1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3, Open-label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661 in Combination With Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous or Heterozygous for the *F508del-CFTR* Mutation

Vertex Study Number: VX15-661-113

[redacted]

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2 PROTOCOL SYNOPSIS

Title A Phase 3, Open-label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661 in Combination With Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous or Heterozygous for the *F508del-CFTR* Mutation

Brief Title A Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661/Ivacaftor in Pediatric Subjects With Cystic Fibrosis

Clinical Phase and Clinical Study Type Phase 3, pharmacokinetic (PK), safety, and tolerability (pediatric population)

Objectives

Part A

Primary Objective

To evaluate the PK of VX-661 and ivacaftor after administration of multiple doses of VX-661 in combination with ivacaftor

Secondary Objectives

- To evaluate the PK of VX-661 metabolites, M1-661 and M2-661, and ivacaftor metabolites, M1-ivacaftor and M6-ivacaftor, after administration of multiple doses of VX-661 in combination with ivacaftor
- To evaluate the safety and tolerability of multiple doses of VX-661 in combination with ivacaftor

Part B

Primary Objective

To evaluate the safety and tolerability of VX-661 in combination with ivacaftor through Week 24

Secondary Objectives

- To evaluate the PK of VX-661, M1-661, M2-661, ivacaftor, M1-ivacaftor, and M6-ivacaftor after administration of multiple doses of VX-661 in combination with ivacaftor
- To evaluate the efficacy of VX-661 in combination with ivacaftor through Week 24

Endpoints

Part A

Primary Endpoint

VX-661 and ivacaftor PK parameters, including maximum observed concentration (C_{max}), area under the concentration versus time curve during a dosing interval (AUC_{τ}), and other PK parameters as appropriate

Secondary Endpoints

- M1-661, M2-661, M1-ivacaftor, and M6-ivacaftor PK parameters, including C_{max}, AUC_{τ}, and other PK parameters as appropriate
- Safety and tolerability of VX-661 in combination with ivacaftor as determined by adverse events (AEs), clinical laboratory values (serum chemistry, hematology, coagulation studies, lipids, vitamins, and urinalysis), standard 12-lead electrocardiogram (ECGs), vital signs, pulse oximetry, and spirometry

[redacted]

Part B

Primary Endpoint

Safety and tolerability of VX-661 in combination with ivacaftor as determined by AEs, clinical laboratory values (serum chemistry, hematology, coagulation studies, lipids, vitamins, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, ophthalmologic examinations, and spirometry

Secondary Endpoints

- VX-661, M1-661, M2-661, ivacaftor, M1-ivacaftor, and M6-ivacaftor PK parameters, including C_{max}, AUC_{τ}, and other PK parameters as appropriate
- Absolute change in $ppFEV_1$ from baseline through Week 24
- Relative change in $ppFEV_1$ from baseline through Week 24
- Absolute change in weight and weight-for-age z-score from baseline at Week 24
- Absolute change in height and height-for-age z-score from baseline at Week 24
- Absolute change in body mass index (BMI) and BMI-for-age z-score from baseline at Week 24
- Absolute change in sweat chloride from baseline through Week 4
- Absolute change in sweat chloride from baseline through Week 24
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline through Week 24

[redacted]

Number of Subjects

Part A

Up to approximately 16 subjects total are planned for enrollment across Cohort 1 (subjects weighing <25 kg at baseline) and Cohort 2 (subjects weighing ≥25 kg at baseline). Subjects who participate in Part A may participate in Part B if Part B eligibility criteria are met.

Part B

Approximately 56 subjects are planned for enrollment. Assuming a 10% dropout rate, approximately 50 subjects are expected to complete Part B.

Study Population

Part A and Part B

Male and female subjects 6 through 11 years of age with cystic fibrosis (CF), homozygous or heterozygous for the *F508del-CFTR* Mutation. Subjects in Part A may participate in Part B if Part B eligibility criteria are met.

Investigational Drug

Part A

Active substance: VX-661

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

Strength and Route of Administration: VX-661 50-mg tablets for oral administration

Active substance: Ivacaftor

Activity: CFTR potentiator (increased Cl^- secretion)

Strength and Route of Administration: Ivacaftor 75-mg granules or 150-mg tablet for oral administration

Part B

Active substances: VX-661 and ivacaftor

Activity: CFTR corrector and potentiator (increased Cl^- secretion)

Strength and Route of Administration:

VX-661 50-mg/ivacaftor 75-mg fixed-dose combination (FDC) tablet or VX-661 100-mg/ivacaftor 150-mg FDC tablet for oral administration

Active substance: Ivacaftor

Activity: CFTR potentiator (increased Cl^- secretion)

Strength and Route of Administration: Ivacaftor 75-mg tablet or 150-mg tablet for oral administration

Study Duration

Part A

Excluding the Screening Period, subject participation will be up to 31 days (Day 1 through the Safety Follow-up Visit). The planned treatment duration of VX-661 in combination with ivacaftor is 14 days.

Part B

Excluding the Screening Period, subject participation will be up to 29 weeks (Day 1 through the Safety Follow-up Visit). The planned treatment duration of VX-661 in combination with ivacaftor is 24 weeks.

Study Design

This is a Phase 3, 2-part (Part A and Part B), open-label, multicenter study evaluating the PK, safety, and tolerability of multiple doses of VX-661 in combination with ivacaftor in subjects 6 through 11 years of age with CF who are homozygous or heterozygous for the *F508del-CFTR* mutation. Efficacy will also be evaluated in Part B. Part A is composed of 2 weight-based cohorts, which will be enrolled simultaneously, and Part B is composed of a single cohort.

Part A

Part A includes the following:

- Screening Period (Day -28 through Day -1)
- Treatment Period (Day 1 through Day 14)
- Washout Period (Day 14 to Day 28 [± 3 days])
- Safety Follow-up Visit (14 [± 3] days after the last dose of study drug)

Screening Period

After obtaining written informed consent (and assent, if applicable), Screening Visit assessments will be completed at any time during the period of 4 weeks (Day -28 through Day -1) before the first dose of the study drug (Day 1).

Treatment Period

During the Treatment Period, subjects will be administered VX-661 50 mg daily (qd) in combination with ivacaftor, either 75 mg (subjects <25 kg at baseline) or 150 mg (subjects ≥25 kg baseline), every 12 hours (q12h) for 14 days. On Day 14, only the morning dose of study drug will be administered.

Washout Period

A 2-week Washout Period (Day 14 to Day 28 [± 3 days]) will be included in order to evaluate the off-drug response.

Safety Follow-up Visit

A Safety Follow-up Visit is scheduled to occur 14 (± 3) days after the last dose of study drug for all subjects, including subjects who permanently discontinue from study treatment for any reason.

A review of safety, tolerability, and PK data will be completed by an internal Vertex team after Part A to select the VX-661 dose for Part B.

Part B

Part B includes the following:

- Screening Period (Day -28 through Day -1)
- Treatment Period (Day 1 through Week 24 [± 5 days])
- Safety Follow-up Visit (4 weeks [± 7 days] after the last dose of study drug)

Screening Period

After obtaining written informed consent (and assent, if applicable), Screening Visit assessments will be completed at any time during the period of 4 weeks (Day -28 through Day -1) before the first dose of study drug (Day 1).

Treatment Period

During the Treatment Period, subjects will be administered VX-661 50 mg qd in combination with ivacaftor 75 mg q12h (subjects <40 kg at baseline) or VX-661 100 mg qd in combination with ivacaftor 150 mg q12h (subjects ≥40 kg at baseline) for 24 weeks. No dose adjustments will be made throughout the duration of treatment in this study.

Safety Follow-up Visit

A Safety Follow-up Visit is scheduled to occur 4 weeks (± 7 days) after the last dose of study drug. The Safety Follow-up Visit is not required for subjects who have enrolled in the extension study (see below) within 28 days after the last dose of study drug. Subjects who permanently discontinue study drug treatment will have an Early Treatment Termination (ETT) Visit and a Safety Follow-up Visit.

Extension Study

At the Week 24 Visit in Part B, subjects who complete study drug treatment will be offered the opportunity to enroll in an extension study evaluating VX-661 in combination with ivacaftor (enrollment will be based on the eligibility criteria specified within the extension study). Subjects who prematurely discontinue study drug treatment are not eligible to rollover into the extension study.

Assessments

PK Assessments

Part A and Part B

VX-661, M1-661, M2-661, ivacaftor, M1-ivacaftor, and M6-ivacaftor plasma PK parameters

Safety Assessments

Part A and Part B

Adverse events, clinical laboratory assessments (serum chemistry, hematology, coagulation studies, lipids, vitamins, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, spirometry, and physical examinations (PEs)

Part B will also include ophthalmologic examinations.

Efficacy Assessments

Part A

Spirometry

Part B

Spirometry, weight, height, BMI, sweat chloride, and CFQ-R

[redacted]

Statistical Analyses

Part A

Sample size calculations conducted using noncompartmental analysis-based PK parameters, such as clearance and volume, in adults indicate that data from 8 subjects will allow 80% power to target a 95% CI within 60% and 140% of the geometric mean estimate of clearance for VX-661 in each pediatric subgroup (cohort).

There will be no statistical analyses for the safety variables in Part A. All safety analyses will be performed descriptively.

Part B

An important safety endpoint is the incidence of AEs. With 50 subjects completing the study, there is a 92.3% chance of observing AEs in at least 1 subject if the true incidence rate is 5%, and a 99.5% chance of observing AEs in at least 1 subject if the true incidence rate is 10%.

For the primary endpoints, summary statistics will be provided for treatment-emergent adverse events (TEAEs), clinical laboratory assessments (serum chemistry, hematology, lipids, vitamins, and coagulation studies), standard 12-lead ECGs, vital signs, pulse oximetry, and spirometry during the treatment-emergent period.

IDMC Reviews

Part A

An independent data monitoring committee (IDMC) will be formed. The IDMC objectives and operational details will be defined in a separate document (the IDMC Charter), which will be finalized before the first subject is screened in Part B. The IDMC will conduct a planned review of study data for the purpose of safety monitoring as outlined in the IDMC Charter.

Part B

The IDMC 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 reviews of study data for the purpose of safety monitoring as outlined in the IDMC Charter.

3 SCHEDULE OF ASSESSMENTS

The schedules of assessments for Study VX15-661-113 (Study 113) are shown in Table 3-1 (Part A Screening), Table 3-2 (Part A Treatment Period and Safety Follow-up Visit), Table 3-3 (Part B Screening), and Table 3-4 (Part B Treatment Period and Safety Follow-up Visit).

Table 3-1 Study VX15-661-113: Part A Screening

Assessment	Screening Visit (Day -28 to Day -1)
Informed consent (and assent, if applicable)	X
Demographics	X
Medical history	X
Ophthalmological history[a]	X
Weight, height, and vital signs[b,c]	X
Pulse oximetry[c]	X
Ophthalmologic examination[a,d]	X
Full physical examination[e]	X
Standard 12-lead ECG[f]	X
Spirometry[g]	X
Sweat chloride[h]	X
CFTR genotype[i,j]	X
Serum pregnancy test (female subjects of childbearing potential)[i,k]	X
Serum chemistry[i]	X
Vitamin levels[i]	X
Hematology and coagulation studies[i]	X
Urinalysis[i]	X
Inclusion/exclusion criteria review	X
Prior and concomitant medications	Continuous from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit
AEs and SAEs	Continuous from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit

AE: adverse event; BMI: body mass index; CF: cystic fibrosis; *CFTR*: *CF transmembrane conductance regulator* gene; ECG: electrocardiogram; ICF: informed consent form; SAE: serious adverse event

[a] Refer to Section 11.7.6 for details.
[b] Weight and height will be measured with shoes off. BMI will be derived from assessment of height and weight.
[c] Vital signs and pulse oximetry will be collected after the subject has been seated or supine for at least 5 minutes (see Section 11.7.4).
[d] An ophthalmologic examination will be conducted by a licensed ophthalmologist. The 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 start of the Screening Period. Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination. Subjects with clinically significant cataracts, lens opacity, Y suture, or lamellar rings will be excluded (refer to Section 9.2).
[e] Refer to Section 11.7.4 for details.
[f] A standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes (refer to Section 11.7.5). The ECG will be performed before any other procedures that may affect heart rate.
[g] Spirometry may be performed pre- or post-bronchodilator (refer to Section 11.6.1).
[h] A sweat chloride test must be performed if an eligible sweat chloride value is not available in the subject's medical records (refer to Section 11.6.2). For subjects using a sweat chloride value documented in their medical record to establish eligibility, the sweat chloride test at the Screening Visit is optional.
[i] Refer to Section 11.7.2 for details.
[j] All subjects will be tested to assess *CFTR* genotype, regardless of availability of a previous *CFTR* genotype lab report. In subjects with the *R117H* mutation, linkage to poly-T tract polymorphisms will also be determined from a second specimen. Specific instructions will be provided in the Laboratory Manual.
[k] Any female subject who does not meet the criteria for non-childbearing potential (refer to Section 11.7.8.1) is considered to be of childbearing potential and must have a serum pregnancy test.

Table 3-2 Study VX15-661-113: Part A Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Day 1	Day 2	Day 4 (± 1 day)	Day 7 (± 1 day)	Day 14	Day 21 (± 1 day)	Day 28 Safety Follow-up Visit (14 [± 3] days after the last dose)
Clinic visit	X	X		X	X	X	X
Telephone contact[b]			X				
Safety Assessments							
Weight and height[c]	X				X		X
Vital signs[d]	X	X		X	X		X
Pulse oximetry[d]	X	X		X	X		X
Full physical examination[e]	X				X		X
Standard 12-lead ECG[f]	X[g]	X		X	X		X
Spirometry[h]	X	X		X	X		X
Pregnancy test (female subjects of childbearing potential)[i,j]	X (urine)						X (serum)
Serum chemistry[j]	X			X	X		X
Lipid panel[j,k]	X				X		
Vitamin levels[j]					X		
Hematology[j]	X			X	X		X

[a] All assessments will be performed before study drug dosing unless noted otherwise (refer to Section 11.1). When repeats of an assessment are required postdose at a given visit, the assessment will be collected only once if study drug is not administered on the day of the visit (i.e., study drug interruption or permanent discontinuation of study drug).

[b] Telephone contact will be made to assess the subject's status, any AEs, concomitant medications, treatments, and procedures.

[c] Weight and height will be measured with shoes off. BMI will be derived from assessment of height and weight.

[d] Vital signs and pulse oximetry will be collected after the subject has been seated or supine for at least 5 minutes (refer to Section 11.7.4).

[e] At other visits, symptom-directed physical examinations will occur if triggered by AEs or if deemed necessary by the investigator (refer to Section 11.7.4).

[f] Standard 12-lead ECGs will be performed before study drug dosing (unless noted otherwise) after the subject has been supine for at least 5 minutes (refer to Section 11.7.5).

[g] ECGs collected on Day 1 before study drug dosing will be performed in triplicate.

[h] Spirometry must be performed for all subjects before dosing and should be performed pre-bronchodilator (refer to Section 11.6.1).

[i] Any female subject who does not meet the criteria for non-childbearing potential (refer to Section 11.7.8.1) is considered to be of childbearing potential and must have a pregnancy test.

[j] Refer to Section 11.7.2 for details.

[k] Blood samples will be collected for the lipid panel following at least a 4-hour fast.

Table 3-2 Study VX15-661-113: Part A Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Day 1	Day 2	Day 4 (± 1 day)	Day 7 (± 1 day)	Day 14	Day 21 (± 1 day)	Day 28 Safety Follow-up Visit (14 [± 3] days after the last dose)
Coagulation studies[j]						X	
Urinalysis[j]	X				X		
Concomitant medications, treatments, and procedures	Continuous from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit						
AEs and SAEs	Continuous from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit						
PK Assessments							
PK Sampling	X[l]	X[l]			X[m]	X[m]	X[m]
Study Drug Administration							
VX-661 + IVA[n]	**VX-661 qd + IVA q12h Day 1 through Day 14 (morning dose only on Day 14)**						

AE: adverse event; BMI: body mass index; CF: cystic fibrosis; ECG: electrocardiogram; ICF: informed consent form; IVA: ivacaftor; PK: pharmacokinetic; q12h: every 12 hours; qd: daily; SAE: serious adverse event

[l] PK blood samples will be collected on Day 1 at 1, 2, 4, 5, and 24 hours (i.e., predose on Day 2) after the morning dose of study drug on Day 1. Acceptable windows for sampling times are shown in Table 11-1.

