1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety of VX-152 Combination Therapy in Adults With Cystic Fibrosis

Vertex Study Number: VX16-152-102

[redacted]

Date of Protocol: 14 April 2017 (Version 3.0)
Replaces 27 January 2017, Version 2.0

Vertex Pharmaceuticals Incorporated
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2 PROTOCOL SYNOPSIS

Title A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety of VX-152 Combination Therapy in Adults With Cystic Fibrosis

Brief Title A Study Evaluating the Safety of VX-152 Combination Therapy in Adults With Cystic Fibrosis

Clinical Phase and Clinical Study Type Phase 2 safety

Objectives

Primary Objectives

- To evaluate the safety and tolerability of VX-152 in triple combination (TC) with VX-661 and ivacaftor (IVA) in adults with cystic fibrosis (CF)

Secondary Objectives

- To evaluate the pharmacodynamic (PD) effect of VX-152 in TC with VX-661 and IVA on CFTR function
- To evaluate the efficacy of VX-152 in TC with VX-661 and IVA
- To evaluate the pharmacokinetics (PK) of VX-152 when administered in TC with VX-661 and IVA
- To evaluate the PK of VX-661, IVA, and their respective metabolites when administered with VX-152

Endpoints

Primary Endpoints

- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, standard 12-lead electrocardiograms (ECGs), vital signs, and pulse oximetry

Secondary Endpoints

- Absolute change in sweat chloride concentrations from baseline at Day 15 (Parts 1 and 2) and through Day 29 (Part 2, Cohort 2B only)
- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline at Day 15 (Parts 1 and 2) and through Day 29 (Part 2, Cohort 2B only)
- Relative change in $ppFEV_1$ from baseline at Day 15 (Parts 1 and 2) and through Day 29 (Part 2, Cohort 2B only)
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline at Day 15 (Parts 1 and 2) and at Day 29 (Part 2, Cohort 2B only)
- PK parameters of VX-152, VX-661, M1-661, IVA, and M1-IVA

[redacted]

Number of Subjects Up to approximately 72 subjects will be randomized: up to approximately 36 subjects in each of Part 1 and Part 2

Study Population Male and female subjects with CF, 18 years of age or older

Part 1: *F508del*/minimal function (MF) genotype

Part 2: *F508del*/*F508del* genotype

Investigational Drug

Active substance: VX-152

Activity: CF transmembrane conductance regulatory (CFTR) corrector (increased chloride ion [Cl^-] secretion)

Strength and route of administration: 100-mg tablet for oral administration

Active substance: VX-661 and IVA

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

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

Active substance: IVA

Activity: CFTR potentiator (increased Cl^- secretion)

Strength and route of administration: 150-mg IVA (light blue) film-coated tablet for oral administration

Active substance: not applicable

Activity: VX-152-matching placebo, VX-661/IVA-matching placebo, IVA-matching placebo

Strength and route of administration: 0-mg film-coated matching placebo tablets for oral administration

Study Duration

Part 1

The total study duration is approximately 10 weeks. Subjects will receive study drug for approximately 2 weeks.

Part 2

The total study duration is approximately 16 weeks for subjects in Cohort 2A and 18 weeks for subjects in Cohort 2B.

Study drug will be administered for approximately 8 weeks in Cohort 2A and approximately 10 weeks in Cohort 2B.

Study Design

This is a Phase 2, 2-part (Parts 1 and 2), randomized, double-blind, placebo- and VX-661/IVA-controlled, parallel-group, multicenter study designed to evaluate the safety of VX-152 in TC with VX-661 and IVA.

Parts 1 and 2 will enroll multiple cohorts, with each cohort evaluating 1 dose level of VX-152 as part of TC with VX-661/IVA (100 mg daily [qd]/150 mg every 12 hours [q12h]). Each cohort will enroll up to approximately 12 subjects in Part 1 and Part 2 Cohort 2A and up to approximately 24 subjects in Part 2 Cohort 2B. Subjects in all cohorts will be randomized 3:1 (active TC:comparator). Triple placebo will be the comparator in Part 1, and VX-661/IVA will be the comparator in Part 2.

