpreted as sufficient evidence to reject the null hypothesis. The assumption of the main treatment effect of VX-661/ivacaftor combination therapy over ivacaftor monotherapy and a 7 percentage point SD is based on the results from the Phase 2 Study 101, Group 7.

With 160 subjects and assuming 10% lost to follow-up, the study has limited power to detect a treatment effect in CFQ-R respiratory domain score, i.e., a power of 32% to detect a treatment effect (SD) of 4 (16) in absolute change in CFQ-R respiratory domain score. The assumption of the treatment effect of VX-661/ivacaftor combination therapy over the ivacaftor monotherapy and the SD are all based on the within group treatment effect observed in the Phase 2 Study 101, Group 7.

[redacted]

12.2 Analysis Sets

Assignment of subjects to analysis sets will be done before the clinical data lock for the study.

The All Subjects Set is defined as all subjects who were enrolled, randomized, or received at least 1 dose of study drug in either the Ivacaftor Run-in Period or the Active Comparator Treatment Period (i.e., all subjects in the study). This analysis set will be used in subject listings and disposition summary table unless otherwise specified.

The Active Comparator Subjects Set includes all subjects randomized in the Active Comparator Treatment Period or dosed with at least 1 dose of blinded study drug. This analysis set will be used for specific disposition for the Active Comparator Treatment Period and subject listings related to the Active Comparator Treatment Period only.

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

The Safety Set, defined separately for the Ivacaftor Run-in Period and the Active Comparator Treatment Period, includes all subjects who received at least 1 dose of study drug in the corresponding treatment period. The Safety Set is to be used for all safety analyses in which subjects will be analyzed according to the treatment they received.

12.3 Statistical Analysis

The primary objective of this study is to evaluate the efficacy of VX-661 in combination with ivacaftor in subjects with CF who are heterozygous for the *F508del* mutation on the *CFTR* gene and a second *CFTR* allele with a gating defect that is clinically demonstrated to be ivacaftor responsive.

This section presents a summary of the planned statistical analyses of efficacy and safety for this study. The Vertex Biometrics department or a designated CRO will analyze the data derived from this study. Statistical Analysis System Version 9.2 or higher will be used to generate all statistical outputs (tables, figures, listings, and data sets).

Statistical analysis and presentation details will be provided in the SAP for the study.

12.3.1 General Considerations

All individual subject data for subjects exposed to study drug will be presented in data listings.

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

Categorical variables will be summarized using counts and percentages.

Baseline value, absolute change from baseline, and relative change from baseline will be defined separately for the Ivacaftor Run-in Period and the Active Comparator Treatment Period:

- **Baseline value**:
  - Unless otherwise specified, baseline for the Ivacaftor Run-in Period will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to initial administration of Ivacaftor monotherapy.
  - Unless otherwise specified, the baseline for the Active Comparator Treatment Period will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to initial administration of the VX-661/ivacaftor combination therapy, but no earlier than the measurement at Week -2.
  - For spirometry, the baseline value used for the Active Comparator Treatment Period will be the average of the measurement at Week -2 and the measurement on Day 1 predose. If a subject has an AE leading to an approved extension of the Ivacaftor Run-in Period, and the Week -2 spirometry assessment is between the start and end date (inclusive) of the AE, then the measurement on Day 1 predose will serve as baseline for the Active Comparator Treatment Period.
  - For ECG, the baseline will be defined as the average of the 3 pretreatment measurements at the first day of the corresponding treatment period.
- **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 be defined separately for the Ivacaftor Run-in Period and the Active Comparator Treatment Period:

- The TE Period for the Ivacaftor Run-in Period is defined as the first dose in the Ivacaftor Run-in Period to the earlier of the last day prior to the first dose of the Active Comparator Treatment Period or either the Safety Follow-up Visit or 28 days (inclusive) after the last dose for subjects who do not have Safety Follow-up Visit in the Ivacaftor Run-in Period.
- The TE Period for the Active Comparator Treatment Period is defined as the first dose of the Active Comparator Treatment Period to the Safety Follow-up Visit or 28 days (inclusive) after the last dose for subjects who do not have Safety Follow-up Visit in the Active Comparator Treatment Period.

The TE Period will be used for all safety analyses in the corresponding treatment period.