[m] PK blood samples will be collected before the morning dose of study drug on Day 14 and at 1, 2, 4, and 5 hours after the morning dose of study drug on Day 14. A PK blood sample will also be collected at 168 hours (i.e., Day 21) after the morning dose of study drug on Day 14 and at the Safety Follow-up Visit. Acceptable windows for sampling times are shown in Table 11-1.

[n] The study drug should be administered approximately 30 minutes after the start of consuming a fat-containing meal or snack. Refer to Section 9.3 for details on study restrictions and Section 10.2 for details on study drug administration (e.g., fasting requirements). On days of scheduled visits, the dose of study drug will be administered at the clinical site after predose assessments have been completed. The last dose of study drug will be the morning dose on Day 14.

Table 3-3 Study VX15-661-113: Part B Screening

Assessment	Screening Visit (Day -28 through Day -1)
Informed consent (and assent, if applicable)	X
Demographics	X
Medical history	X
Ophthalmological history[a]	X
Weight, height, and vital signs[b,c]	X
Pulse oximetry[c]	X
Ophthalmologic examination[a,d]	X
Full physical examination[e]	X
Standard 12-lead ECG[f]	X
Spirometry[g]	X
Sweat chloride[h]	X
CFTR genotype[i,j]	X
Serum pregnancy test (female subjects of childbearing potential)[i,k]	X
Serum chemistry[i]	X
Hematology[i]	X
Coagulation studies[i]	X
Urinalysis[i]	X
Inclusion/exclusion criteria review	X
Prior and concomitant medications	Continuous from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit
AEs and SAEs	Continuous from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit

AE: adverse event; BMI: body mass index; CF: cystic fibrosis; *CFTR*: *CF transmembrane conductance regulator* gene; ECG: electrocardiogram; ICF: informed consent form; SAE: serious adverse event

[a] Refer to Section 11.7.6 for details.
[b] Weight and height will be measured with shoes off. BMI will be derived from assessment of height and weight.
[c] Vital signs and pulse oximetry will be collected after the subject has been seated or supine for at least 5 minutes (refer to Section 11.7.4).
[d] An ophthalmologic examination will be conducted by a licensed ophthalmologist. The 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 start of the Screening Period. Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination. Subjects with clinically significant cataracts, lens opacity, Y suture, or lamellar rings will be excluded (refer to Section 9.2).
[e] Refer to Section 11.7.4 for details.
[f] A standard 12-lead ECG will be performed after the subject has been supine for at least 5 minutes (refer to Section 11.7.5). The ECG will be performed before any other procedures that may affect heart rate (e.g., blood draws).
[g] Spirometry may be performed pre- or post-bronchodilator (refer to Section 11.6.1).
[h] A sweat chloride test must be performed if an eligible sweat chloride value is not available in the subject's medical records (refer to Section 11.6.2). For subjects using a sweat chloride value documented in their medical record to establish eligibility, the sweat chloride test at the Screening Visit is optional.
[i] Refer to Section 11.7.2 for details.
[j] All subjects will be tested to assess *CFTR* genotype, regardless of availability of a previous *CFTR* genotype lab report. In subjects with the *R117H* mutation, linkage to poly-T tract polymorphisms will also be determined from a second specimen. Specific instructions will be provided in the Laboratory Manual.
[k] Any female subject who does not meet the criteria for non-childbearing potential (refer to Section 11.7.8.1) is considered to be of childbearing potential and must have a serum pregnancy test.

Table 3-4 Study VX15-661-113: Part B Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Day 1	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)[b]	ETT Visit[c]	Safety Follow-up Visit (4 weeks [± 7 days] after last dose)[d]
Clinic visit	X	X	X	X		X		X	X	X
Telephone contact[e]					X		X			
Inclusion and exclusion criteria review	X									
CFQ-R[f]	X	X	X	X		X		X	X	
Weight, height, and vital signs[g,h]	X	X	X	X		X		X	X	X
Pulse oximetry[h]	X	X	X	X		X		X	X	X
Ophthalmologic examination								X[i]	X[i]	X[i]
Full physical examination[j]	X							X		

[a] All assessments will be performed before study drug dosing unless noted otherwise (refer to Section 11.1). When repeats of an assessment are required postdose at a given visit, the assessment will be collected only once if study drug is not administered on the day of the visit (i.e., study drug interruption or permanent discontinuation of study drug).

[b] At the Week 24 Visit, subjects who complete study drug treatment will be offered the opportunity to enroll in an extension study evaluating VX-661 in combination with ivacaftor. Subjects who prematurely discontinue study drug treatment are not eligible to rollover into the extension study.

[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 (refer to Section 8.1.5). Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 4 weeks (± 7 days) after their last dose of study drug. If the ETT Visit occurs 3 weeks or later after the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

[d] The Safety Follow-up Visit is not required for subjects who have enrolled in the extension study within 28 days after the last dose of study drug.

[e] Telephone contacts will be made to assess the subject's status, any AEs, concomitant medications, treatments, and procedures.

[f] The CFQ-R should be completed before the start of any other assessments (refer to Section 11.1).

[g] Weight and height will be measured with shoes off. BMI will be derived from assessment of height and weight.

[h] Vital signs and pulse oximetry will be collected after the subject has been seated or supine for at least 5 minutes (refer to Section 11.7.4).

[i] An ophthalmologic examination will be conducted by a licensed ophthalmologist at or within 28 days before the Week 24 Visit OR at or within 35 days before the Safety Follow-up Visit (refer to Section 11.7.6). For subjects who discontinue treatment after receiving at least 1 dose of study drug, this examination may be completed at the ETT Visit OR at or within 35 days before the Safety Follow-Up Visit (if applicable [refer to Section 8.1.5]). Subjects who have documentation of bilateral lens removal are not required to complete the eye examination at the Week 24 Visit, the ETT Visit, or Safety Follow-up Visit.

[j] At other visits, symptom-directed physical examinations will occur if triggered by AEs or if deemed necessary by the investigator (refer to Section 11.7.4).

Table 3-4 Study VX15-661-113: Part B Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Day 1	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)[b]	ETT Visit[c]	Safety Follow-up Visit (4 weeks [± 7 days] after last dose)[d]
Standard 12-lead ECG[k]	X[l]	X	X	X		X		X	X	X
[redacted]										
Spirometry[n]	X	X	X	X		X		X	X	X
Sweat chloride[o]	X		X					X		
Pregnancy test (female subjects of childbearing potential)[p,q]	X (urine)	X (serum)	X (serum)	X (serum)		X (serum)		X (serum)	X (serum)	X (serum)
Serum chemistry[q]	X	X	X	X		X		X	X	X
Lipid panel[q]	X			X		X		X	X	
Vitamin levels[q]	X			X				X	X	
Hematology[q]	X	X	X	X		X		X	X	X
Coagulation studies[q]	X							X	X	X
Urinalysis[q]	X							X	X	X

[k] All standard 12-lead ECGs will be performed before study drug dosing (unless noted otherwise) and after the subject has been supine for at least 5 minutes (refer to Section 11.7.5). ECGs will be performed before any other procedures that may affect heart rate (e.g., blood draws).

[l] ECGs collected on Day 1 before study drug dosing will be performed in triplicate.

[redacted]

[n] Spirometry must be performed for all subjects before dosing and should be performed pre-bronchodilator (refer to Section 11.6.1).

[o] Sweat collection will be done approximately at the same time as predose blood collections (refer to Section 11.1 and Section 11.6.2).

[p] Any female subject who does not meet the criteria for non-childbearing potential (refer to Section 11.7.8.1) is considered to be of childbearing potential and must have a pregnancy test.

[q] Refer to Section 11.7.2 for details.

Table 3-4 Study VX15-661-113: Part B Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Day 1	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)[b]	ETT Visit[c]	Safety Follow-up Visit (4 weeks [± 7 days] after last dose)[d]
[redacted]										
Single PK sampling[r]			X[s]	X[s]						
Serial PK sampling[t]						X[s]				
Study drug count		X	X	X		X		X		
Concomitant medications, treatments, and procedures	Continuous from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit									
AEs and SAEs	Continuous from signing of ICF (and assent form, if applicable) through Safety Follow-up Visit									
Study Drug Administration										
VX-661 + IVA[u]	**VX-661 qd + IVA q12h**									

AE: adverse event; BMI: body mass index; CF: cystic fibrosis; CFQ-R: CF Questionnaire-Revised; ECG: electrocardiogram; ETT: Early Treatment Termination; ICF: informed consent form; IVA: ivacaftor; [redacted]; PK: pharmacokinetic; q12h: every 12 hours; SAE: serious adverse event

[r] At the Week 4 and Week 8 Visits, PK blood samples will be collected before dosing. Blood samples collected before dosing must be collected within 60 minutes before dosing.

[s] At the Week 16 Visit, subjects will fast for at least 2 hours after administration of the morning dose of study drug.

[t] At the Week 16 Visit, PK blood samples will be collected before the morning dose and at 1, 2, 4, and 5 hours after the morning dose. Acceptable windows for sampling times are shown in Table 11-1. 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 PK blood sample will be collected.

[u] The study drug should be administered within 30 minutes after consuming a fat-containing meal or snack. Refer to Section 9.3 for details on study restrictions and Section 10.2 for details on study drug administration. On days of scheduled visits, the dose of study drug will be administered at the site after predose assessments have been completed. At the Week 24 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 24 Visit.

4 TABLE OF CONTENTS

1 Title Page 1
[redacted]
2 Protocol Synopsis 3
3 Schedule of Assessments 9
4 Table of Contents 16
List of Tables 19
List of Figures 19
5 Introduction 20
5.1 Background 20
5.2 Study Rationale 21
6 Study Objectives 22
6.1 Primary Objectives 22
6.2 Secondary Objectives 22
7 Study Endpoints 22
7.1 Primary Endpoints 22
7.2 Secondary Endpoints 23
[redacted]
8 Study Design 24
8.1 Overview of Study Design 24
8.1.1 Screening 26
8.1.1.1 Repetition of Screening Period Assessments 26
8.1.1.2 Rescreening 27
8.1.1.3 Extension of Screening Period Window 27
8.1.2 Treatment Period 27
8.1.3 Washout Period 28
8.1.4 Safety Follow-up 28
8.1.5 Early Discontinuation/Early Treatment Termination 28
8.1.6 Lost to Follow-up 29
8.1.7 Independent Data Monitoring Committee 29
8.2 Rationale for Study Design and Study Drug Regimens 30
8.2.1 Study Design 30
8.2.2 Study Drug Dose and Duration 30
8.2.2.1 VX-661 Dose 30
8.2.2.2 Ivacaftor Dose 31
8.2.2.3 Study Drug Duration 31
8.2.3 Rationale for Study Assessments 31
9 Study Population 33
9.1 Inclusion Criteria 33
9.2 Exclusion Criteria 36
9.3 Study Restrictions 38
9.4 Prior and Concomitant Medications 40
9.5 Removal of Subjects 41
9.6 Replacement of Subjects 42

10 Study Drug Administration and Management 42
10.1 Preparation and Dispensing 42
10.2 Administration 42
10.3 Dose Modification for Toxicity 45
10.4 Study Drug Interruption 45
10.5 Missed Doses 45
10.6 Method of Assigning Subjects to Treatment Groups 46
10.7 Packaging and Labeling 46
10.8 Study Drug Supply, Storage, and Handling 46
10.9 Drug Accountability 47
10.10 Disposal, Return, or Retention of Unused Drug 47
10.11 Compliance 47
10.12 Blinding and Unblinding 48
11 Assessments 48
11.1 Timing of Assessments 48
11.2 Informed Consent/Assent 49
11.3 Subject and Disease Characteristics 49
11.4 Pharmacokinetics 49
11.4.1 Blood Sampling 49
11.4.2 Processing and Handling of Pharmacokinetic Samples 50
11.4.3 Bioanalysis 50
[redacted]
11.6 Efficacy 51
11.6.1 Spirometry 52
11.6.2 Sweat Chloride 53
11.6.3 Weight, Height, and BMI 53
11.6.4 Cystic Fibrosis Questionnaire-Revised 53
11.7 Safety 53
11.7.1 Adverse Events 54
11.7.2 Clinical Laboratory Assessments 54
11.7.3 Liver Function Test Parameters 56
11.7.4 Physical Examinations, Vital Signs, and Pulse Oximetry 57
11.7.5 Electrocardiograms 58
11.7.6 Ophthalmologic Examination 58
11.7.7 Spirometry 59
11.7.8 Contraception and Pregnancy 59
11.7.8.1 Contraception 60
11.7.8.2 Pregnancy 64
12 Statistical and Analytical Plans 64
12.1 Sample Size and Power 64
12.2 Analysis Sets 65
12.3 Statistical Analysis 65
12.3.1 General Considerations 65

12.3.2 Background Characteristics 66
12.3.2.1 Subject Disposition 66
12.3.2.2 Demographics and Baseline Characteristics 67
12.3.2.3 Prior and Concomitant Medications 67
12.3.2.4 Study Drug Exposure and Compliance 68
12.3.3 Efficacy Analysis 68
12.3.3.1 Analysis of Primary Efficacy Variables 69
12.3.3.2 Analysis of Secondary Efficacy Variables 69
12.3.4 Safety Analysis 70
12.3.4.1 Adverse Events 71
12.3.4.2 Clinical Laboratory Assessments 72
12.3.4.3 Electrocardiogram 72
12.3.4.4 Vital Signs 72
12.3.4.5 Physical Examination 73
12.3.4.6 Other Safety Analysis 73
12.3.4.6.1 Pulse Oximetry 73
12.3.4.6.2 Ophthalmologic Examinations 73
12.3.4.6.3 Spirometry 73
12.3.5 Interim and IDMC Analyses 73
12.3.5.1 Interim Analysis 73
12.3.5.2 IDMC Analysis 74
12.4 Clinical Pharmacology Analysis 74
13 Procedural, Ethical, Regulatory, and Administrative Considerations 74
13.1 Adverse Event and Serious Adverse Event Documentation, Severity Grading, and Reporting 74
13.1.1 Adverse Events 74
13.1.1.1 Definition of an Adverse Event 74
13.1.1.2 Clinically Significant Assessments 74
13.1.1.3 Documentation of Adverse Events 75
13.1.1.4 Adverse Event Severity 75
13.1.1.5 Adverse Event Causality 76
13.1.1.6 Study Drug Action Taken 76
13.1.1.7 Adverse Event Outcome 77
13.1.1.8 Treatment Given 77
13.1.2 Serious Adverse Events 77
13.1.2.1 Definition of a Serious Adverse Event 77
13.1.2.2 Documentation of Serious Adverse Events 78
13.1.2.3 Reporting Serious Adverse Events 79
13.1.2.4 Expedited Reporting and Investigator Safety Letters 79
13.2 Administrative Requirements 79
13.2.1 Ethical Considerations 79
13.2.2 Subject Information and Informed Consent 79
13.2.3 Investigator Compliance 79
13.2.4 Access to Records 80
13.2.5 Subject Privacy 80

13.2.6 Record Retention 80
13.2.7 Study Termination 81
13.3 Data Quality Assurance 81
13.4 Monitoring 81
13.5 Electronic Data Capture 82
13.6 Publications and Clinical Study Report 82
[redacted]
13.6.2 Clinical Study Report 83
14 References 84
15 Protocol Signature Pages 88
15.1 Sponsor Signature Page 88
15.2 Investigator Signature Page 89
16 Appendix A: *CFTR* Allele Mutations 90