Up to 3 cohorts are planned for Part 1 (Cohorts 1A, 1B, and 1C). Up to 2 cohorts are planned for Part 2 (Cohorts 2A and 2B). The doses of VX-152 planned for evaluation are 100 mg q12h in Cohort 1A, 200 mg q12h in Cohorts 1B and 2A, and 300 mg q12h in Cohorts 1C and 2B. The dose of VX-152 may be adjusted to be lower or the same as the dose level evaluated in the previous cohort.

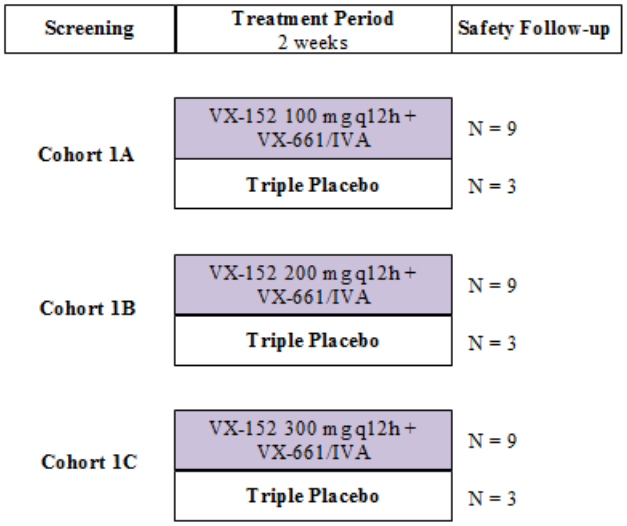
The actual number of cohorts enrolled in each part may be modified based on emerging safety and PK data. Blinded reviews of safety and available PK data will be conducted by the Vertex study team and lead investigator(s) on an ongoing basis.

Cohorts will initiate dosing as follows:

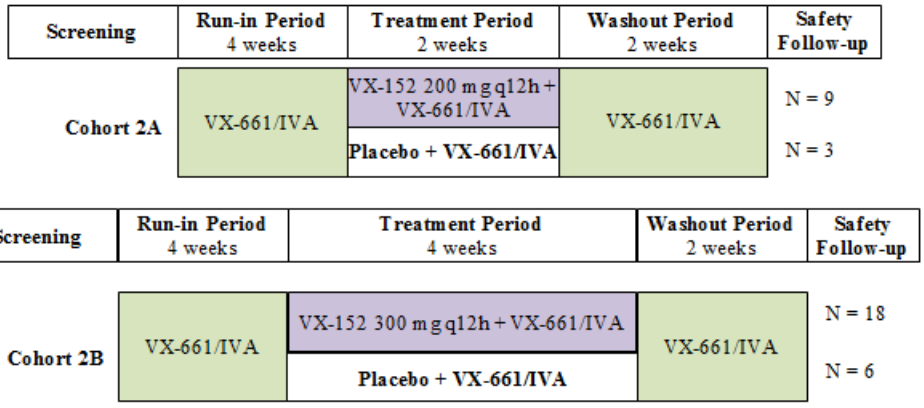
- Cohort 1A will initiate dosing first.
- Cohorts 1B and 2A may initiate dosing if supported by blinded review of safety and available PK data after all subjects in Cohort 1A complete the Day 15 Visit.
- Cohorts 1C and 2B may initiate dosing if supported by blinded review of safety and available PK data after any of the following has occurred:
  - All subjects in Cohort 1B complete the Day 15 Visit.
  - All subjects in Cohort 2A complete the Day 15 Visit.
  - At least 12 subjects across Cohorts 1B and 2A complete the Day 15 Visit.

A schematic of the study design is shown below.

Part 1: *F508del*/MF (up to ~12 subjects per cohort; randomized 3:1)



Part 2: *F508del*/*F508del* (up to ~12 subjects in Cohort 2A, up to ~24 subjects in Cohort 2b; randomized 3:1)



Assessments

Safety: AEs, clinical laboratory assessments, ECGs, vital signs, pulse oximetry, physical examinations (PEs), and ophthalmologic examinations

PD: sweat chloride

Efficacy: spirometry, CFQ-R

PK: Plasma concentrations of VX-152, VX-661, M1-661, IVA, M1-IVA

[redacted]

Statistical Analyses

Primary Objective:

The primary objective of the study is the evaluation of safety and tolerability of VX-152 in TC with VX-661/IVA.