12.3.2 Background Characteristics

Subject disposition, demographic and baseline characteristics, prior and concomitant medications, study drug exposure and compliance, and other background characteristics will be summarized. Additionally, all subject data will be presented in subject data listings. No statistical hypothesis testing will be performed on background characteristics.

12.3.2.1 Subject Disposition

Number and percentage of subjects in the following categories will be summarized separately for the Ivacaftor Run-in Period and the Active Comparator Treatment Period, as appropriate:

- All Subjects Sets
- Dosed (Safety Set) in the Ivacaftor Run-in Period
- Completed treatment in the Ivacaftor Run-in Period
- Prematurely discontinued the treatment during the Ivacaftor Run-in Period and the reasons for treatment discontinuation
- Prematurely discontinued the study during the Ivacaftor Run-in Period and the reasons for study discontinuation
- Active Comparator Subjects Set (Randomized or dosed) in the Active Comparator Treatment Period
- Randomized in the Active Comparator Treatment Period
- Dosed (Safety Set) in the Active Comparator Treatment Period
- Randomized and dosed (FAS) in the Active Comparator Treatment Period
- Completed treatment in the Active Comparator Treatment Period
- Prematurely discontinued the treatment during the Active Comparator Treatment Period and the reasons for treatment discontinuation
- Prematurely discontinued the study during the Active Comparator Treatment Period and the reasons for study discontinuation
- Completed study/Safety Follow-up Visit
- Prematurely discontinued the study after the Active Comparator Treatment Period and the reasons for study discontinuation
- Rollover to extension study

12.3.2.2 Demographics and Baseline Characteristics

Demographic, background (e.g., medical history), and baseline characteristics will be summarized separately for the Ivacaftor Run-in Period and the Active Comparator Treatment Period. Protocol deviations/violations will be provided as a subject data listing only.

The following demographics and baseline characteristics will be summarized: sex, race, ethnicity, age, weight, height, BMI, region, baseline percent predicted FEV_1, baseline sweat chloride, and baseline score of CFQ-R respiratory domain. The summary will be based on the Safety Set for the Ivacaftor Run-in Period. For the Active Comparator Treatment Period, the summary will be based on the FAS.

12.3.2.3 Prior and Concomitant Medications

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

- **Prior medication:** any medication that started before initial dosing of study drug in the Ivacaftor Run-in Period, regardless of when it ended.
- **Concomitant medication during the Ivacaftor Run-in Period**: medication continued or newly received at or after initial dosing of the study drug through the end of the TE Period for the Ivacaftor Run-in Period.
- **Concomitant medication during the Active Comparator Treatment Period:** medication continued or newly received at or after initial dosing of study drug through the end of the TE Period of the Active Comparator Treatment Period.
- **Post-treatment medication:** medication continued or newly received beyond the TE Period of the Active Comparator Treatment Period.

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

Prior medications and concomitant medications in the Ivacaftor Run-in Period will be summarized descriptively based on the Safety Set in that period.

Prior medications, concomitant medication in the Ivacaftor Run-in Period will be summarized descriptively again based on the FAS for the Active Comparator Treatment Period. Concomitant medications in the Active Comparator Treatment Period will also be summarized descriptively based on the FAS.

Post-treatment medications will be listed for each subject.

12.3.2.4 Study Drug Exposure and Compliance

Study drug exposure and compliance will be summarized separately for the Ivacaftor Run-in Period and Active Comparator Treatment Period. Exposure to study drug (i.e., duration of treatment) will be summarized for the Safety Set for the Ivacaftor Run-in Period and the FAS for the Active Comparator Treatment Period in terms of duration of treatment a subject received (in days), defined as the last day minus the first day of study drug in the corresponding treatment period plus 1, regardless of any interruptions in dosing. Dosing compliance is calculated as the actual number of dosing occasions at which study drug was administered, as a percentage of the planned number of dosing occasions, for the corresponding treatment period. Dosing compliance will be summarized for the Safety Set for the Ivacaftor Run-in Period and for the FAS for the Active Comparator Treatment Period.

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

12.3.3 Efficacy Analysis

12.3.3.1 Analysis of Primary Variables

The primary efficacy endpoint is the absolute change in percent predicted FEV_1 from baseline through Week 8 in the Active Comparator Treatment Period.