List of Tables

Table 3-1 Study VX15-661-113: Part A Screening 9
Table 3-2 Study VX15-661-113: Part A Treatment Period and Safety Follow-up Visit 10
Table 3-3 Study VX15-661-113: Part B Screening 12
Table 3-4 Study VX15-661-113: Part B Treatment Period and Safety Follow-up Visit 13
Table 9-1 Lifestyle Guidelines and Study Restrictions (Part A) 38
Table 9-2 Lifestyle Guidelines and Study Restrictions (Part B) 40
Table 10-1 Study Drug Administration 43
Table 10-2 Study Drug Administration 44
Table 10-3 Study Drug 46
Table 11-1 Acceptable Pharmacokinetic Sampling Windows 49
Table 11-2 Safety Laboratory Test Panels 55
Table 11-3 Acceptable Methods of Contraception 63
Table 12-1 Probability of Observing At Least 1 Subject With an AE in the Study if the AE Incidence (θ) is 5% and 10% 65
Table 13-1 Grading of AE Severity 76
Table 13-2 Classifications for AE Causality 76
Table 13-3 Classifications for Study Drug Action Taken With Regard to an AE 77
Table 13-4 Classifications for Outcome of an AE 77

List of Figures

Figure 8-1 Schematic of Study Design for Part A 25
Figure 8-2 Schematic of Study Design for Part B 26

5 INTRODUCTION

5.1 Background

Cystic fibrosis (CF) affects an estimated 70,000 children and adults worldwide[2] and is the most common fatal genetic disease in persons of European descent.[3] Based on the size of the population, CF qualifies as an orphan disease.[4,5] Despite progress in the treatment of CF with antibiotics and mucolytics, the predicted median age of survival for a person with CF is approximately 40 years.[3,6] Although the disease affects multiple organs, most morbidity and mortality are caused by progressive loss of lung function.[7]

CF is an autosomal recessive genetic disease caused by a defect in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR), an epithelial chloride ion (Cl^-) channel activated by cyclic AMP-dependent protein kinase A that is responsible for aiding in the regulation of salt and water absorption and secretion in various tissues.[3] 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.[8] Mutations in the *CFTR* gene have been classified based on the molecular and functional consequence of the mutation on the CFTR protein[9,10,11] 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).[11] In the US, almost 87% of patients with CF have at least 1 copy of the *F508del-CFTR* mutation and about 47% have 2 copies.[12] In the European Union, approximately 83% of patients with CF have 1 or 2 copies of the *F508del-CFTR* mutation, and approximately 38.7% of patients with CF in the United Kingdom have 2 copies.[13] 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.[14,15] 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.[16]

Two complementary approaches to increase CFTR-mediated Cl^- secretion in the airway epithelia have been studied.[10] 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 CFTR corrector that works by facilitating the processing and trafficking of F508del-CFTR and other mutant CFTR forms, thereby increasing the amount of functional CFTR protein at the cell surface, resulting in enhanced chloride transport.[17] 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.[17] 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).[18]

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 Investigator's Brochure[19] 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.[19,2021,22]

5.2 Study Rationale

Vertex is currently evaluating VX-661 and ivacaftor combination therapy in subjects aged 12 years and older with CF who are homozygous or heterozygous for the *F508del-CFTR*

mutation in 4 Phase 3 studies (Studies VX14-661-106, VX14-661-107, VX14-661-108, and VX14-661-109). The present study is designed to obtain pharmacokinetic (PK), safety, and tolerability information in the pediatric population (subjects 6 through 11 years of age) to expand the evaluation of VX-661 and ivacaftor combination therapy in subjects 6 through 11 years of age who are homozygous or heterozygous for the *F508del-CFTR* mutation. Efficacy will also be evaluated in Part B of this study.

6 STUDY OBJECTIVES

6.1 Primary Objectives

Part A

To evaluate the PK of VX-661 and ivacaftor after administration of multiple doses of VX-661 in combination with ivacaftor

Part B

To evaluate the safety and tolerability of VX-661 in combination with ivacaftor through Week 24

6.2 Secondary Objectives

Part A

- To evaluate the PK of VX-661 metabolites, M1-661 and M2-661, and ivacaftor metabolites, M1-ivacaftor and M6-ivacaftor, after administration of multiple doses of VX-661 in combination with ivacaftor
- To evaluate the safety and tolerability of multiple doses of VX-661 in combination with ivacaftor

Part B

- To evaluate the PK of VX-661, M1-661, M2-661, ivacaftor, M1-ivacaftor, and M6-ivacaftor after administration of multiple doses of VX-661 in combination with ivacaftor
- To evaluate the efficacy of VX-661 in combination with ivacaftor through Week 24

7 STUDY ENDPOINTS

7.1 Primary Endpoints

Part A

VX-661 and ivacaftor PK parameters, including maximum observed concentration (C_{max}), area under the concentration versus time curve during a dosing interval (AUC_{τ}), and other PK parameters as appropriate

Part B

Safety and tolerability of VX-661 in combination with ivacaftor as determined by adverse events (AEs), clinical laboratory values (serum chemistry, hematology, coagulation studies, lipids, vitamins, and urinalysis), standard 12-lead electrocardiograms (ECGs), vital signs, pulse oximetry, ophthalmologic examinations, and spirometry

7.2 Secondary Endpoints

Part A

- M1-661, M2-661, M1-ivacaftor, and M6-ivacaftor PK parameters, including C_{max}, AUC_{τ}, and other PK parameters as appropriate
- Safety and tolerability of VX-661 in combination with ivacaftor as determined by AEs, clinical laboratory values (serum chemistry, hematology, coagulation studies, lipids, vitamins, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, and spirometry

Part B

- VX-661, M1-661, M2-661, ivacaftor, M1-ivacaftor, and M6-ivacaftor PK parameters, including C_{max}, AUC_{τ}, and other PK parameters as appropriate
- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline through Week 24
- Relative change in $ppFEV_1$ from baseline through Week 24
- Absolute change in weight and weight-for-age z-score from baseline at Week 24
- Absolute change in height and height-for-age z-score from baseline at Week 24
- Absolute change in body mass index (BMI) and BMI-for-age z-score from baseline at Week 24
- Absolute change in sweat chloride from baseline through Week 4
- Absolute change in sweat chloride from baseline through Week 24
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline through Week 24

[redacted]

8 STUDY DESIGN

8.1 Overview of Study Design

This is a Phase 3, 2-part (Part A and Part B), open-label, multicenter study evaluating the PK, safety, and tolerability of multiple doses of VX-661 in combination with ivacaftor in subjects 6 through 11 years of age with CF who are homozygous or heterozygous for the *F508del-CFTR* mutation. Efficacy will also be evaluated in Part B. Part A is composed of 2 weight-based cohorts, which will be enrolled simultaneously, and Part B is composed of a single cohort. Subjects who participate in Part A may participate in Part B if Part B eligibility criteria are met.

Part A

Up to approximately 16 subjects total are planned for enrollment across Cohort 1 (subjects weighing <25 kg at baseline) and Cohort 2 (subjects weighing ≥25 kg at baseline).

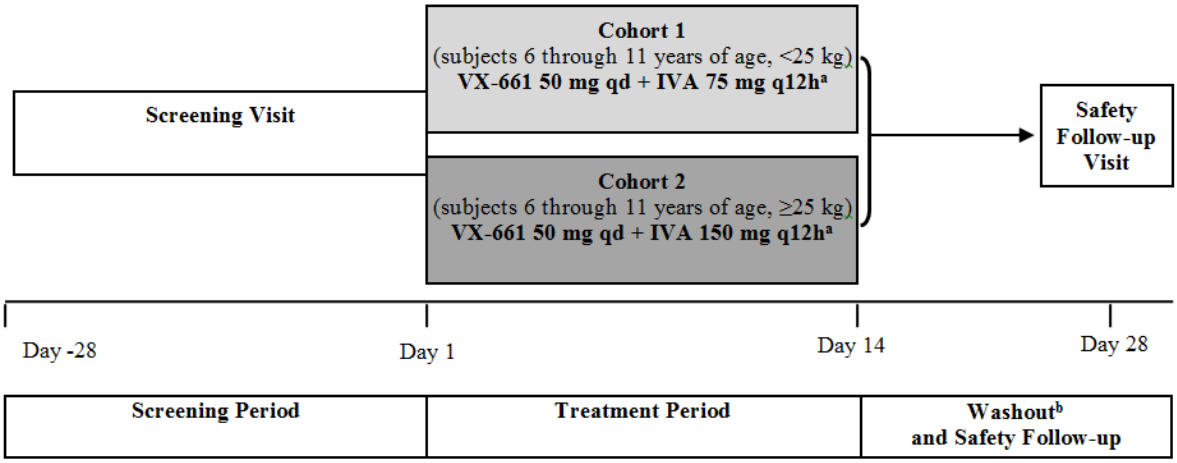
Part A includes the following:

- Screening Period (Day -28 through Day -1)
- Treatment Period (Day 1 through Day 14)
- Washout Period (Day 14 to Day 28 [± 3 days])
- Safety Follow-up Visit (14 [± 3] days after the last dose of study drug)

Figure 8-1 depicts the schematic for the Part A study design. After obtaining written informed consent (and assent, if applicable), Screening Visit assessments will be completed at any time during the period of 4 weeks (Day -28 through Day -1) before the first dose of the study drug (Day 1). During the Treatment Period, subjects will be administered VX-661 50 mg daily (qd) in combination with ivacaftor, either 75 mg (subjects <25 kg at baseline) or 150 mg (subjects ≥25 kg at baseline), every 12 hours (q12h) for 14 days. A 2-week Washout Period (Day 14 to Day 28 [± 3 days]) will be included in order to evaluate the off-drug response. A Safety Follow-up Visit is scheduled to occur 14 (± 3) days after the last dose of study drug for all subjects, including subjects who permanently discontinue from study treatment for any reason.

A review of safety, tolerability, and PK data will be completed by an internal Vertex team after Part A to select the VX-661 dose for Part B.

Figure 8-1 Schematic of Study Design for Part A



IVA: ivacaftor; n: number of subjects; q12h: every 12 hours; qd: daily.
Note: Up to approximately 16 subjects total are planned for enrollment across Cohort 1 and Cohort 2.
[a] Weight refers to weight at baseline. Study drug will be administered from Day 1 through Day 14. On Day 14, only the morning dose of study drug will be administered.
[b] A 2-week Washout Period (Day 14 to Day 28 ± 3 days) will be included in order to evaluate the off-drug response.

Part B

Approximately 56 subjects are planned for enrollment. Assuming a 10% dropout rate, approximately 50 subjects are expected to complete Part B.

Part B includes the following:

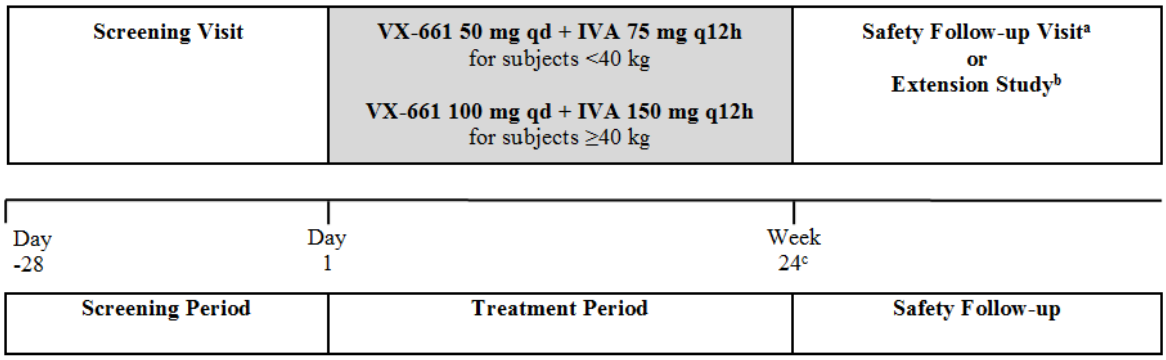
- Screening Period (Day -28 through Day -1)
- Treatment Period (Day 1 through Week 24 [± 5 days])
- Safety Follow-up Visit (4 weeks [± 7 days] after the last dose of study drug)

Figure 8-2 depicts the schematic for the Part B study design. After obtaining written informed consent (and assent, if applicable), Screening Visit assessments will be completed at any time during the period of 4 weeks (Day -28 through Day -1) before the first dose of study drug (Day 1). During the Treatment Period, subjects will be administered VX-661 50 mg qd in combination with ivacaftor 75 mg q12h (subjects <40 kg at baseline) or VX-661 100 mg qd in combination with ivacaftor 150 mg q12h (subjects ≥40 kg at baseline) for 24 weeks. No dose adjustments will be made throughout the duration of treatment in this study. At the Week 24 Visit, subjects who complete study drug treatment will be offered the opportunity to enroll in an extension study evaluating VX-661 in combination with ivacaftor (enrollment will be based on the eligibility criteria specified within the extension study). Subjects who prematurely discontinue study drug treatment are not eligible to rollover into the extension study.

A Safety Follow-up Visit is scheduled to occur 4 weeks (± 7 days) after the last dose of study drug. The Safety Follow-up Visit is not required for subjects who have enrolled in the

extension study within 28 days after the last dose of study drug. Subjects who permanently discontinue study drug treatment will have an Early Treatment Termination (ETT) Visit and a Safety Follow-up Visit.

Figure 8-2 Schematic of Study Design for Part B



IVA: ivacaftor; q12h: every 12 hours; qd: daily.
Note: Weight refers to weight at baseline.

[a] The Safety Follow-up Visit will occur 4 weeks [± 7 days] after last dose and is not required for subjects who have enrolled in the extension study within 28 days after the last dose of study drug.

[b] At the Week 24 Visit, subjects who complete study drug treatment will be offered the opportunity to enroll in an extension study evaluating VX-661 in combination with ivacaftor. Subjects who prematurely discontinue study drug treatment are not eligible to rollover into the extension study.

[c] The last dose of study drug will be the evening dose administered the day before the Week 24 Visit.

8.1.1 Screening

Part A and Part B

Screening Visit assessments are listed in Table 3-1 (Part A) and Table 3-3 (Part B).

The Screening Period will occur within 28 days before the first dose of study drug to confirm that subjects meet the selection criteria for the study. To participate in the study, the subject's parent or legal guardian must sign and date a study-specific informed consent form (ICF) and the subject must sign an assent form (if applicable) before any study-specific procedures can be performed. The ICF (and assent form, if applicable) will comply with all applicable regulations governing the protection of human subjects and will be approved by Vertex and the site's institutional review board (IRB).

To prepare for study participation, subjects will be instructed on the Study Restrictions (Section 9.3) and use of concomitant medications (Section 9.4).

8.1.1.1 Repetition of Screening Period Assessments

Part A and Part B

Repetition of any individual Screening Visit assessment(s) that do 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 may be permitted after discussion with the Vertex medical monitor or authorized designee.

- If a convincing alternative etiology is identified for elevated transaminases, exclusionary liver function test (LFT) levels may be retested within 14 days of the original Screening Visit date.

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

8.1.1.2 Rescreening

Part A and Part B

Subjects may be rescreened after discussion with, and approval from, the Vertex medical monitor or authorized designee to account for exclusionary events that may not reflect the subject's true baseline due to an acute event, which may resolve. Subjects who complete Part A or who discontinue treatment for other reasons than safety reasons and wish to participate in Part B, must be rescreened and meet all eligibility criteria before enrolling in Part B. Subjects who were not eligible to participate in Part A may be rescreened for Part B after discussion with, and approval from, the Vertex medical monitor or authorized designee.

If a subject is rescreened, all Screening Visit assessments will be repeated except for CF genotyping and the ophthalmologic examination (if the ophthalmologic examination was performed within 3 months before the Rescreening Visit). If a subject is rescreened, the screening window will begin after the first rescreening assessment has been initiated.

8.1.1.3 Extension of Screening Period Window

Part A and Part B

A subject may have the Screening Period window extended by 2 weeks after approval by the medical monitor or authorized designee for the following reasons:

- Repetition of the Screening Period assessments (Section 8.1.1.1)
- Unexpected operational or logistic delays, or to meet the eligibility criteria
- Scheduling of the ophthalmologic examination (Section 11.7.6)

8.1.2 Treatment Period

Part A and Part B

Study drug will be dispensed to the subject's legally appointed and authorized representative (e.g., parent or legal guardian) for administration to the study subjects on study days where a clinic visit is not scheduled, as described in Section 10.1.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled visit, the Vertex medical monitor or authorized designee will be notified, and the investigator will make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

Part A

Table 3-2 lists the Treatment Period Visits and assessments for Part A. Subjects will be outpatients during the Treatment Period. All visits should occur within the windows specified.