The safety endpoints include AEs, clinical laboratory values, 12-lead ECGs, vital signs, and pulse oximetry through the Safety Follow-up Visit. The safety analysis for all treatment groups in both parts will be descriptive only.

Secondary Objectives:

The secondary objectives of the study include the evaluation of the PD effect of VX-152 in TC with VX-661/IVA, and the evaluation of the efficacy of VX-152 in TC with VX-661/IVA.

The PD endpoint is the absolute change in sweat chloride from baseline at Day 15 of a non-decreasing dose-response trend in the mean absolute change from baseline at Day 15 for sweat chloride, between placebo and the TC dose groups will be tested using a multiple comparisons procedure based on the 1-sided maximum *t*-statistic. In both parts, the null within-group hypothesis of no decrease in the mean absolute change from baseline at Day 15, for sweat chloride in the TC treatment groups, will be tested using a 1-sided 1-sample *t*-test within the mixed-effects model for repeated measures (MMRM) framework at a 5% alpha level, with baseline value as a covariate. The adjusted means and 2-sided 95% confidence intervals of the treatment effect at Day 15, for all within-group and between-group comparisons will be estimated within MMRM.

The efficacy endpoint is the absolute change from baseline at Day 15 for $ppFEV_1$. In both parts, the null within-group hypothesis of no increase in the mean absolute from baseline at Day 15, for $ppFEV_1$ in the TC treatment groups, will be tested using a 1-sided 1-sample *t*-test within MMRM at a 5% alpha level. The adjusted means and 2-sided 95% confidence intervals of the treatment effect at Day 15, for all within-group and between-group comparisons will be estimated within MMRM.

Interim Analyses

Interim analyses for each cohort may be performed after all subjects in the cohort have completed the Day 15 Visit.

IDMC Reviews

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

3 SCHEDULE OF ASSESSMENTS

The schedule of assessments from the Screening Period through the Safety Follow-up Visit is provided in Table 3-1 for Part 1, and Table 3-2 and Table 3-3 for Part 2.

All visits will be scheduled relative to the Day 1 Visit (first dose of VX-152 or placebo). Assessments will be performed in the order presented, unless specified otherwise.

Table 3-1 Study VX16-152-102: Schedule of Assessments for Part 1

Event/Assessment[a]	Screening	Treatment Period[b]					ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose
	Days -28 to -1[d]	Day 1	Days 3 and 5[e] (or Days 4/6 or Days 3/6)[f]	Day 8 (± 1 day)	Day 11[e] (± 1 day)	Day 15 (± 1 day)		
Informed consent	X							
Randomization[g]		X						
Demographics	X							
Medical history	X							
Ophthalmological history	X							
CFQ-R[h,i]		X				X	X[j]	X
Weight[k]	X	X		X		X	X	X
Height[k]	X							
Vital signs[l]	X	X		X		X	X	X

[a] Assessments will be performed in the order presented, unless noted otherwise. All assessments will be performed before dosing, unless noted otherwise. Assessments that are collected before and after dosing will only be collected once if study drug is not administered on the day of the visit (i.e., premature discontinuation of study drug treatment).

[b] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 8.1.3.

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

[d] All screening results must be reviewed before randomization, unless noted otherwise.

[e] Days 3, 5, and 11 assessments may be collected at the clinic, at a local laboratory, or during a visit by a qualified individual (e.g., home nurse).

[f] Day 3 and Day 5 assessments will be performed at least 2 days apart, with the first day of assessments occurring no earlier than Day 3 and the second day of assessments occurring no later than Day 6. (i.e., Assessments will be performed on Days 3 and 5, Days 4 and 6, or Days 3 and 6.)

[g] Randomization may occur on the previous day (Day -1) after all inclusion and exclusion criteria have been confirmed. See Section 8.1.3.

[h] CFQ-R must be completed before the start of any other assessments scheduled at that visit.

[i] The predose assessment on Day 1 may be performed on the previous day (Day -1) if randomization has occurred.

[j] Subjects will complete the CFQ-R at the ETT Visit only if it has been 2 weeks or more since their last visit.