The primary analysis will be based on a mixed effects model for repeated measures (MMRM) with absolute change in percent predicted FEV_1 from baseline at each time point through Week 8 in the Active Comparator Treatment Period as the outcome variable. The null hypothesis to be tested is that the mean absolute change in percent predicted FEV_1 from baseline through Week 8 in the Active Comparator Treatment Period is the same for the 2 treatment arms. A *P* value of 0.05 or less will be interpreted as sufficient evidence to reject the null hypothesis.

The model will include the absolute change in percent predicted FEV_1 from baseline at each visit (including all measurements up to Week 8 [inclusive]) as the dependent variables; treatment, visit, and treatment-by-visit interaction as fixed effects; and subject as a random effect. The model will also adjust for age group at the Screening Visit (<18 versus ≥18 years old), type of mutation on the second *CFTR* allele (*R117H* versus other allowed mutations; Section 16), and percent predicted FEV_1 severity determined at the end of the Ivacaftor Run-in Period (<70 versus ≥70).

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

The primary result obtained from the model will be the estimated treatment effect during the Active Comparator Treatment Period through Week 8. Descriptive summary statistics (including number of subjects, mean, standard error, and least square means [LS means]), a 2-sided 95% confidence interval, and a *P* value will be provided at each postbaseline visit. Furthermore, the difference in LS means and the corresponding 95% confidence interval will be provided along with the *P* values to assess the treatment difference between treatment groups. The *P* value testing the treatment-by-visit interaction will also be provided to assess the consistency of treatment effect over different visits.

[redacted]

12.3.3.2 Analysis of Key Secondary Efficacy Variables

- **Relative change in percent predicted FEV_1 from baseline through Week 8 in the Active Comparator Treatment Period:** Analysis of this variable will be similar to the primary analysis.

- **Absolute change in the CFQ-R respiratory domain score from baseline through Week 8 in the Active Comparator Treatment Period:** Analysis of this domain will be similar to that of the primary analysis of the primary efficacy endpoint, with the addition of the CFQ-R respiratory domain score at baseline as a covariate.

Adjustment for Multiple Comparisons

A hierarchical testing procedure will be used to control the Type I error for the multiple endpoints tested at $\alpha = 0.05$. For a test at any step to be considered statistically significant within the testing hierarchy, it must be statistically significant, and all previous tests (if any) within the hierarchy must be statistically significant, at the 0.05 level. The testing hierarchy is as follows:

1. Absolute change in percent predicted FEV_1 from baseline through Week 8
2. Relative change in percent predicted FEV_1 from baseline through Week 8
3. Absolute change in CFQ-R respiratory domain score from baseline through Week 8

12.3.3.3 Analysis of Secondary Efficacy Variables

Absolute change in sweat chloride from baseline through Week 8 in the Active Comparator Treatment Period: Analysis of this variable will be performed using the same model as described for the absolute change in percent predicted FEV_1 from baseline, with the addition of baseline sweat chloride value as a covariate.

12.3.4 Safety Analysis

Safety analyses will be based on the Safety Set with the associated TE Period and separately for the Ivacaftor Run-in Period and the Active Comparator Treatment Period, as appropriate.

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

- Incidence of treatment-emergent adverse event (TEAEs)
- Clinical laboratory values (i.e., urinalysis, hematology, serum chemistry, coagulation studies, vitamin levels, lipid panel)
- ECGs
- Vital signs
- Pulse oximetry
- Spirometry

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

12.3.4.1 Adverse Events

For analysis purposes, AEs will be classified as pretreatment AEs, TEAEs during the Ivacaftor Run-in Period, TEAEs during the Active Comparator Treatment Period, or post-treatment AEs, defined as follows:

- **Pretreatment AE:** any AE that started before initial dosing of study drug in the Ivacaftor Run-in Period.
- **TEAEs during the Ivacaftor Run-in Period**: any AE that increased in severity or that was newly developed at or after initial dosing of study drug through the end of the TE Period for the Ivacaftor Run-in Period.
- **TEAEs during the Active Comparator Treatment Period:** any AE that increased in severity or that was newly developed at or after initial dosing of study drug through the end of the TE Period for the Active Comparator Treatment Period.
- **Post-treatment AE:** any AE that increased in severity or that was newly developed beyond the TE Period.