The duration of the Treatment Period is 14 days. The first dose of the study drug will be administered on Day 1, and the last dose of study drug will be the morning dose administered on Day 14 (Figure 8-1). Dosing details are given in Section 10.2. Subjects must return to the clinical site on Day 21 for PK assessments (Table 3-2).

Subjects who prematurely discontinue study drug dosing will be asked to return to the clinical site for a Safety Follow-up Visit (Section 8.1.5).

Part B

Table 3-4 lists the Treatment Period visits and assessments for Part B. Subjects will be outpatients during the Treatment Period. All visits should occur within the windows specified.

The planned duration of the Treatment Period is 24 weeks. The first dose of the study drug will be administered on Day 1 and the last dose of study drug will be the evening dose administered the day before the Week 24 Visit. Dosing details are given in Section 10.2.

8.1.3 Washout Period

Part A

A 2-week Washout Period (Day 14 to Day 28 ± 3 days) will be included in order to evaluate the off-drug response.

Part B

Not applicable

8.1.4 Safety Follow-up

Part A

Table 3-2 lists the Safety Follow-up Visit assessments for Part A. Subjects will have a Safety Follow-up Visit 14 (± 3) days after the last dose of study drug.

Part B

Table 3-4 lists the Safety Follow-up Visit assessments for Part B. Subjects will have a Safety Follow-up Visit 4 weeks (± 7 days) after the last dose of study drug. The Safety Follow-up Visit is not required for subjects who have enrolled in the extension study within 28 days after the last dose of study drug.

8.1.5 Early Discontinuation/Early Treatment Termination

Part A

Subjects who prematurely discontinue study drug dosing will be asked to return to the clinical site 14 (± 3) days after their last dose of study drug for a Safety Follow-up Visit. Safety Follow-up Visit assessments are listed in Table 3-2.

Part B

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 4 weeks ± 7 days after their last dose of study drug. The assessments performed at the Safety Follow-up Visit are listed in Table 3-4.

If the ETT Visit occurs 3 weeks or later after the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required.

During the course of study conduct, if local health authorities decline to approve, or if clinical benefit is not demonstrated for the use of VX-661 in combination with ivacaftor for the treatment of CF in a corresponding adult population, pediatric subjects with the relevant *CFTR* genotypes may be discontinued after communication to investigators and IRBs/ independent ethics committees (IECs) of the risks/benefits related to the safety and efficacy observed for the subset of adult subjects. If subjects are discontinued from the study, an ETT Visit should occur as soon as possible after the last dose of study drug and a Safety Follow-up Visit should occur approximately 4 weeks ± 7 days after the last dose of study drug.

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

8.1.6 Lost to Follow-up

Part A and Part B

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

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

8.1.7 Independent Data Monitoring Committee

Part A

An independent data monitoring committee (IDMC) will be formed using the [redacted] (Section 12.3.5.2). The IDMC objectives and operational details will be defined in a separate document (the IDMC Charter), which will be finalized before the first subject is screened in Part B. The IDMC will conduct a planned review of study data for the purpose of safety monitoring as outlined in the IDMC Charter.

Part B

The IDMC 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 reviews of study data for the purpose of safety monitoring as outlined in the IDMC Charter.

8.2 Rationale for Study Design and Study Drug Regimens

8.2.1 Study Design

This is a Phase 3, 2-part (Part A and Part B), open-label, multicenter study evaluating the PK, safety, and tolerability of multiple doses of VX-661 in combination with ivacaftor in subjects 6 through 11 years of age with CF who are homozygous or heterozygous for the *F508del-CFTR* mutation. Efficacy will also be evaluated in Part B. Part A is composed of 2 cohorts and Part B is composed of a single cohort. The open-label design is considered adequate to evaluate the PK and safety of VX-661 in combination with ivacaftor in this pediatric population. Subjects will be divided into 2 weight-based cohorts in Part A so that the relationship between VX-661 PK and body weight can be explored across the entire weight range expected in the 6 to 11 year old population.

The subjects studied are from the population that is expected to benefit from VX-661 in combination with ivacaftor. Part B is designed to evaluate the long term safety, tolerability, and PK, as well as efficacy, of VX-661 in combination with ivacaftor in the pediatric CF population. This design is in harmony with guidelines for the study of human subjects, especially children, and balances safety concerns with potential benefits for the individual.

8.2.2 Study Drug Dose and Duration

8.2.2.1 VX-661 Dose

Part A

The 50 mg qd dose of VX-661 has been selected for evaluation in pediatric subjects 6 through 11 years of age in Part A of this study. A population PK model was used to simulate VX-661 exposure in subjects weighing 15 to 40 kg to represent the pediatric population in this study. The simulations indicate that a 50 mg qd dose in subjects weighing 15 to 25 kg and 25 to 40 kg will yield exposures comparable or lower to those observed at the 100 mg qd dose in adults, which has been demonstrated to be safe and efficacious. Therefore, the dose selected for Part A is expected to be safe in pediatric subjects 6 through 11 years of age.

Part B

A review of safety, tolerability, and PK data was completed by an internal Vertex team after Part A to select the VX-661 dose for Part B. The PK data in Part A were consistent with the predictions from the population PK model. Consequently, this model was used to simulate exposures for different VX-661 doses in weight ranges expected for subjects 6 through 11 years of age. Based on these simulations, VX-661 doses of 50 mg qd in subjects weighing <40 kg and 100 mg qd in subjects weighing >40 kg were selected for Part B to match the exposures observed at the dose of 100 mg qd in subjects 12 years and older. These exposures were shown to be safe and efficacious in Phase 2 and Phase 3 clinical studies (VX11-661-101, VX13-661-103, VX14-661-106, and VX14-661-108).

8.2.2.2 Ivacaftor Dose

Part A

Ivacaftor doses have been selected to provide similar exposures to those observed at the efficacious dose in adults. Based on population PK simulations, an ivacaftor dose of 75 mg q12h in subjects 6 through 11 years of age weighing <25 kg and a dose of 150 mg q12h in subjects 6 through 11 years of age weighing ≥25 kg is expected to yield similar exposures to those observed in adults administered 150 mg q12h.

Therefore, the ivacaftor doses chosen for the pediatric population in this study (6 through 11 years of age) are:

- 75 mg q12h in subjects <25 kg at baseline
- 150 mg q12h in subjects ≥25 kg at baseline

Part B

For Part B, it was desired to provide similar IVA exposures to those observed at the efficacious dose in adults while maintaining the same TEZ:IVA ratio in adult and pediatric populations. Following review of the safety, tolerability, and PK data from Part A, additional population PK simulations of IVA were performed to evaluate the impact on IVA exposures of increasing the weight cutoff from 25 kg to 40 kg to maintain consistency with TEZ dosing and the adult TEZ:IVA ratio. As expected, these simulations demonstrated that lowering the IVA dose from 150 mg q12h to 75 mg q12h in subjects weighing between 25 kg and 40 kg lowered predicted IVA exposures. However, IVA exposures were similar to those observed at the efficacious dose in adults. Additionally, the majority of subjects still achieved IVA exposures exceeding the model-predicted EC_{90} calculated for $ppFEV_1$ in the G551D gating population. [23] Given that the IVA EC_{90} for *G551D* exceeds that for *F508del* and other mutations that are responsive to IVA in vitro (that is, these same exposures are predicted to exceed the EC90 for these mutations by even more than for G551D) [24], increasing the IVA weight cut off from 25 kg to 40 kg is not predicted to impact efficacy.

8.2.2.3 Study Drug Duration

Part A

Based on the PK of VX-661 and ivacaftor in adults, dosing for 14 days in Part A is considered sufficient to achieve steady-state exposures of VX-661, ivacaftor, and their metabolites.

Part B

The 24-week duration of dosing in Part B was chosen to provide an adequate assessment of long-term safety.

8.2.3 Rationale for Study Assessments

The safety and PK assessments are standard parameters for clinical studies in drug development and are generally recognized as reliable, accurate, and relevant to the study of subjects with CF. Ophthalmologic examinations were added to the standard safety assessments.

Ophthalmologic Examinations: A juvenile rat toxicity study performed to support dosing of ivacaftor in subjects <2 years of age demonstrated lens opacities in some animals.[19] Prior studies in rats and dogs of older age did not demonstrate similar findings. Given substantial differences between human and rat lens development, the finding is of unlikely relevance to humans. Periodic ophthalmologic examinations for children aged 11 years and younger receiving ivacaftor are being performed to confirm this interpretation. The overall data acquired to-date does not suggest an association between ivacaftor treatment and cataract development; however, a potential association has not been fully excluded.

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.

Nutritional Status (measured by weight and BMI): Malnutrition is common in patients with CF because of increased energy expenditures due to lung disease and fat malabsorption. Given that VX-661 in combination with ivacaftor is a systemic therapy, it has the potential to improve extrapulmonary manifestations of CF, including those in the gastrointestinal system. Improved nutritional status, defined as an increase in weight and/or BMI, is considered an appropriate endpoint for therapies targeting CFTR and was used in previous clinical studies of CFTR-targeted therapies (Studies VX08-770-102 and VX08-770-103). To evaluate the effect of VX-661 in combination with ivacaftor on growth, change in weight and BMI will be determined.

As children gain weight and height as part of normal growth, adjustment for age and sex is necessary to assess changes in nutritional status in a population of boys and girls in varying stages of growth. To evaluate the effect of VX-661 in combination with ivacaftor on growth and nutrition adjusted for age and sex, weight-for-age, height-for-age, BMI-for-age, and the respective z-scores will be determined. Height and weight will be collected at the study visits indicated in the schedule of assessments.

Sweat Chloride: In patients with CF, the underlying CFTR ion transport defect results in elevated sweat electrolyte levels.[25,26] 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 be diagnostic of 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 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.[27,28,29] As VX-661 in combination with ivacaftor is a systemic therapy, it has the potential to improve respiratory symptoms as well as other extrapulmonary manifestations of CF. These improvements can be captured by the non-respiratory symptoms domains of the CFQ-R. Linguistically validated versions of the CFQ-R[30,31] are available, thereby allowing consistent interpretation of the results in this global study. The CFQ-R will be used to capture and evaluate the impact of VX-661 in combination with ivacaftor on patient report of respiratory symptoms and other aspects of health-related quality of life.

[redacted]

9 STUDY POPULATION

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

9.1 Inclusion Criteria

Subjects who meet all of the following inclusion criteria will be eligible for **Part A** and **Part B**. Subjects who participate in Part A may participate in Part B if Part B eligibility criteria are met.

1. Subject (or his or her legally appointed and authorized representative) will sign and date an ICF and the subject will sign and date an assent form (if applicable) (separately for **Part A** and **Part B**).
2. Subjects (male and female) will be between the ages of 6 and 11 years, inclusive, on the date(s) of informed consent (and assent, if applicable) for each relevant part of the study (**Part A** and/or **Part B**, as applicable).
3. Subjects who weigh ≥15 kg without shoes at the Screening Visit.
4. All genotypes listed in Section 16 are eligible in **Part A**. Each genotype for which clinical benefit has been demonstrated in the corresponding adult population will be eligible in **Part B**. Genotype is to be confirmed at the Screening Visit. If the *CFTR* screening genotype result is not received before enrollment, a previous *CFTR* genotype lab report may be used to establish eligibility. Subjects who have been enrolled and whose screening genotype does not confirm study eligibility must be discontinued from the study as described in Section 9.5.

Subjects with a confirmed diagnosis of CF[37] (as determined by meeting 1 of the following criteria [5 through 8]):

5. For subjects who are homozygous for the *F508del-CFTR* mutation
   a. Confirmed diagnosis of CF defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis (as documented in the subject's medical record OR from the sweat chloride test result obtained at the Screening Visit).
6. For subjects who are heterozygous for the *F508del-CFTR* mutation and with a second *CFTR* mutation that is not likely to respond to VX-661 and/or ivacaftor therapy (refer to Section 16). Subjects with these mutations are not eligible for **Part B.**

a. Confirmed diagnosis of CF defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis (as documented in the subject's medical record OR from the sweat chloride test result obtained at the Screening Visit).

7. For subjects who are heterozygous for the *F508del-CFTR* mutation and with a second allele with a *CFTR* mutation predicted to have residual function (refer to Section 16)

   a. Confirmed diagnosis of CF defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis (as documented in the subject's medical record OR from the sweat chloride test result obtained at the Screening Visit).

   b. If the sweat chloride value is <60 mmol/L, there must be documented evidence of chronic sinopulmonary disease[37] and/or gastrointestinal disease consistent with a diagnosis of CF as judged by the principal investigator, manifest by at least 1 of the following:

      - Persistent colonization/infection, defined as ≥2 positive respiratory cultures within a 6 month period, with 1 or more typical CF pathogens (e.g., *Staphylococcus aureus*, *Haemophilus influenzae*, mucoid and nonmucoid *Pseudomonas aeruginosa*)
      - Chronic cough and sputum production
      - Persistent chest radiograph abnormalities consistent with CF pulmonary disease (e.g., bronchiectasis, atelectasis, infiltrates, hyperinflation)
      - Nasal polyps, chronic sinusitis as manifest by radiographic or computed tomographic abnormalities of the paranasal sinuses
      - Evidence of gastrointestinal disease consistent with the diagnosis of CF
      - Significant delays in growth and/or weight gain consistent with the diagnosis of CF

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

8. For subjects who are heterozygous for the *F508del-CFTR* mutation and with a second CFTR allele with a gating defect that is clinically demonstrated to be ivacaftor responsive (refer to Section 16)

a. Confirmed diagnosis of CF defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis (as documented in the subject's medical record [this value may be obtained from a record collected prior to use of Kalydeco] OR from the sweat chloride test result obtained at the Screening Visit).

b. If the sweat chloride value is <60 mmol/L, there must be documented evidence of chronic sinopulmonary disease[37] and/or gastrointestinal disease consistent with a diagnosis of CF as judged by the principal investigator, manifest by at least 1 of the following:

- Persistent colonization/infection, defined as ≥2 positive respiratory cultures within a 6 month period, with 1 or more typical CF pathogens (e.g., *Staphylococcus aureus*, *Haemophilus influenzae*, mucoid and nonmucoid *Pseudomonas aeruginosa*)
- Chronic cough and sputum production
- Persistent chest radiograph abnormalities consistent with CF pulmonary disease (e.g., bronchiectasis, atelectasis, infiltrates, hyperinflation)
- Nasal polyps, chronic sinusitis as manifest by radiographic or computed tomographic abnormalities of the paranasal sinuses
- Evidence of gastrointestinal disease consistent with the diagnosis of CF
- Significant delays in growth and/or weight gain consistent with the diagnosis of CF

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

9. Subjects with ppFEV$_1$ of ≥40 percentage points adjusted for age, sex, height, and ethnicity using the Global Lung Initiative (GLI) equation[38] at the Screening Visit (Section 11.6.1).
10. Subjects with stable CF disease as deemed by the investigator at the Screening Visit.
11. Subjects who are willing to remain on their stable CF medication regimen through Day 14 (**Part A**) or through Week 24 (**Part B**) or, if applicable, through the Safety Follow-up Visit.
12. Subjects who are able to swallow tablets.
13. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Day 1 Visit before receiving the first dose of study drug.
14. Subjects of childbearing potential who are sexually active must meet the contraception requirements outlined in Section 11.7.8.1.
15. As deemed by the investigator, the subject's legally appointed and authorized representative (e.g., parent or legal guardian) must be able to understand protocol requirements, restrictions, and instructions. The subject's legally appointed and

authorized representative should be able to ensure that the subject will comply with and is likely to complete the study as planned.

9.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will **not** be eligible for **Part A** and **Part B**.