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

Table 3-1 Study VX16-152-102: Schedule of Assessments for Part 1

Event/Assessment[a]	Screening	Treatment Period[b]					ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose
	Days -28 to -1[d]	Day 1	Days 3 and 5[e] (or Days 4/6 or Days 3/6)[f]	Day 8 (± 1 day)	Day 11[e] (± 1 day)	Day 15 (± 1 day)		
Pulse oximetry[l]	X	X		X		X	X	X
Physical examination[m]	Complete	Abbreviated		Abbreviated		Abbreviated	Abbreviated	Complete
Ophthalmologic examination[n]	X							
Standard 12-lead ECG[o]	X	X		X		X	X	X
Sweat chloride[i,p]	X	X		X		X	X	X
Spirometry[q]	X	X		X		X	X	X
Urinalysis[i]	X	X		X		X	X	X
Pregnancy test (all females of childbearing potential)	Serum	Urine					Serum	Serum
CFTR genotype[r]	X							

[l] Vital signs and pulse oximetry will be collected after the subject has been seated for at least 5 minutes.

[m] Complete and abbreviated PEs are described in Section 11.7.3. Symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator or healthcare provider.

[n] The ophthalmological examination can be performed at any time during the Screening Period through the Day 1 Visit (before the first dose of study drug). The screening ophthalmological examination does not have to be performed if there is documentation of an examination that met protocol criteria and was within 3 months before the date of informed consent, or if there is documentation of bilateral lens removal for the subject.

[o] All standard 12-lead ECGs will be performed after the subject has been seated for at least 5 minutes. ECGs will be collected before procedures that may affect heart rate (e.g., blood sampling). On Days 1 and 15, ECGs will be collected before dosing and 4 hours (± 1 hour) after dosing. At all other visits, ECGs will be collected before dosing (as applicable). ECGs collected on Day 1 before dosing will be performed in triplicate.

[p] Sweat chloride will be measured in all subjects. If the value cannot be determined from the screening test, a sweat chloride value documented in the subject's medical record may be used to establish eligibility.

[q] Spirometry may be performed pre- or post-bronchodilator at the Screening Visit. Spirometry will be performed pre-bronchodilator, before the morning dose of study drugs, and should be performed at approximately the same time at every other study visit. On Days 1 and 15, spirometry will also be performed pre-bronchodilator 5 hours (± 1 hour) after study drug administration.

Table 3-1 Study VX16-152-102: Schedule of Assessments for Part 1

Event/Assessment[a]	Screening	Treatment Period[b]					ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose
	Days -28 to -1[d]	Day 1	Days 3 and 5[e] (or Days 4/6 or Days 3/6)[f]	Day 8 (± 1 day)	Day 11[e] (± 1 day)	Day 15 (± 1 day)		
FSH[s]	X							
G6PD activity test[t]	X							
[redacted]								
Serum chemistry and hematology[i]	X	X	X[e,v]	X	X[e,v]	X	X	X
Coagulation[i]	X	X		X		X		X
PK sampling[w]		X		X		X	X	
Study drug dosing[x]		Day 1 through Day 15						
AEs, medications[y], treatments, and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit							

r *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used to establish eligibility.

s FSH will be measured for any suspected postmenopausal female subjects with at least 12 months of continuous spontaneous amenorrhea.

t A single blood sample will be collected for the G6PD activity test.

[redacted]

v On Days 3, 5, and 11, the following parameters will be measured: lactate dehydrogenase, total and direct bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase.

w Blood samples will be collected for PK analysis of VX-152, VX-661, M1-661, IVA, and M1-IVA. On Day 1, samples will be collected before dosing (0 hours) and at 1, 2, 4, and 6 hours after dosing (relative to the morning dose). On Day 8, a predose sample will be collected before the morning dose of study drug (0 hours). On Day 15, samples will be collected before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing. At the ETT Visits, a single blood sample for PK analysis will be collected.

x The last dose of study drug will be the morning dose on Day 15.

y Refer to Section 9.4 for details.

Table 3-2 Study VX16-152-102: Schedule of Assessments for Part 2, Cohort 2A

Event/Assessment[a]	Screening	Run-in Period		Treatment Period[b]					Washout Period	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose[d]
	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Days 3 and 5[g] (or Days 4/6 or Days 3/6)[h]	Day 8 (± 1 day)	Day 11[g] (± 1 day)	Day 15 (± 1 day)	Day 29 (± 3 days)		
Informed consent	X										
Randomization[i]				X							
Demographics	X										
Medical history	X										
Ophthalmological history	X										
CFQ-R[j,k]				X		X		X	X	X[l]	X
Weight[m]	X	X		X		X		X	X	X	X

[a] Assessments will be performed in the order presented, unless noted otherwise. All assessments will be performed before dosing, unless noted otherwise. Assessments that are collected before and after dosing will only be collected once if study drug is not administered on the day of the visit (i.e., premature discontinuation of study drug treatment).