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

AE summary tables will be presented for TEAEs, separately for the Ivacaftor Run-in Period and the Active Comparator Treatment Period, and will include the following:

- All TEAEs
- TEAEs by relationship
- TEAEs by maximal severity
- TEAEs leading to treatment discontinuation
- Serious TEAEs
- TEAEs leading to death
- 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 as well as total number of events). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once, only the maximum severity level will be presented in the severity summaries, and the worst/highest relationship level will be presented in the relationship summaries. An AE overview table will be provided. A separate table will summarize all TEAEs when each of them is considered unique, hereafter referred to as an AE count table. In addition, a listing containing individual subject AE data for all deaths and other serious and significant AEs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

12.3.4.2 Clinical Laboratory Assessments

The raw values and change from the corresponding treatment period baseline values of the continuous laboratory parameters will be summarized in SI units at each scheduled time point during the TE Period based on the corresponding Safety Set for the Ivacaftor Run-in

Period, and by treatment group for the Active Comparator Treatment Period, separately. In addition, mean value at each visit will be plotted for each of the liver function parameters. The plots will be separate for the Ivacaftor Run-in Period and by treatment groups in the Active Comparator Treatment Period.

The number and percentage of subjects with at least 1 potentially clinically significant (PCS) event during the treatment-emergent period will be summarized for the Ivacaftor Run-in Period and by treatment group during the Active Comparator Treatment Period, separately. The PCS (postbaseline) shift from the corresponding treatment period baseline will also be summarized for selected laboratory parameters for the Ivacaftor Run-in Period and by treatment groups in the Active Comparator Treatment Period, separately, separately. The PCS criteria and the parameter selection criteria will be provided in the SAP.

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

12.3.4.3 Electrocardiogram

The raw values and change from the corresponding treatment period baseline values will be summarized at each scheduled time point during the TE Period based on the corresponding Safety Set for the Ivacaftor Run-in Period and by treatment group for the Active Comparator Treatment Period. The analyzed standard digital ECG measurements include PR, QT, and QTc for heart rate (HR) interval (QTcF), QRS duration, and HR. In addition, the mean value of QTc at each visit will be plotted for the Safety Set in the Ivacaftor Run-in Period and by treatment groups for the Active Comparator Treatment Period, separately.

The number and percentage of subjects with at least 1 PCS event in the corresponding TE Period will be tabulated for the Ivacaftor Run-in Period and by treatment group for the Active Comparator Treatment Period, separately. The PCS criteria for ECG data will be provided in the SAP.

Additional ECG analyses will be described in the SAP.

12.3.4.4 Vital Signs

The raw values and change from the corresponding treatment period baseline values will be summarized at each scheduled time point during the TE Period based on the corresponding Safety Set in the Ivacaftor Run-in Period and by treatment group in the Active Comparator Treatment Period: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute [bpm]), and respiratory rate (breaths per minute).

The number and percentage of subjects with at least 1 PCS event during the TE Period based on the corresponding Safety Set will be tabulated for the Ivacaftor Run-in Period and by treatment group for the Active Comparator Treatment Period. The PCS criteria for vital signs data will be provided in the SAP.

Additional vital sign analyses will be described in the SAP.

12.3.4.5 Physical Examination

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

12.3.4.6 Other Safety Analysis

12.3.4.6.1 Pulse Oximetry

The raw values and change from the corresponding treatment period baseline values will be summarized at each scheduled time point during the TE Period based on the corresponding Safety Set for the Ivacaftor Run-in Period and by treatment groups for the Active Comparator Treatment Period, separately. In addition, the mean value at each visit during the TE Period will be plotted for the Ivacaftor Run-in Period and by treatment group for the Active Comparator for the percent of oxygen saturation.

12.3.4.6.2 Postdose Spirometry

For the 2-hour and 4-hour postdose spirometry measurements on Day 1 and Day 15, a summary of raw values for percent predicted FEV_1 will be provided by treatment group at each time point. The absolute change from the predose value of percent predicted FEV_1 on the same day will be provided by treatment group at each time point. In addition, a boxplot by time point will be provided. Within each treatment group, Day 1 and Day 15 values will be presented on the same plot.

The above analyses will be repeated for FEV_1.

In addition, the number and percentage of subjects with percent predicted FEV_1 decline $\geq$10, $\geq$15, and $\geq$20 percentage points in the absolute change from the predose value will be summarized by treatment group and by assessment day and time.

12.3.5 Interim and IDMC Analyses

12.3.5.1 Interim Analysis

No interim analyses of efficacy are planned.