1. History of any comorbidity reviewed at the Screening Visit that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject. For example:
   - history of cirrhosis with portal hypertension
   - 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, intracranial trauma), and autonomic neuropathy
2. Any clinically significant laboratory abnormalities at the Screening Visit that would interfere with the study assessments or pose an undue risk for the subject (as deemed by the investigator).
3. 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
     - ≥2 × ULN total bilirubin
   - Abnormal liver function defined as any increase of ≥5 × ULN ALT or AST
   - Abnormal renal function defined as glomerular filtration rate ≤45 mL/min/1.73 m^2 (calculated by the Counahan-Barratt equation)[39]
4. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug).
5. Colonization with organisms associated with a more rapid decline in pulmonary status (e.g., *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*) at the Screening Visit. The investigator could be guided by the following suggested criteria for a subject to be considered free of colonization:

- The subject should have had at least 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.

6. A standard 12-lead ECG demonstrating QTc >450 msec at the Screening Visit. If QTc exceeds 450 msec at the Screening Visit, 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.
7. History of solid organ or hematological transplantation at the Screening Visit.
8. Ongoing or prior participation in an investigational drug study or use of commercially available CFTR modulator that does not align with the following requirements:
   - A washout period of 30 days or 5 terminal half-lives of the previous investigational study drug, whichever is longer, must elapse before screening.
     - The duration of the elapsed time may be longer if required by local regulations.
   - A washout period of 28 days for investigational lumacaftor/ivacaftor or physician-prescribed Orkambi must elapse before the Day 1 Visit.
   - Investigational ivacaftor or physician-prescribed Kalydeco can be taken until the Day 1 Visit, at which time ivacaftor will be dispensed from the investigational study drug supply.

   Note: Ongoing participation in a noninterventional study (including observational studies) is permitted.
9. Use of restricted medication or food within a specified duration before the Screening Visit or first dose of study drug and/or unwillingness to maintain the restrictions as defined in Table 9-1 (**Part A**) or Table 9-2 (**Part B**).
10. History or evidence of cataract, lens opacity, Y-suture, or lamellar rings determined to be clinically significant by the ophthalmologist during the ophthalmologic examination at the Screening Visit. The Screening Visit ophthalmologic examination does not need to be repeated if there is documentation of an examination meeting protocol criteria (Section 11.7.6) that was conducted within 3 months before the start of the Screening Period. If the subject has documentation of bilateral lens removal, an ophthalmologic examination is not required and this criterion is not applicable.
11. Pregnant and nursing females.
12. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study.

9.3 Study Restrictions

Part A

To avoid variable PK results because of uncontrolled use of dietary/nutritional supplements, tobacco, juices, or other foods that may affect drug metabolizing enzymes and transporters, it is important to exclude subjects who do not meet or cannot comply with the lifestyle guidelines and study restrictions summarized in Table 9-1.

Table 9-1 Lifestyle Guidelines and Study Restrictions (Part A)

Restricted Medication/Food/ Activity[a]	Timing of Restriction	
	From (Minimum)	To
Investigational (from another study) or physician-prescribed Kalydeco	Day 1	Until last dose of study drug
Investigational or physician-prescribed Orkambi (LUM/IVA)	None allowed within 28 days before the Day 1 Visit	Completion of Safety Follow-up assessments
Other investigational drugs or devices	30 days or 5 half-lives before screening, or time determined by local requirements; whichever is longer	Completion of Safety Follow-up assessments
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of the study drug	Until last PK sample is taken
Strong and moderate CYP3A inhibitors (except Ciprofloxacin)	None allowed within 14 days before the first dose of the study drug	Until last PK sample is taken
Nonprescription medications	14 days or 5 half-lives (whichever is longer) before first study drug dose Occasional, limited ibuprofen (≤1200 mg/day) and acetaminophen at doses of ≤2 g/day is allowed for pain.	Completion of Safety Follow-up assessments
Herbal and dietary supplements	14 days before first study drug dose	Completion of Safety Follow-up assessments
Tobacco or nicotine-containing product	45 days before first study drug dose	Until last PK sample is taken
Grapefruit or grapefruit juice, pomelos, star fruit, Seville oranges or Seville orange juice	7 days before first study drug dose	Until last PK sample is taken
Orange juice, vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, brussels sprouts, mustard), and charbroiled meats	7 days before first study drug dose	Until last PK sample is taken

Table 9-1 Lifestyle Guidelines and Study Restrictions (Part A)

Restricted Medication/Food/ Activity[a]	Timing of Restriction	
	From (Minimum)	To
Alcohol[b]	Not more than 2 drinks/day before screening AND none 48 hours before first study drug dose[c]	Completion of Safety Follow-Up assessments
Caffeine	An average of no more than five 240 mL servings per day of coffee or other caffeinated beverages per day beginning at screening AND none 24 hours before first study drug dose	Until last PK sample is taken
Strenuous exercise (e.g., heavy lifting, weight training, and aerobics)[d]	• 24 hours before the Screening Visit • 24 hours before Day 1 • 24 hours before Day 7 • 24 hours before Day 14 • 24 hours before Safety Follow-up Visit	• Not applicable • After end of the Day 2 Visit • After end of the Day 7 Visit • After end of the Day 14 Visit • After the Safety Follow-up Visit

CFTR: cystic fibrosis transmembrane conductance regulator; CYP: cytochrome P450; IVA: ivacaftor; LUM: lumacaftor; PK: pharmacokinetic.
Note: The use of restricted medication in subjects with a medical need will be addressed on a case-by-case basis with the medical monitor or authorized designee. See the Study Reference Manual for a more complete list of medications prohibited/restricted in the study.
[a] Refer Section 9.4 for guidance for concomitant medications.
[b] Subjects may undergo alcohol testing if deemed appropriate by the investigator (Section 11.7.2).
[c] One drink equals 5 ounces/150 mL of wine, 12 ounces/360 mL of beer, or 1.5 ounces/45 mL of hard liquor.
[d] Walking at a normal pace will be permitted.

Detailed restrictions for fluid and food intake during study drug administration are presented in Section 10.2.

Part B

Prohibited medications and certain foods are not allowed in Part B (Screening Period through Week 24) as summarized in Table 9-2. Both VX-661 and ivacaftor are metabolized predominantly via the hepatic enzymatic pathway using 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.

Table 9-2 Lifestyle Guidelines and Study Restrictions (Part B)

	Study Period	
Restricted Medication/Food	**Screening Period**	**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	None allowed through the Safety Follow-up Visit
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of the study drug	None allowed through the Safety Follow-up Visit
Strong and moderate CYP3A inhibitors (except Ciprofloxacin)	None allowed within 14 days before the first dose of the study drug	None allowed through the Safety Follow-up Visit
Investigational (from another study) or physician-prescribed Kalydeco	None allowed after the first dose of the study drug (no restriction during the Screening Period)	Last dose of study drug
Investigational or physician-prescribed Orkambi (LUM/IVA)	None allowed within 28 days before the Day 1 Visit	None allowed through the Safety Follow-up Visit
Other investigational drugs or devices	None allowed within 30 days or 5 half-lives before screening, or time determined by local requirements; whichever is longer	None allowed through the Safety Follow-up Visit

CFTR: cystic fibrosis transmembrane conductance regulator; CYP: cytochrome P450; IVA: ivacaftor; LUM: lumacaftor.
Note: The use of restricted medication in subjects with a medical need will be addressed on a case-by-case basis with the medical monitor or authorized designee. See the Study Reference Manual for a more complete list of medications prohibited/restricted in the study.

Detailed restrictions for fluid and food intake during study drug administration are presented in Section 10.2.

9.4 Prior and Concomitant Medications

Part A and Part B

Subjects will abstain from all restricted concomitant medications as described in the exclusion criteria (Section 9.3).

Information regarding all prior and concomitant medications, including the subject's CF medications, other medications, and herbal and naturopathic remedies administered from 4 weeks before the Screening Period through the Safety Follow-up Visit will be recorded in each subject's source documents and electronic case report form (eCRF).

- It is recommended that subjects remain on their stable medication regimen for CF from 4 weeks before Day 1 through Day 14 (**Part A**) or through Week 24 (**Part B**) or, if applicable, through the Safety Follow-up Visit. Stable medication regimen is defined as the current medication regimen for CF (except for commercially available CFTR modulators) that subjects have been following for at least 4 weeks before Day 1. Subjects must not initiate long-term treatment with new medication from 28 days before Day 1 through the Safety Follow-up Visit unless discussed and approved by the Vertex medical monitor. Guidelines for stable medication regimens for CF are as follows:

- Subjects who are taking daily inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.
- Subjects who are on inhaled cycling antibiotics should continue on their prior schedule. The timing of the first dose of study drug should be synchronized as closely as possible to the first day of inhaled cycling antibiotics in the cycle.
- Subjects who alternate 2 different antibiotics monthly should remain on the same schedule during the study. The timing of the first dose of study drug should be synchronized as closely as possible to the first day of 1 of the inhaled alternating antibiotics.

- Subjects may receive doses of prednisone (or prednisolone) of up to 10 mg/day (chronically), or prednisone (or prednisolone) 60 mg qd for up to 5 days with tapering down to 10 mg/day within 2 weeks, 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, even though the effect of VX-661 in combination with ivacaftor on the QT interval has been evaluated in a thorough QT study, which demonstrated no prolongation of the QT interval. Consideration should be given to obtaining an ECG when concomitant medication known to prolong the QT interval is administered.

9.5 Removal of Subjects

Part A

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

Part B

Subjects may withdraw from the study at any time at their own request. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. If a subject has been withdrawn from study drug treatment, the subject will continue to be followed, provided the subject has not withdrawn consent.

Part A and Part B

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 an ETT Visit, if applicable (see Section 8.1.5 [Part B]), and a Safety Follow-up Visit, if applicable (see Section 8.1.5), and follow up with the subject regarding any unresolved AEs.

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

Subjects who are enrolled on the basis of a historical genotype result and whose screening genotype does not confirm study eligibility will be discontinued from study drug treatment, will undergo ETT and/or Safety Follow-up Visits per Section 8.1.5, and will then be discontinued from the study. After discontinuation of study drug treatment, these subjects will not undergo any further assessments other than those performed at the ETT and/or Safety Follow-up Visits.

9.6 Replacement of Subjects

Part A and Part B

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

10 STUDY DRUG ADMINISTRATION AND MANAGEMENT

10.1 Preparation and Dispensing

Part A and Part B

Study drug may be dispensed only under the supervision of the investigator or an authorized designee to the subject's legally appointed and authorized representative (e.g., parent or legal guardian) for administration to the study subject.

VX-661 and ivacaftor tablets and ivacaftor capsules containing granules will be dispensed at the clinical site to individual dosing containers by 2 operators, 1 of whom is a qualified pharmacist, and following national and local laws and regulations.

10.2 Administration

Part A

On Day 1 through the morning dose on Day 14 (last dose of study drug), study drug tablets and granules will be orally administered with water (tablets and granules) and applesauce or other appropriate food listed in the study manual (granules) (see details below) as shown in Table 10-1.

Table 10-1 Study Drug Administration

Subjects	Treatment Arm	Time	VX-661	IVA
Subjects <25 kg at baseline	VX-661 50 mg qd + IVA 75 mg q12h	AM	1 × 50-mg tablet	1 capsule containing 75-mg of granules
		PM	none	1 capsule containing 75-mg of granules
Subjects ≥25 kg at baseline	VX-661 50 mg qd + IVA 150 mg q12h	AM	1 × 50-mg tablet	1 × 150-mg tablet
		PM	none	1 × 150-mg tablet

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

The granule formulation will be dispensed by opening the capsules containing the granules and mixing the granules in applesauce (or other appropriate food listed in the study manual). Each dose will comprise 10 mL of applesauce in which the granules from 1 capsule are mixed. The subject will consume the applesauce and granule mixture followed by 240 mL ambient temperature water. Details on preparing the study drug will be provided in the Pharmacy Manual.

Study drug should be administered approximately 30 minutes after the start of consuming a fat-containing meal or snack according to the following guidelines:

1. The morning dose of study drug will be administered at the clinical site on Days 1, 2, 7, and 14. In the event a subject's scheduled visit occurs in the afternoon, all assessments will be collected relative to the evening dose.
2. Study drug will be administered after all predose safety and PK assessments have been performed.
3. VX-661 doses should be administered every 24 hours (± 1 hour) and ivacaftor should be administered every 12 hours (± 1 hour). For each subject, all doses (morning and evening) of study drugs should be administered at approximately the same time each day. For example, if the morning doses of study drug are administered at 08:00 hour on Day 1, all subsequent morning doses should be administered between 07:00 hour and 09:00 hour.
4. Study drug tablets (or tablets and granules, if applicable) will be administered within 5 minutes of each other.
5. On Day 1 and Day 14, subjects will fast for at least 4 hours before and 2 hours after administration of the morning dose of study drug (except for meal or snack given with study drug administration).
6. Study drug will be administered with approximately 240 mL (approximately 1 cup, 8 ounces, or half a pint) of water (tablets and granules) and 10 mL applesauce or other appropriate food listed in the study manual (granules).
7. 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.

8. On Day 1 and Day 14, subjects will be instructed not to drink fluids from 1 hour before to 1 hour after administration of the morning dose of study drug, except for approximately 240 mL (approximately 1 cup, 8 ounces, or half a pint) of water that will be used for the administration of study drug, or the beverage provided with the standard meal or snack. Outside of this time window, fluids may be taken ad libitum.
9. The last dose of study drug will be the morning dose on Day 14.

Part B

A review of safety, tolerability, and PK data was completed by an internal Vertex team after Part A to select the VX-661 dose for Part B (Section 8.1).

On Day 1 through the evening dose administered the day before the Week 24 Visit (last dose of study drug), study drug tablets will be orally administered with water as shown in Table 10-2.

Table 10-2 Study Drug Administration

Subjects	Treatment Arm	Time	VX-661/IVA	IVA
Subjects <40 kg at baseline	VX-661 50 mg qd + IVA 75 mg q12h	AM	1 × 50-mg VX-661/ 75-mg IVA tablet	none
		PM	none	1 × 75-mg tablet
Subjects ≥40 kg at baseline	VX-661 100 mg qd + IVA 150 mg q12h	AM	1 × 100-mg VX-661/ 150-mg IVA tablet	none
		PM	none	1 × 150-mg tablet

IVA: ivacaftor; q12h: every 12 hours; qd: daily.
Note: No dose adjustments will be made throughout the duration of treatment in this study. Additional details regarding study drug administration for VX-661 and ivacaftor will be included in the Pharmacy Manual.

Study drug should be administered within 30 minutes after consuming a fat-containing meal or snack according to the following guidelines:

1. Study drug should be administered q12h (± 2 hours). For each subject, all doses (morning and evening) of study drugs will be taken at approximately the same time each day. For example, the morning dose could be taken at 08:00 every morning and the evening dose could be taken at 20:00 every evening throughout the study.
2. At Week 16, subjects will fast for at least 2 hours after administration of the morning dose of study drug.
3. Study drug will be administered with approximately 240 mL (approximately 1 cup, 8 ounces, or half a pint) of water.
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 (Day 1, Day 15, Weeks 4, 8, and 16), with the exception of afternoon visits addressed below, the morning dose of study drug will be administered at the site after predose assessments have been completed.

6. If a subject's scheduled visit is to occur in the afternoon, the following guidelines must be used for administering either the morning or evening dose:
    - If the dose in the clinic will be within 6 hours of the subject's scheduled morning dose, the subject should withhold their morning dose of study drug and the morning dose will be administered in the clinic.
    - If the dose in the clinic will be more than 6 hours after the subject's scheduled morning dose, the subject should take the morning dose at home and the evening dose will be administered in the clinic. In this event, all assessments will be collected relative to the evening dose.
7. For visits after the Day 1 Visit, subjects will be instructed to bring all used and unused study drug to the site; study drug will be dispensed at each visit, as appropriate.
8. At the Week 24 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 24 Visit.

10.3 Dose Modification for Toxicity

Part A and Part B

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

10.4 Study Drug Interruption

Part A and Part B

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 11.7.3 and Section 11.7.5, respectively.

10.5 Missed Doses

Part A and Part B

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

- if the morning dose of study drug should have been taken at approximately 08:00 hour, and the subject remembers at 12:00 hour 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 hour, and greater than 6 hours have elapsed beyond the scheduled dosing time (i.e., the time is past 14:00 hour), the subject would resume dosing with the evening dose at approximately 20:00 hour.