[b] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 8.1.3.

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

[d] Subjects who meet criteria specified in Section 8.1.5 will not have a Safety Follow-up Visit.

[e] All screening results must be reviewed before the subject receives VX-661/IVA in the Run-in Period on Day -28, unless noted otherwise.

[f] The Day -14 Visit is only required for subjects who are naïve to VX-661/IVA treatment.

[g] Days 3, 5, and 11 assessments may be collected at the clinic, at a local laboratory, or during a visit by a qualified individual (e.g., home nurse).

[h] Day 3 and Day 5 assessments will be performed at least 2 days apart, with the first day of assessments occurring no earlier than Day 3 and the second day of assessments occurring no later than Day 6. (i.e., Assessments will be performed on Days 3 and 5, Days 4 and 6, or Days 3 and 6.)

[i] Randomization may occur on the previous day (Day -1) after all inclusion and exclusion criteria and criteria for entry into the Treatment Period have been confirmed. See Section 8.1.3.

[j] CFQ-R must be completed before the start of any other assessments scheduled at that visit.

[k] The predose assessment on Day 1 may be performed on the previous day (Day -1) if randomization has occurred.

[l] Subjects will complete the CFQ-R at the ETT Visit only if it has been 2 weeks or more since their last visit.

Table 3-2 Study VX16-152-102: Schedule of Assessments for Part 2, Cohort 2A

Event/Assessment[a]	Screening	Run-in Period		Treatment Period[b]					Washout Period	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose[d]
	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Days 3 and 5[g] (or Days 4/6 or Days 3/6)[h]	Day 8 (± 1 day)	Day 11[g] (± 1 day)	Day 15 (± 1 day)	Day 29 (± 3 days)		
Height[m]	X										
Vital signs[n]	X	X		X		X		X	X	X	X
Pulse oximetry[n]	X	X		X		X		X	X	X	X
Physical examination[o]	Complete	Abbrev-iated		Abbreviated		Abbreviated		Abbreviated	Abbreviated	Abbreviated	Complete
Ophthalmologic examination[p]	X										
Standard 12-lead ECG[q]	X	X		X		X		X	X	X	X
Sweat chloride[k,r]	X		X	X		X		X	X	X	
Spirometry[s]	X		X	X		X		X	X	X	X
Urinalysis[k]	X	X		X		X		X	X	X	X

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

[n] Vital signs and pulse oximetry will be collected after the subject has been seated for at least 5 minutes.

[o] Complete and abbreviated PEs are described in Section 11.7.3. Symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator or healthcare provider.

[p] The ophthalmological examination can be performed at any time during the Screening Period through the Day 1 Visit (before the first dose of study drug). The screening ophthalmological examination does not have to be performed if there is documentation of an examination that met protocol criteria and was within 3 months before the date of informed consent, or if there is documentation of bilateral lens removal for the subject.

[q] All standard 12-lead ECGs will be performed after the subject has been seated for at least 5 minutes. ECGs will be collected before procedures that may affect heart rate (e.g., blood sampling). On Days 1 and 15, ECGs will be collected before dosing and 4 hours (± 1 hour) after dosing. At all other visits, ECGs will be collected before dosing (as applicable). ECGs collected on Day 1 before dosing will be performed in triplicate.

[r] Sweat chloride will be measured in all subjects. If the value cannot be determined from the screening test, a sweat chloride value documented in the subject's medical record may be used to establish eligibility.

[s] Spirometry may be performed pre- or post-bronchodilator at the Screening Visit. Spirometry will be performed pre-bronchodilator, before the morning dose of study drugs, and should be performed at approximately the same time at every other study visit. On Days 1 and 15, spirometry will also be performed pre-bronchodilator 5 hours (± 1 hour) after study drug administration.