12.3.5.2 IDMC Analysis

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

12.4 Clinical Pharmacology Analysis

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

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

13.1.1.2 Clinically Significant Assessments

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

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

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

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

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

13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time ICF is signed until the following time points:

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit

- For enrolled subjects who do not have a Safety Follow-up Visit: the earliest of
  - 28 days after the last dose of study drug
  - The ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (Section 8.1.5)
  - prior to the first dose of study drug in the extension study

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

- Description of the event
- Classification of "serious" or "nonserious"
- Date of first occurrence and date of resolution (if applicable)
- Severity
- Causal relationship to study drug(s)
- Action taken
- Outcome
- Concomitant medication or other treatment given
- 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 August 2012). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." In considering the severity of an AE in a pediatric subject, the investigator will consider that reference ranges for pediatric clinical laboratory parameters may differ from those given in the CTCAE. The severity of an AE that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

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

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	Not applicable for this study
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 Global Patient Safety via
Email: [redacted] (Preferred Choice)
Or via Fax: [redacted]
Contact Telephone: [redacted]

13.1.2.4 Expedited Reporting and Investigator Safety Letters

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

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

13.2 Administrative Requirements

13.2.1 Ethical Considerations

The study will be conducted in accordance with the current ICH GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and in accordance with local applicable laws and regulations. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, sample ICF, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or Vertex, as allowable by local applicable laws and regulations.

13.2.2 Subject Information and Informed Consent and Assent

After the study has been fully explained, written informed consent will be obtained from the subject or legal representative or guardian (if applicable), and assent will be obtained from

the subject (if applicable), before study participation. The method of obtaining and documenting the informed consent and assent (if applicable) and the contents of the consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

13.2.3 Investigator Compliance

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

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

13.2.4 Access to Records

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

13.2.5 Subject Privacy

To maintain subject confidentiality, all electronic case report forms (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 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/IECs may terminate the study at their center.

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

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

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

13.3 Data Quality Assurance

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

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

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

13.4 Monitoring

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

The study will be monitored by Vertex or its designee. Monitoring will be done by personal visits from a representative of Vertex, or designee (study site monitor), who will review the

eCRFs/SAE Forms and source documents. The study site monitor will ensure that the investigation is conducted according to the protocol design and regulatory requirements.

13.5 Electronic Data Capture

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

eCRFs 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 eCRFs. 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 eCRFs 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 must 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 eCRFs in the form of a compact disc or other electronic media will be placed in the investigator's study file.

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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX14-661-109	Version #: 4.0	Version Date 18 April 2017
Study Title: A Phase 3, Randomized, Double-Blind, Ivacaftor-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Heterozygous for the *F508del-CFTR* Mutation and a Second *CFTR* Allele With a Gating Defect That Is Clinically Demonstrated to be Ivacaftor Responsive		

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

[redacted]

15.2 Investigator Signature Page

Protocol #: VX14-661-109	Version #: 4.0	Version Date 18 April 2017
Study Title: A Phase 3, Randomized, Double-Blind, Ivacaftor-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Heterozygous for the *F508del-CFTR* Mutation and a Second *CFTR* Allele With a Gating Defect That Is Clinically Demonstrated to be Ivacaftor Responsive		

I have read Protocol VX14-661-109, Version 4.0 and agree to conduct the study according to its terms. I understand that all information concerning VX-661 and ivacaftor and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date

16 APPENDIX A: SECOND *CFTR* ALLELE MUTATIONS INCLUDED FOR SUBJECTS WHO ARE HETEROZYGOUS FOR THE *F508del-CFTR* MUTATION

Per the study eligibility criteria, heterozygous *F508del-CFTR* subjects must have a second *CFTR* allele that encodes a mutation with a gating defect clinically demonstrated to be ivacaftor-responsive. The list below represents acceptable mutations.

***CFTR* Mutations With a Gating Defect Clinically Demonstrated to be Ivacaftor-Responsive**

R117H
G178R
S549N
S549R
G551D
G551S
G1244E
S1251N
S1255P
G1349D

Source: CFTR2.org [Internet]. Baltimore (MD): Clinical and functional translation of CFTR. The Clinical and Functional Translation of CFTR (CFTR2), US Cystic Fibrosis Foundation, Johns Hopkins University, the Hospital for Sick Children. Available at: http://www.cftr2.org/. Accessed 15 September 2014