10.6 Method of Assigning Subjects to Treatment Groups

Part A and Part B

This is an open-label study. Randomization is not required because all subjects will be treated identically (i.e., dosage is based on weight at baseline).

10.7 Packaging and Labeling

Part A and Part B

Vertex will supply the VX-661 and ivacaftor tablets and ivacaftor granules. The tablets will be supplied in child-resistant weekly blister cards and the granule formulation will be supplied in capsules in bottles. Study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing for VX-661 and ivacaftor will be included in the Pharmacy Manual.

10.8 Study Drug Supply, Storage, and Handling

Part A and Part B

The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for as described in Section 10.9.

Table 10-3 Study Drug

Drug Name	Formulation/ Route	Dosage	Packaging (Formulation Strength)	Storage Condition
Part A				
VX-661	Tablet/Oral	VX-661 50 mg	Supplied as 50-mg VX-661 tablets	Store at ≤25ºC (77ºF) with excursions to 30ºC (86ºF)
IVA	Tablet/Oral	IVA 150 mg	Supplied as 150-mg IVA tablets	Store at ≤30ºC
IVA	Granule/Oral	IVA 75 mg	Supplied as 75-mg IVA granules in capsules	Store at ≤30ºC

Table 10-3 Study Drug

Drug Name	Formulation/ Route	Dosage	Packaging (Formulation Strength)	Storage Condition
Part B				
VX-661/IVA	Fixed-dose tablet/Oral	VX-661 100 mg/ IVA 150 mg	Supplied as 100 mg VX-661/150 mg IVA tablets	≤25°C (77°F) with excursions to 30°C (86°F)
VX-661/IVA	Fixed-dose tablet/Oral	VX-661 50 mg/ IVA 75 mg	Supplied as 50 mg VX-661/75 mg IVA tablets	≤25°C (77°F) with excursions to 30°C (86°F)
IVA	Tablet/Oral	IVA 150 mg	Supplied as 150-mg IVA tablets	≤25°C (77°F) with excursions to 30°C (86°F)
IVA	Tablet/Oral	IVA 75 mg	Supplied as 75 mg IVA tablets	≤25°C (77°F) with excursions to 30°C (86°F)

IVA: ivacaftor.
Note: Additional details regarding packaging, labeling, and dispensing for VX-661 and ivacaftor will be included in the Pharmacy Manual.

10.9 Drug Accountability

Part A and Part B

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

10.10 Disposal, Return, or Retention of Unused Drug

Part A and Part B

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

10.11 Compliance

Part A and Part B

For study drug doses administered at study visits, doses will be administered under the direct supervision of the investigator or designee.

For study drug doses administered during the outpatient periods of the study, drug accountability will be assessed at each visit by counting returned dosage units. Discrepancies will be discussed with the subject and recorded in the source documents. If subjects demonstrate continued noncompliance of study drug dosing despite educational efforts, the investigator will contact the medical monitor to discuss discontinuing the subject from the study.

10.12 Blinding and Unblinding

Part A and Part B

This will be an open-label study; however, subjects and their legally appointed and authorized representative (e.g., parent or legal guardian) should not be informed of their study-related spirometry (**Part A and Part B**), sweat chloride (**Part B**) [redacted] results during the Treatment Period.

11 ASSESSMENTS

11.1 Timing of Assessments

The timing of assessments is shown in Table 3-1 through Table 3-4.

The following assessments must be performed in the order specified below when more than 1 assessment is required at a particular time point:

Part A

1. Vital signs
2. Pulse oximetry
3. Standard 12-lead ECG recordings
4. Spirometry
5. PK sampling and safety laboratory assessments (i.e., blood draws). PK blood samples collected before dosing must be collected within 60 minutes before dosing as described in Section 11.4.

Part B

1. The CFQ-R should be completed before the start of any other assessments scheduled at that visit.
2. ECGs will be performed before dosing and before any other procedures that may affect heart rate (e.g., blood draws).

[redacted]

4. PK blood samples collected before dosing must be collected within 60 minutes before dosing as described in Section 11.4.1.

Additional timing note for **Part A** and **Part B**

When repeats of an assessment are required postdose at a given visit, the assessment will be collected only once if study drug is not administered on the day of the visit (i.e., study drug interruption or permanent discontinuation of study drug).

11.2 Informed Consent/Assent

Part A and Part B

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, if applicable), approved by Vertex and the site's IRB, must be used.

11.3 Subject and Disease Characteristics

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

11.4 Pharmacokinetics

11.4.1 Blood Sampling

Part A and Part B

For the evaluation of plasma concentrations of VX-661, M1-661, M2-661, ivacaftor, M1-ivacaftor, and M6-ivacaftor, blood samples will be collected from all subjects according to the Schedule of Assessments for Part A (Table 3-2) and Part B (Table 3-4).

All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. Acceptable windows for sampling times are shown in Table 11-1. Samples collected outside of these acceptable windows will be considered protocol deviations. The exact time of the sample collection will be recorded. For each PK blood draw, a record of study drug administration will be collected as described in Section 10.2.

Table 11-1 Acceptable Pharmacokinetic Sampling Windows

Sampling Time	Time From Scheduled Sampling Allowed
0 (before morning dose)	within 60 minutes before dosing
1 hour after morning dose	± 10 minutes
2 to ≤5 hours after morning dose	± 30 minutes
24 hours after morning dose	± 60 minutes
168 hours after morning dose	± 24 hours

[redacted]

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

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

11.4.2 Processing and Handling of Pharmacokinetic Samples

Part A and Part B

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

Part A and Part B

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

[redacted]

11.6 Efficacy

[redacted]

Part B

The assessments described in Section 11.6.1 through Section 11.6.4 will be performed in Part B.

11.6.1 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines[40] at the time points noted in Table 3-1, Table 3-2, Table 3-3, and Table 3-4 according to the additional guidelines that follow.

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

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

During the Screening Period, spirometry assessments may be performed pre- or post-bronchodilator. At all other visits, all spirometry assessments should be performed "pre-bronchodilator." During the Treatment Period, spirometry assessments must be performed before dosing, unless noted otherwise. In the event that a subject forgets to withhold bronchodilator(s), spirometry should be performed according to the following:

- If a subject's Day 1 spirometry is pre-bronchodilator, but on a subsequent visit, the subject forgets to withhold bronchodilator use, a post-bronchodilator spirometry will be obtained for that visit only, and the visit will not be rescheduled.
- If on Day 1, the subject forgets to withhold his/her dose of bronchodilator, spirometry should be performed post-bronchodilator and all subsequent spirometric measurements (according to the Schedule of Assessments detailed in Table 3-4) should be performed post-bronchodilator.
- Each spirometry assessment will be recorded in the source documents as pre-bronchodilator or post-bronchodilator.

The parameters listed below will be normalized using the standards of GLI.[38]

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

All sites will be provided with spirometers and associated materials to be used for all study assessment by the central spirometry service. 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 Treatment Period.

11.6.2 Sweat Chloride

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 3-4 using an approved collection device (**Part B**). 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 test must be conducted predose relative to the morning dose of study drug during the Treatment Period. At each time point, 2 samples will be collected, 1 sample from each arm (left and right).

In addition, sweat collection must be performed at the Screening Visit (Table 3-1 [**Part A**] and Table 3-3 [**Part B**]) if an eligible sweat chloride value is not available in the subject's medical record (NOTE: for subjects who are heterozygous for the *F508del-CFTR* mutation and with a second CFTR allele with a gating defect that is clinically demonstrated to be ivacaftor responsive, this value may be obtained from a record collected prior to use of Kalydeco). For subjects using a sweat chloride value documented in their medical record 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.

Subjects and their parent/caregiver should not be informed of their study-related sweat chloride results during the Treatment Period.

11.6.3 Weight, Height, and BMI

Weight, height, and BMI (derived) will be assessed. Weight and height will be measured with shoes off at time points noted in Table 3-2 and Table 3-4. Weight and height will be measured before the dose of the study drug during the Treatment Period.

In addition, weight, height, and BMI (derived) will be assessed at the Screening Visit (Table 3-1 [**Part A**] and Table 3-3 [**Part B**]).

11.6.4 Cystic Fibrosis Questionnaire-Revised

Subjects will be asked to complete the CFQ-R in their native language. The CFQ-R will be completed before dosing at visits noted in Table 3-4. The version and format of CFQ-R will be based on age at baseline, regardless of whether the subject changes age during the study. 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 of the CFQ-R, if available, will be provided for participating centers in non-English-speaking countries (if applicable).[30,31] The CFQ-R should be completed before the start of any assessments scheduled at that visit.

11.7 Safety

Part A and Part B

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, ECGs, and physical examinations (PEs).

11.7.1 Adverse Events

Part A and Part B

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

11.7.2 Clinical Laboratory Assessments

Part A and Part B

Blood and urine samples will be analyzed at a central laboratory with the exception of urine pregnancy tests, which will be analyzed at the clinical site. Blood samples requiring a 4-hour fast for clinical laboratory assessments will be collected on Day 1 and Day 14 in Part A. Fasting is not required at other time points unless specified otherwise (see Section 10.2). All blood samples will be collected while subjects are in a seated or supine position. Specific instructions for the collection, processing, and shipment of samples will be provided in a separate Laboratory Manual.

Blood and urine samples for clinical laboratory assessments will be collected as shown in Table 3-1, Table 3-2, Table 3-3, and Table 3-4. Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1).

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

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	Platelets	Urine blood
Chloride	Reticulocytes	Specific gravity
Magnesium	Leukocytes	Urine ketones
Bicarbonate	Differential (absolute and percent):	Urine bilirubin
Phosphate	Eosinophils	Urine glucose
Bilirubin, direct bilirubin	Basophils	
Alkaline phosphatase	Neutrophils	
Aspartate aminotransferase (=SGOT)	Lymphocytes	
Alanine aminotransferase (=SGPT)	Monocytes	
Lactate dehydrogenase	**Coagulation**	
Amylase	Activated partial thromboplastin time	
Lipase	Prothrombin time	
Gamma glutamyl transferase	Prothrombin time International Normalized Ratio	
Protein		
Albumin		
Creatine kinase		
Vitamin Levels		
Vitamins A, D, E, K, and B12		
Lipid Panel		
Total cholesterol, triglycerides		
Low-density lipoprotein (LDL)		
High-density lipoprotein (HDL)		

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

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

Pregnancy testing for female subjects of childbearing potential who are not abstinent (Section 11.7.8.1):

Part A

Female subjects of childbearing potential must have a negative pregnancy test at the Screening Visit (serum test), on Day 1 (urine test), and at the Safety Follow-up Visit (serum test).

Part B

Female subjects of childbearing potential must have a negative pregnancy test at the Screening Visit (serum test), on Day 1 (urine test), and every study visit thereafter (serum test).

Part A and Part B

If a urine pregnancy test is positive on Day 1, study drug will not be administered and the pregnancy will be confirmed with a serum beta-human chorionic gonadotropin test. If confirmed, the subject is not eligible for the study.

For pregnancy tests conducted after dosing, if a serum beta-human chorionic gonadotropin test is positive, the pregnancy will be reported and the subject will be permanently withdrawn from study drug dosing as discussed in Section 11.7.8.2. If a pregnancy test is positive, the procedures outlined in Section 11.7.8.2 will be followed.

CF genotype (**Screening Period only**): CF genotyping will be performed on all subjects to confirm the genotype documented in the subject's medical record. This assessment does not need to be repeated in the case of rescreening or for confirmed subjects in Part A who wish to participate in Part B. In subjects with the *R117H* mutation, linkage to poly-T tract polymorphisms will also be determined from a second specimen. Specific instructions will be provided in the Laboratory Manual.

Alcohol Screening (**Part A Only**): Subjects may undergo random urine alcohol testing if deemed appropriate by the investigator.

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

For purposes of study conduct, only laboratory tests done in the central laboratory may be used. Local laboratories may be used at the discretion of the local investigator for management of urgent medical issues. If a local laboratory test value is found to be abnormal and clinically significant, it will be verified by the central laboratory as soon as possible after the investigator becomes aware of the abnormal result. 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 Liver Function Test Parameters

Part A and Part B

Liver Function Testing

Liver function testing (ALT, AST, GGT, ALP, direct bilirubin, and total bilirubin) must be performed as noted in Table 3-2 and Table 3-4 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 confirmatory liver function testing, a local laboratory may be used. Elevations in LFTs at the local laboratory must be reported immediately to the

medical monitor, and the subject must have the tests repeated and sent to the central laboratory as soon as possible (ideally within 48 to 72 hours).

Study Drug Interruption

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

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

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

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

Resumption of Study Drug

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

11.7.4 Physical Examinations, Vital Signs, and Pulse Oximetry

Part A and Part B

A PE of all body systems and vital signs assessment will be performed at screening and select study visits (Table 3-1, Table 3-2, Table 3-3, and Table 3-4). At other visits, symptom-directed PEs and symptom-directed vital sign assessments can be performed at the discretion of the investigator or healthcare provider.

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

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

Arterial oxygen saturation by pulse oximetry is a noninvasive measure of oxygen delivery to the tissues and has been correlated with clinical status and lung function. These will be assessed following at least a 5-minute rest in the seated or supine position.

11.7.5 Electrocardiograms

Part A and Part B

Standard 12-lead ECGs will be performed using a machine with printout according to the Schedule of Assessments (Table 3-1, Table 3-2, Table 3-3, and Table 3-4). 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 drug treatment may be required after discussion with the medical monitor. Subjects in whom treatment is discontinued for increased QTc should have their QTc monitored closely until it normalizes or returns to baseline.

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

11.7.6 Ophthalmologic Examination

Part A and Part B

Subjects will undergo an ophthalmologic examination performed by a licensed ophthalmologist at the Screening Visit (**Part A and Part B**) and at the Week 24 Visit OR the Safety Follow-up Visit (**Part B only**), which includes

- measurement of best corrected distance visual acuity of each eye

- pharmacologically dilated examination of the lens with a slit lamp

The screening ophthalmologic examination must be completed and the results reviewed to determine subject eligibility. 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. Subjects with documentation of bilateral lens removal do not need the ophthalmologic examination.

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

In addition to the Screening Visit examination, an ophthalmologic examination will be performed by a licensed ophthalmologist at or within 28 days before the Week 24 Visit OR at or within 35 days before the Safety Follow-up Visit (**Part B only**). For subjects who discontinue treatment after receiving at least 1 dose of study drug, the ophthalmologic examination may be completed at the ETT Visit OR at or within 35 days before the Safety Follow-Up Visit (if applicable [Section 8.1.5]). Subjects who have documentation of bilateral lens removal are not required to complete the eye examination at the Week 24 Visit, 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 the results of any additional ophthalmologic examinations.

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

- history of steroid use
- history of trauma to the eye
- any family history of glaucoma, congenital cataracts, or cataracts arising later in life

11.7.7 Spirometry

Refer to Section 11.6.1 for the spirometry assessment.

11.7.8 Contraception and Pregnancy

Standard contraception- and pregnancy-related information and requirements are provided below. It should be noted that some of this information and requirements may have limited applicability in this pediatric population.

11.7.8.1 Contraception

Part A

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.[19,20] Subjects should follow the contraception requirements outlined in this study protocol. Hormonal contraception is not an acceptable method of contraception for female subjects though it is acceptable for the female partners of male subjects.

At this stage in the development of VX-661 in combination with ivacaftor, participation in this study requires a commitment from the research subject and his/her partner to use at least 1 effective method of birth control. Acceptable methods of contraception for participants of this study and their partners are listed below. Methods of contraception should be in successful use from signing of consent, approximately 28 days before the first dose of study drug (unless otherwise noted), and until 90 days following the last dose of study drug.

Contraception for the couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and postovulation methods) and withdrawal are not acceptable methods of contraception.
- If the male is infertile (e.g., bilateral orchiectomy). Infertility may be documented through examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound or medical record before the first dose of the study drug.
- If the female is of non-childbearing potential, per the following:
  - 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.
- Same sex relationships.