Table 3-2 Study VX16-152-102: Schedule of Assessments for Part 2, Cohort 2A

Event/Assessment[a]	Screening	Run-in Period		Treatment Period[b]					Washout Period	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose[d]
	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Days 3 and 5[g] (or Days 4/6 or Days 3/6)[h]	Day 8 (± 1 day)	Day 11[g] (± 1 day)	Day 15 (± 1 day)	Day 29 (± 3 days)		
Pregnancy test (all females of childbearing potential)	Serum	Urine		Urine				Urine		Serum	Serum
CFTR genotype[t]	X										
FSH[u]	X										
G6PD activity test[v]	X										
[redacted]											
Serum chemistry and hematology[k]	X	X		X	X[g,x]	X	X[g,x]	X	X	X	X
Coagulation[k]	X	X		X		X		X			X
PK sampling[y]				X		X		X		X[y]	
VX-661/IVA dosing[z]		Day -28 through Day 29									

t *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before Day -28, a previous *CFTR* genotype laboratory report may be used to establish eligibility.

u FSH will be measured for any suspected postmenopausal female subjects with at least 12 months of continuous spontaneous amenorrhea.

v A single blood sample will be collected for the G6PD activity test.

■ [redacted]

x On Days 3, 5, and 11, the following parameters will be measured: lactate dehydrogenase, total and direct bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase.

y Blood samples will be collected for PK analysis of VX-152, VX-661, M1-661, IVA, and M1-IVA. On Day 1, samples will be collected before dosing (0 hours) and at 1, 2, 4, and 6 hours after dosing (relative to morning dose). On Day 8, a predose sample will be collected before the morning dose of study drug (0 hours). On Day 15, samples will be collected before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing. At ETT Visits, a single blood sample for PK analysis will only be collected from subjects who discontinued study drug after Day 1, but before Day 15 PK was collected.

z The last dose of VX-661/IVA will be the morning dose on Day 29.

Table 3-2 Study VX16-152-102: Schedule of Assessments for Part 2, Cohort 2A

Event/Assessment[a]	Screening	Run-in Period		Treatment Period[b]					Washout Period	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose[d]
	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Days 3 and 5[g] (or Days 4/6 or Days 3/6)[h]	Day 8 (± 1 day)	Day 11[g] (± 1 day)	Day 15 (± 1 day)	Day 29 (± 3 days)		
VX-152 or placebo dosing[aa]				Day 1 through Day 15							
AEs, medications[bb], treatments and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit										

[aa] The last dose of VX-152 or placebo will be the morning dose on Day 15.
[bb] Refer to Section 9.4 for details.

Table 3-3 Study VX16-152-102: Schedule of Assessments for Part 2, Cohort 2B

	Screening	Run-in Period		Treatment Period[b]					Washout Period		Safety Follow-up 28 (± 7) Days After Last Dose[d]
Event/Assessment[a]	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Days 3 and 5[g] (or Days 4/6 or Days 3/6)[h]	Day 8 (± 1 day)	Day 11[g] (± 1 day)	Day 15 and Day 29 (± 1 day)	Day 43 (± 3 days)	ETT Visit[c]	
Informed consent	X										
Randomization[i]				X							
Demographics	X										
Medical history	X										
Ophthalmological history	X										
CFQ-R[j,k]				X		X		X	X	X[l]	X

[a] Assessments will be performed in the order presented, unless noted otherwise. All assessments will be performed before dosing, unless noted otherwise. Assessments that are collected before and after dosing will only be collected once if study drug is not administered on the day of the visit (i.e., premature discontinuation of study drug treatment).

[b] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 8.1.3.

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

[d] Subjects who meet criteria specified in Section 8.1.5 will not have a Safety Follow-up Visit.

[e] All screening results must be reviewed before the subject receives VX-661/IVA in the Run-in Period on Day -28, unless noted otherwise.

[f] The Day -14 Visit is only required for subjects who are naïve to VX-661/IVA treatment.

[g] Days 3, 5, and 11 assessments may be collected at the clinic, at a local laboratory, or during a visit by a qualified individual (e.g., home nurse).

[h] Day 3 and Day 5 assessments will be performed at least 2 days apart, with the first day of assessments occurring no earlier than Day 3 and the second day of assessments occurring no later than Day 6. (i.e., Assessments will be performed on Days 3 and 5, Days 4 and 6, or Days 3 and 6.)