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

Additional notes:

- Acceptable methods of contraception listed above are examples. Local requirements may prohibit the use of some of these examples. Please contact the medical monitor with any questions.
- A female condom cannot be used with male condom (as a double method of contraception) due to risk of tearing.
- Male and female subjects who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study if they become sexually active with a partner of the opposite sex.

- If applicable, additional contraception requirements may need to be followed according to local regulations and/or requirements.
- Male subjects must not donate sperm after the first dose of study drug, throughout the study, and for 90 days following the last dose of study drug.
- Female subjects and female partners of male subjects should not plan to become pregnant during the study through 90 days following the last dose of study drug.
- Male subjects whose female partner becomes pregnant through well-documented in vitro fertilization (donated sperm) or banked sperm (collected before the subject received study drug) must be compliant with the contraception requirements. In this scenario, the male subject and his female partner must commit to using barrier methods of contraception (to ensure there is no exposure of the fetus to study drug) for the duration of the study and until 90 days after the last dose of study drug.
- Female subjects should not nurse a child from the start of study drug dosing through 90 days following the last dose of study drug.
- Unique situations that may not fall within the above specifications should be discussed with the medical monitor.

Part B

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

For female subjects using oral hormonal contraceptives:

1. The oral hormonal contraceptives should be in successful use from at least 60 days before the first dose of study drug (unless otherwise noted) and until 90 days following the last dose of study drug.
2. Female subjects who change their method of contraception to hormonal contraceptive during Study 113 must use a second form of approved contraception for at least 60 days after beginning oral contraceptives.

Contraception for the couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
- If the male is infertile (e.g., bilateral orchiectomy). Infertility may be documented through examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound before the first dose of the study drug.
- If the female is of non-childbearing potential, per the following:
    - Documented hysterectomy or a bilateral oophorectomy/salpingo-oophorectomy.

- Has not achieved menarche (has not had her first menstrual period). If a female achieves menarche during the study, she will need to follow acceptable methods of contraception or abstinence.

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

Table 11-3 Acceptable Methods of Contraception

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

Important notes:

- Local requirements may prohibit the use of some of these acceptable methods listed above. Please contact the medical monitor with any questions.
- If applicable, additional contraception requirements may need to be followed according to local regulations and/or requirements.
- Male and female subjects who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study if they become sexually active.
- Female condom used with male condom (as a double method of contraception) is not an acceptable method of contraception due to risk of tearing; a different acceptable method of birth control must be used as described in Table 11-3.
- Male subjects must not donate sperm after the first dose of study drug, throughout the study, and for 90 days following the last dose of study drug.
- Female subjects and female partners of male subjects should not plan to become pregnant during the study through 90 days following the last dose of study drug.
- Female subjects should not nurse a child from the start of study drug dosing through 90 days following the last dose of study drug.

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

11.7.8.2 Pregnancy

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

If a female subject or the female partner of a male subject becomes pregnant while participating in the study, study drug must be permanently discontinued immediately. For male subjects, study drug does not need to be permanently discontinued if the female partner's pregnancy resulted from donated sperm or sperm banked before study drug exposure (Section 11.7.8.1). The investigator must notify the medical monitor and Vertex GPS within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy using the Pregnancy Information Collection Form.

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

12 STATISTICAL AND ANALYTICAL PLANS

This section presents a summary of the planned analyses for this protocol. Statistical analysis details will be provided in the Statistical Analysis Plan (SAP), and PK data 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.

12.1 Sample Size and Power

Part A

Sample size calculations were conducted to estimate the precision in determining VX-661 clearance in pediatric subjects in the 2 weight-based cohorts. The method used noncompartmental analysis-based PK parameters, such as clearance and volume, in adults with the assumption that there is similar variability in clearance in adults and pediatric subjects 6 through 11 years of age within each weight group. The calculations indicate that data from 8 subjects will allow 80% power to target a 95% CI within 60% and 140% of the geometric mean estimate of clearance for VX-661 in each pediatric subgroup (cohort).

Part B

Planned enrollment is approximately 56 subjects. Assuming a 10% dropout rate, approximately 50 subjects are expected to complete Part B. An important safety endpoint is the incidence of AEs. Table 12-1 presents estimates of the probability for observing at least 1 subject with an AE for the given incidence (θ) and sample size. With a total sample size of 50 subjects (completer), there is a 92.3% chance of observing AEs in at least 1 subject if the true incidence rate is 5%, and a 99.5% chance of observing AEs in at least 1 subject if the true incidence rate is 10%. The probabilities have been calculated by assuming a binomial distribution for the number of AEs using SAS®.

Table 12-1 Probability of Observing At Least 1 Subject With an AE in the Study if the AE Incidence (θ) is 5% and 10%

Treatment	Sample Size	θ = 5%	θ = 10%
VX-661 50 mg qd + IVA 75 mg q12h OR VX-661 100 mg qd + IVA 150 mg q12h	50	92.3%	99.5%

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

12.2 Analysis Sets

Assignment of subjects to analysis sets will be done before the clinical data lock for the study. The analysis set will be defined separately for Part A and Part B.

Safety Set (Part A and Part B)

The Safety Set will include all subjects who received at least 1 dose of study drug.

Full Analysis Set (Part B Only)

Full Analysis Set (FAS) will include subjects who carry the intended *CFTR* mutations (see Section 16) and received at least 1 dose of study drug. The FAS will be used for all efficacy analyses.

PK Set (Part A and Part B)

The PK Set is defined as subjects who received at least 1 dose of study drug and for whom the primary PK data are considered to be sufficient and interpretable.

All Subjects Set (Part A and Part B)

The All Subjects Set is defined as subjects who are eligible for study enrollment and received a subject identification number, or were dosed. All subject data listings will be presented using the All Subjects Set, unless otherwise specified.

12.3 Statistical Analysis

This section presents a summary of the planned statistical analyses of safety and efficacy data. The Vertex Biometrics department or a designated contract research organization (CRO) will analyze the data derived from this study. SAS 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. Details of additional supportive efficacy and safety analyses not included in the protocol may be provided in the SAP.

12.3.1 General Considerations

Data from Part A and Part B will be analyzed separately.

All individual subject data for those who were eligible for study enrollment and received a subject identification number, or were dosed, will be presented in data listings.

Continuous variables will be summarized by the treatment group (VX-661 50 mg qd + ivacaftor 75 mg q12h, VX-661 50 mg qd + ivacaftor 150 mg q12h) and overall for Part A and by treatment group (VX-661 50 mg qd + ivacaftor 75 mg q12h, VX-661 100 mg qd + ivacaftor 150 mg q12h) and overall for Part B using the following descriptive summary statistics: number of subjects (n), mean, standard deviation (SD), standard error (SE), median, minimum value (min), and maximum value (max). The precision of the measurement for each continuous variable will be specified in the SAP.

Categorical variables will be summarized by the treatment group (VX-661 50 mg qd + ivacaftor 75 mg q12h, VX-661 50 mg qd + ivacaftor 150 mg q12h) and overall for Part A and by treatment group (VX-661 50 mg qd + ivacaftor 75 mg q12h, VX-661 100 mg qd + ivacaftor 150 mg q12h) and overall for Part B using counts and percentages. Percentages will be presented to 1 decimal place.

Treatment emergent (TE) period for Part A will correspond to data from the first dose of study drug in Part A to the Safety Follow-up Visit or 14 days after the last dose in Part A for subjects who do not have a Safety Follow-up Visit. Similarly, the TE period for Part B will correspond to data from first dose of study drug in Part B through the Safety Follow-up Visit or 28 days after the last dose in Part B for subjects who do not have an Safety Follow-up Visit.

Baseline for Part A is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in Part A. For ECGs, baseline will be the average of the 3 pretreatment measurements on Day 1. For sweat chloride, the baseline value will be the mean of assessment values on the left and the right arm at the most recent time point prior to the first dose of study drug. The measurement end time should also be before dosing to be considered in the calculation for baseline sweat chloride. Baseline for Part B will be similarly defined.

Absolute change from baseline will be calculated as post-baseline value – baseline value.

Relative change from baseline will be calculated as 100 x (post-baseline value – baseline value)/ baseline value.

12.3.2 Background Characteristics

Subject disposition, demographic and baseline characteristics, prior and concomitant medications, study drug exposure, and other background characteristics will be summarized by the treatment group (VX-661 50 mg qd + ivacaftor 75 mg q12h, VX-661 50 mg qd + ivacaftor 150 mg q12h) and overall for Part A and by treatment group (VX-661 50 mg qd + ivacaftor 75 mg q12h, VX-661 100 mg qd + ivacaftor 150 mg q12h) and overall for Part B. All summaries described above will be based on the Safety Set for Part A and the FAS for Part B, unless otherwise specified.

12.3.2.1 Subject Disposition

Part A

The number and percentage of subjects in the following categories: All Subjects Set and Safety Set will be summarized. In addition, the number and percentage (based on Safety Set) of subjects in each disposition category (e.g., completed treatment, completed study; with a

breakdown of the reason for study discontinuation or treatment discontinuation) will be summarized.

Part B

The number and percentage of subjects in the following categories: All Subjects Set, FAS, and Safety Set will be summarized. In addition, the number and percentage (based on FAS) of subjects in each disposition category (e.g., completed treatment, completed study; with a breakdown of the reason for study discontinuation or treatment discontinuation) will be summarized.

12.3.2.2 Demographics and Baseline Characteristics

Demographic, background (e.g., medical history), and baseline characteristics will be summarized separately for Part A and Part B. Important Protocol deviations will be provided as a subject data listing.

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

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

12.3.2.3 Prior and Concomitant Medications

Medications used in this study will be coded by using the World Health Organization Drug Dictionary Enhanced.

Part A

Medications in Part A will be categorized as the following:

- **Prior medication:** any medication that started before the first dose of study drug in Part A, regardless of when it ended.
- **Concomitant medication:** medication continued or newly received during the TE period for Part A.
- **Post-treatment medication:** medication continued or newly received after the TE period for Part A. For those subjects from Part A who enrolled in Part B, medications that continued or were newly received on or after the first dose of study drug in Part B will not be considered as post-treatment medication.

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

Prior and post-treatment medications will only be listed and not summarized. The concomitant medications will be summarized descriptively based on the Safety Set.

Part B

Medications in Part B will be categorized as the following:

- **Prior medication:** any medication that started before the first dose of study drug in Part B, regardless of when it ended.
- **Concomitant medication:** medication continued or newly received during the TE period for Part B.
- **Post-treatment medication:** medication continued or newly received after the TE period for Part B.

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

The prior medications and concomitant medications will be summarized descriptively based on the FAS. Post-treatment medications will only be listed.

12.3.2.4 Study Drug Exposure and Compliance

Part A

Duration of study drug exposure will be summarized for the Safety Set in terms of duration of treatment a subject received (in days), defined as the last day minus the first day of study drug plus 1 within Part A.

Part B

Duration of study drug exposure will be summarized for the FAS in terms of duration of treatment a subject received (in days), defined as the last day minus the first day of study drug plus 1 within Part B.

Study drug compliance will be measured by the exposure ratio, which is calculated as follows:

$$100 \times [1 - (\text{Total number of days study drug interrupted}) / (\text{Duration of study drug exposure})].$$

The total number of days of study drug interrupted is defined as the sum of (number of days of study drug interrupted in each interruption interval); where number of days of study drug interrupted in each interval is defined as the interruption end date - the corresponding interruption start date + 1.

Duration of treatment and exposure ratio will be summarized using descriptive statistics.

12.3.3 Efficacy Analysis

Analysis of efficacy is not a primary or secondary objective of Part A. [redacted]

For Part B, assessment of efficacy is a secondary objective. The rest of the section will describe efficacy analysis of data from Part B.

12.3.3.1 Analysis of Primary Efficacy Variables

Not Applicable

12.3.3.2 Analysis of Secondary Efficacy Variables

Part A

Not applicable

Part B

A summary of observed values and change from baseline by treatment group (VX-661 50 mg qd + ivacaftor 75 mg q12h, VX-661 100 mg qd + ivacaftor 150 mg q12h) and overall will be provided for all secondary efficacy variables based on FAS.

Absolute change in $ppFEV_1$ from baseline through Week 24:

Absolute change from baseline in $ppFEV_1$ will be analyzed using a restricted maximum likelihood (REML)-based mixed effect model repeated measures (MMRM) approach that would include 'treatment', 'visit', and 'treatment by visit' interaction as fixed, categorical effects and 'baseline $ppFEV_1$' as continuous, fixed covariate. An unstructured (co)variance structure will be used to model the within-subject errors. If the model fails to converge, a compound symmetry covariance structure will be considered. The degrees of freedom of the denominator will be approximated by the Kenward-Roger's method.[41] The estimated mean change from baseline through Week 24 within each treatment group and the overall treatment will be calculated using appropriate contrasts. The corresponding LS means, *P* value and the 95% CI will be calculated and presented in a table. The primary assessment of efficacy will be based on these estimates.

The estimated mean changes at post-baseline visits within each treatment group and the overall treatment will also be presented. The least squares (LS) means, *P* values and the 95% CIs will be presented in a table. The LS means (95% CI) for change from baseline at each visit will be plotted for the individual treatment groups and the overall treatment group.

Additional supportive analysis and sensitivity analysis may be described in the SAP.

Relative change in $ppFEV_1$ from baseline through Week 24: Analysis of this variable will be performed using the same approach as described for the absolute change in $ppFEV_1$ from baseline.

Absolute change in weight (/weight-for-age z-score) from baseline at Week 24: Analysis of this variable will be similar to that for the absolute change in $ppFEV_1$ from baseline. The MMRM will use baseline weight (/weight-for-age z-score) as covariate instead of baseline $ppFEV_1$. For this variable, the assessment of efficacy will be primarily based on Week 24.

Absolute change in height (/height-for-age z-score) from baseline at Week 24: Analysis of this variable will be similar to that for the absolute change in $ppFEV_1$ from baseline. The MMRM will use baseline height (/height-for-age z-score) as covariate instead of baseline $ppFEV_1$. For this variable, the assessment of efficacy will be primarily based on Week 24.

Absolute change in BMI (/BMI-for-age z-score) from baseline at Week 24: Analysis of this variable will be similar to that for the absolute change in $ppFEV_1$ from baseline. The MMRM will use baseline BMI (/BMI-age z-score) as covariate instead of baseline $ppFEV_1$. For this variable, the assessment of efficacy will be primarily based on Week 24.

Absolute changes in sweat chloride from baseline through Week 4 and through Week 24: Analysis of this variable will be performed using the same approach as described for the absolute change in $ppFEV_1$ from baseline. The MMRM will use baseline sweat chloride value as covariate instead of baseline $ppFEV_1$. The estimated mean change from baseline through Week 4 and Week 24 within each treatment group and the overall treatment will be calculated using appropriate contrasts. The corresponding LS means, *P* value, and the 95% CI will be calculated and presented in a table. For this variable, the assessment of efficacy will be primarily based on the estimates for mean change from baseline through Week 24. Note that for each scheduled sampling time point, 1 sample from each arm would be obtained. The data analysis will use the average of the results from the 2 samples.

Absolute change in the CFQ-R respiratory domain score from baseline through Week 24: Analysis of this domain will be similar to that for the absolute change in $ppFEV_1$ from baseline. The MMRM will use the baseline CFQ-R respiratory domain score as a covariate instead of baseline $ppFEV_1$.

12.3.4 Safety Analysis

Safety is a secondary objective of Part A, and the primary objective of Part B. The safety endpoints included for analyses are as follows:

Part A and Part B

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (serum chemistry, hematology, coagulation studies, lipids, vitamins, and urinalysis)
- Standard 12-lead ECGs
- Vital signs
- Pulse oximetry
- Ophthalmologic examinations (**Part B**)
- Spirometry

Safety analyses will use the Safety Set. All safety analyses will be based on the set of data associated with the TE period for Part A and Part B. The data will be summarized by the treatment group (VX-661 50 mg qd + ivacaftor 75 mg q12h, VX-661 50 mg qd + ivacaftor 150 mg q12h) and overall for Part A and by treatment group (VX-661 50 mg qd + ivacaftor 75 mg q12h, VX-661 100 mg qd + ivacaftor 150 mg q12h) and overall for Part B.

12.3.4.1 Adverse Events

Part A

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

- **Pretreatment AE:** any AE that started before the first dose of study drug in Part A.
- **TEAE:** any AE that increased in severity or that was newly developed during the TE period for Part A.
- **Post-treatment AE:** any AE that increased in severity or that was newly developed after the TE period for Part A. For subjects from Part A who enrolled in Part B, an AE that increased in severity on or after the first dose of study drug in Part B will not be considered as a post-treatment AE.

Part B

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

- **Pretreatment AE:** any AE that started before the first dose of study drug in Part B.
- **TEAE:** any AE that increased in severity or that was newly developed during the TE period for Part B.
- **Post-treatment AE:** any AE that increased in severity or that was newly developed after the TE period for Part B.

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.

Part A and Part B

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

- All TEAEs
- TEAEs by strongest 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). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once, only the maximum severity level will be presented in the severity summaries, and the strongest

relationship level in the relationship summaries. An AE overview table will be provided. 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 pretreatment and post-treatment AEs, will be presented in individual subject data listings.

12.3.4.2 Clinical Laboratory Assessments

Part A and Part B

The raw values and change from baseline values of the continuous laboratory parameters will be summarized in SI units at each scheduled time point during the TE period. In addition for Part B, the mean value of liver function parameters at each visit will be plotted by the treatment group (VX-661 50 mg qd + ivacaftor 75 mg q12h, VX-661 100 mg qd + ivacaftor 150 mg q12h) and overall.

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

Results of urinalysis will be presented in individual subject data listings only. Additionally, a listing containing individual subject laboratory measurements outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

12.3.4.3 Electrocardiogram

Part A and Part B

A summary of raw values and change from baseline values will be provided at each scheduled time point during the TE period for the following standard digital ECG measurements: PR, QT, and QTc for HR interval (QTcF); QRS duration; and HR. In addition for Part B, the mean QTcF value at each visit will be plotted by treatment group (VX-661 50 mg qd + ivacaftor 75 mg q12h, VX-661 100 mg qd + ivacaftor 150 mg q12h) and overall.

The number and percentage of subjects with at least 1 threshold analysis event during the TE period will be tabulated. The threshold analysis criteria for ECG data will be provided in the SAP.

Additional ECG analyses may be described in the SAP.

12.3.4.4 Vital Signs

Part A and Part B

The raw values and change from baseline values during the TE period will be summarized at each scheduled time point: systolic and diastolic blood pressure (mm Hg), body temperature (°C), heart rate (HR) (beats per minute [bpm]), and respiratory rate (breaths per minute).

The number and percentage of subjects with at least 1 threshold analysis event during the TE period will be tabulated. The threshold analysis criteria for vital signs data will be provided in the SAP.

Additional vital sign analyses may be described in the SAP.

12.3.4.5 Physical Examination

Part A and Part B

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

Part A and Part B

A summary of raw values and change from baseline values during the TE period will be provided at each scheduled time point for the percent of oxygen saturation by pulse oximetry. In addition for Part B, the mean percent of oxygen saturation at each visit will be plotted by treatment group (VX-661 50 mg qd + ivacaftor 75 mg q12h, VX-661 100 mg qd + ivacaftor 150 mg q12h) and overall.

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

12.3.4.6.2 Ophthalmologic Examinations

Part A and Part B

The ophthalmologic examination results will be presented in individual subject data listings.

12.3.4.6.3 Spirometry

Part A

Spirometry data will be listed and descriptively summarized.

Part B

The following summary regarding the decline in spirometry will be provided:

- Number and percentage of subjects with ≥10 or ≥20 percentage points decrease in average absolute change from baseline through Week 24 for $ppFEV_1$.
- Number and percentage of subjects with ≥0.10 L or ≥0.20 L decrease in average absolute change from baseline through Week 24 for FEV_1.

Subjects with ≥10 percentage points decrease in average absolute change from baseline through Week 24 for $ppFEV_1$ or ≥0.10 L decrease in the average absolute change from baseline through Week 24 for FEV_1 will be listed.

12.3.5 Interim and IDMC Analyses

12.3.5.1 Interim Analysis

Part A

Not applicable

Part B

Interim analyses may take place at any time during the study if warranted by the ongoing data, and/or deemed necessary by the internal Vertex team.

12.3.5.2 IDMC Analysis

Part A and Part B

Details of the IDMC (Section 8.1.7) analysis will be provided in the IDMC analysis plan.

12.4 Clinical Pharmacology Analysis

A detailed description of the clinical pharmacology analyses will be provided in the CPAP.

PK parameters of VX-661, M1-661, M2-661, ivacaftor, M1-ivacaftor, and M6-ivacaftor will be estimated using standard noncompartmental methods. The key PK parameters are C_{max} and AUC_{τ}. All PK parameters will be summarized using descriptive statistics for each group. Further details of the planned PK analysis will be provided in the CPAP.

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, 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, or
  - prior to the first dose of study drug in the extension study (**Part B**).

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 CRF and source document. AEs for subjects who are screened but not subsequently enrolled in the study will be recorded only in the subject's source documents. The following data will be documented for each AE:

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

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and non-serious AEs. The guidance available at the following website will be consulted: Common Terminology

Criteria for Adverse Events (CTCAE), Version 4.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed August 2012). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." In considering the severity of an AE in a pediatric subject, the investigator will consider that reference ranges for pediatric clinical laboratory parameters may differ from those given in the CTCAE. The severity of an AE that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

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

13.1.1.5 Adverse Event Causality

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

Table 13-2 Classifications for AE Causality

Classification	Definition
Related	There is an association between the event and the administration of investigational study drug, a plausible mechanism for the event to be related to the investigational study drug and causes other than the investigational study drug have been ruled out, and/or the event re-appeared on re-exposure to the investigational study drug.
Possibly related	There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
Unlikely related	The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.
Not related	The event is related to an etiology other than the investigational study drug (the alternative etiology will be documented in the study subject's medical record).

13.1.1.6 Study Drug Action Taken

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

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

Classification	Definition
Dose not changed	Study drug dose not changed in response to an AE
Dose reduced	Study drug dose reduced in response to an AE
Drug interrupted	Study drug administration interrupted in response to an AE
Drug withdrawn	Study drug administration permanently discontinued in response to an AE
Not applicable	Action taken regarding study drug administration does not apply. "Not applicable" will be used in circumstances such as when the investigational treatment had been completed before the AE began and no opportunity to decide whether to continue, interrupt, or withdraw treatment is possible.

13.1.1.7 Adverse Event Outcome

An AE will be followed until the investigator has determined and provided the final outcome. The outcome will be classified according to the categories shown in Table 13-4.

Table 13-4 Classifications for Outcome of an AE

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

13.1.1.8 Treatment Given

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

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

An SAE is any AE that meets any of the following outcomes:

- Fatal (death, regardless of cause, that occurs during participation in the study or occurs after participation in the study and is suspected of being a delayed toxicity due to administration of the study drug)

- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- Congenital anomaly or birth defect
- Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., an allergic bronchospasm requiring intensive treatment in an emergency room or at home)

If a subject has a hospitalization or procedure (e.g., surgery) for an event or condition that occurred before the subject signed the ICF, and the hospitalization or procedure was planned before the subject signed the ICF, the hospitalization or procedure will not be considered to indicate an SAE, unless an AE caused the hospitalization or procedure to be rescheduled sooner or to be prolonged relative to what was planned. In addition, hospitalizations clearly not associated with an AE (e.g., social hospitalization for purposes of respite care) will not be considered to indicate an SAE.

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

13.1.2.2 Documentation of Serious Adverse Events

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 (SUSARs) involving the study drug(s) to all regulatory authorities and participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable. In addition, Vertex, or authorized designee, will be responsible for the submission of safety letters to central IECs.

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

13.2 Administrative Requirements

13.2.1 Ethical Considerations

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

13.2.2 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject or legal representative or guardian (if applicable), and assent will be obtained from the subject (if applicable), before study participation. The method of obtaining and documenting the informed consent and assent (if applicable) and the contents of the consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

13.2.3 Investigator Compliance

No modifications to the protocol will be made without the approval of both the investigator and Vertex. Changes that significantly affect the safety of the subjects, the scope of the

investigation, or the scientific quality of the study (i.e., efficacy assessments) will require IRB/IEC notification before implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. Vertex will submit all protocol modifications to the required regulatory authorities.

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

13.2.4 Access to Records

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

13.2.5 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all CRFs, study reports, and communications relating to the study will identify subjects by assigned subject numbers and access to subject names linked to such numbers shall be limited to the site and the study doctor and shall not be disclosed to Vertex. As required by applicable laws and regulations in the countries in which the study is being conducted, the investigator will allow Vertex and/or its representatives access to all pertinent medical records to allow for the verification of data gathered in the CRFs/SAE forms and the review of the data collection process. The FDA and regulatory authorities in other jurisdictions, including the IRB/IEC, may also request access to all study records, including source documentation, for inspection.

For sites participating in the study in the US, and in accordance with the Health Insurance Portability and Accountability Act and associated regulations (“HIPAA”), an executed HIPAA authorization shall be obtained by the site from each subject (or the legal representative of the subject) before research activities may begin. Each HIPAA authorization shall comply with all HIPAA requirements including authorization allowing the site access to and use of the subject’s personally identifiable health information, authorization for the site to disclose such information to Vertex, the FDA and other parties requiring access under the Protocol, and statements as to the purpose for which such information may be used and for how long.

13.2.6 Record Retention

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

records, custody will be transferred to a person willing to accept the responsibility and Vertex will be notified.

13.2.7 Study Termination

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

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

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

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

13.3 Data Quality Assurance

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

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

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

13.4 Monitoring

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

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

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

13.5 Electronic Data Capture

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

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

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

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

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

13.6 Publications and Clinical Study Report

[redacted]

[redacted]

13.6.2 Clinical Study Report

A clinical study report, written in accordance with the ICH E3 Guideline, will be submitted in accordance with local regulations.

14 REFERENCES

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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX15-661-113	Version #: 3.0	Version Date 19 July 2017
Study Title: A Phase 3, Open-label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661 in Combination With Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous or Heterozygous for the *F508del-CFTR* Mutation		

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

[redacted]

15.2 Investigator Signature Page

Protocol #: VX15-661-113	Version #: 3.0	Version Date 19 July 2017
Study Title: A Phase 3, Open-label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661 in Combination With Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous or Heterozygous for the *F508del-CFTR* Mutation		

I have read Protocol VX15-661-113, Version 3.0 and agree to conduct the study according to its terms. I understand that all information concerning VX-661/ivacaftor and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date

16 APPENDIX A: *CFTR* ALLELE MUTATIONS

Subjects can either be homozygous for the *F508del-CFTR* mutation, or heterozygous for the *F508del-CFTR* mutation.

Heterozygous subjects must have *F508del* on 1 allele and a second *CFTR* allele that meets at least 1 of the following criteria:

- Encodes a mutation predicted to have residual function
- Encodes a mutation with a gating defect clinically demonstrated to be ivacaftor-responsive (subjects are eligible for **Part A** and may be eligible for **Part B** if clinical benefit has been demonstrated in the corresponding adult population)
- Encodes a mutation that is not likely to respond to VX-661 and/or ivacaftor therapy (subjects are not eligible for **Part B**)

The lists below represent acceptable mutations for the second *CFTR* allele for heterozygous subjects.

CFTR Mutations Predicted to Have Residual Function

2789+5G→A	D110E	A455E	F1074L
3849+10kbC→T	D110H	D579G	D1152H
3272-26A→G	R117C	S945L	D1270N
711+3A→G	E193K	S977F	E831X
E56K	L206W	F1052V	
P67L	A1067T	K1060T	
R74W	R352Q	R1070W	

Note: Characteristics of residual function mutations: population-level average sweat chloride <86 mmol/L (1 standard deviation from the average sweat chloride for the most common processing and trafficking mutation based on CFTR2, *F508del-CFTR*), incidence of pancreatic insufficiency ≤50% based on subjects with at least 1 copy of the mutation from epidemiologic data(CFTR2) or published literature[42-49] and in vitro response to ivacaftor, defined as an increase in percent normal chloride transport of ≥10 percentage points in transfected FRT cells expressing the CFTR form produced by the mutation.

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.

The list below represents acceptable mutations for CFTR mutations that are not likely to respond to VX-661 and/or ivacaftor therapy; however, this list is non-exhaustive and investigators should contact the medical monitor regarding other mutations that may also meet study eligibility criteria. Subjects with these mutations are not eligible for **Part B.**

CFTR Mutations That Are Not Likely to Respond to VX-661 and/or Ivacaftor Therapy (Not eligible for Part B)

Criteria	Mutation				
Truncation mutations • %PI >50% and/or $SwCl^-$ >86 mmol/L • no full-length protein	Q39X	Q290X	G542X	R792X	R1162X
	W57X	G330X	Q552X	E822X	S1196X
	E60X	W401X	R553X	W846X	W1204X
	R75X	Q414X	E585X	R851X	S1255X
	E92X	S434X	G673X	Q890X	W1282X
	Q98X	S466X	R709X	S912X	Q1313X
	Y122X	S489X	K710X	W1089X	
	L218X	Q493X	L732X	Y1092X	
	Q220X	W496X	R764X	E1104X	
	C276X	Q525X	R785X	R1158X	
Canonical splice mutations • %PI >50% and/or $SwCl^-$ >86 mmol/L • no or little mature mRNA	621+1G→T	405+3A→C	1717-1G→A	2622+1G→A	4374+1G→T
	711+1G→T	406-1G→A	1811+1.6kbA→G	3120+1G→A	
	711+5G→A	621+1G→T	1811+1G→C	3120G→A	
	712-1G→T	1248+1G→A	1812-1G→A	3850-1G→A	
	405+1G→A	1341+1G→A	1898+1G→A	4005+1G→A	
Frameshift mutations • %PI >50% and/or $SwCl^-$ >86 mmol/L • garbled or truncated protein	663delT	3905insT	1677delTA	3007delG	2043delG
	2183AA→G	2184delA	3876delA	574delA	2869insG
	CFTRdele2,3	1078delT	2307insA	2711delT	3600+2insT
	3659delC	1154insTC	4382delA[a]	3791delC	3737delA
	394delTT	2183delAA	4016insT	CFTRdele22,23	4040delA
	2184insA	2143delT	2347delG	457TAT→G	541delC

CFTR Mutations That Are Not Likely to Respond to VX-661 and/or Ivacaftor Therapy (Not eligible for Part B)

Criteria	Mutation				
Class II, III, IV mutations not responsive to ivacaftor or VX-661 • %PI >50% and/or $SwCl^-$ >86 mmol/L, OR • not responsive in vitro to ivacaftor and VX-661)	A46D[b]	S341P[b]	R560T	R1066C	N1303K
	T338I[c]	L467P[b]	R560S	R1066M	R347H
	R347P	I507del	A561E	L1077P[b]	
	L927P	V520F	Y569D[b]	H1085R[b]	
	G85E	A559T[b]	L1065P	M1101K	

%PI: percentage of subjects who are pancreatic insufficient; $SwCl^-$: sweat chloride.

Notes: *CFTR* mutations that are not likely to respond to VX-661 and/or ivacaftor therapy were defined using 3 major sources: biological plausibility for the mutation to respond (i.e., class), evidence of clinical severity on a population basis based on the patient registry CFTR2 (average sweat chloride >86 mmol/L, percentage of patients with pancreatic insufficiency [%] is >50%), and in vitro testing (mutations that responded with chloride transport <10% of wild-type CFTR were considered minimal function and nonresponsive). The clinical severity criteria (average sweat chloride >86 mmol/L, %PI >50%) do not specifically apply to the individual subjects to be enrolled in this study, but were used to classify the mutation status.

[a] PI frequency is consistent with a residual function mutation, but this mutation is included because of SwCl- data and biological rationale, which suggests that this type of mutation should be severe and not responsive.

[b] Unpublished data.

[c] PI frequency is consistent with a residual function mutation, but this mutation is included because of SwCl- data, low baseline in vitro conductance, and failure for ivacaftor to improve conductance by at least 10% over baseline.

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