[i] Randomization may occur on the previous day (Day -1) after all inclusion and exclusion criteria and criteria for entry into the Treatment Period have been confirmed. See Section 8.1.3.

[j] CFQ-R must be completed before the start of any other assessments scheduled at that visit.

[k] The predose assessment on Day 1 may be performed on the previous day (Day -1) if randomization has occurred.

[l] Subjects will complete the CFQ-R at the ETT Visit only if it has been 2 weeks or more since their last visit.

Table 3-3 Study VX16-152-102: Schedule of Assessments for Part 2, Cohort 2B

Event/Assessment[a]	Screening	Run-in Period		Treatment Period[b]					Washout Period	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose[d]
	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Days 3 and 5[g] (or Days 4/6 or Days 3/6)[h]	Day 8 (± 1 day)	Day 11[g] (± 1 day)	Day 15 and Day 29 (± 1 day)	Day 43 (± 3 days)		
Weight[m]	X	X		X		X		X	X	X	X
Height[m]	X										
Vital signs[n]	X	X		X		X		X	X	X	X
Pulse oximetry[n]	X	X		X		X		X	X	X	X
Physical examination[o]	Complete	Abbrev-iated		Abbrev-iated		Abbrev-iated		Abbrev-iated	Abbreviated	Abbreviated	Complete
Ophthalmologic examination[p]	X										
Standard 12-lead ECG[q]	X	X		X		X		X	X	X	X
Sweat chloride[k,r]	X		X	X		X		X	X	X	
Spirometry[s]	X		X	X		X		X	X	X	X

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

[n] Vital signs and pulse oximetry will be collected after the subject has been seated for at least 5 minutes.

[o] Complete and abbreviated PEs are described in Section 11.7.3. Symptom-targeted PEs will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator or healthcare provider.

[p] The ophthalmological examination can be performed at any time during the Screening Period through the Day 1 Visit (before the first dose of study drug). The screening ophthalmological examination does not have to be performed if there is documentation of an examination that met protocol criteria and was within 3 months before the date of informed consent, or if there is documentation of bilateral lens removal for the subject.

[q] Standard 12-lead ECGs will be performed after the subject has been seated for at least 5 minutes. ECGs will be collected before procedures that may affect heart rate (e.g., blood sampling). On Days 1, 15, and 29, ECGs will be collected before dosing and 4 hours (± 1 hour) after dosing. At all other visits, ECGs will be collected before dosing (as applicable). ECGs collected on Day 1 before dosing will be performed in triplicate.

[r] Sweat chloride will be measured in all subjects. If the value cannot be determined from the screening test, a sweat chloride value documented in the subject's medical record may be used to establish eligibility.

Table 3-3 Study VX16-152-102: Schedule of Assessments for Part 2, Cohort 2B

	Screening	Run-in Period		Treatment Period[b]					Washout Period		Safety Follow-up 28 (± 7) Days After Last Dose[d]
Event/Assessment[a]	**Days -56 to -29[e]**	**Day -28 (± 1 day)**	**Day -14[f] (± 1 day)**	**Day 1**	**Days 3 and 5[g] (or Days 4/6 or Days 3/6)[h]**	**Day 8 (± 1 day)**	**Day 11[g] (± 1 day)**	**Day 15 and Day 29 (± 1 day)**	**Day 43 (± 3 days)**	**ETT Visit[c]**	
Urinalysis[k]	X	X		X		X		X	X	X	X
Pregnancy test (all females of childbearing potential)	Serum	Urine		Urine				Urine		Serum	Serum
CFTR genotype[t]	X										
FSH[u]	X										
G6PD activity test[v]	X										
[redacted]											
Serum chemistry and hematology[k]	X	X		X	X[g,x]	X	X[g,x]	X	X	X	X
Coagulation[k]	X	X		X		X		X			X
PK sampling[y]				X		X		X		X[y]	

[s] Spirometry may be performed pre- or post-bronchodilator at the Screening Visit. Spirometry will be performed pre-bronchodilator, before the morning dose of study drugs, and should be performed at approximately the same time at every other study visit. On Days 1, 15, and 29, spirometry will be performed pre-bronchodilator 5 hours (± 1 hour) after study drug administration.

[t] *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before Day -28, a previous *CFTR* genotype laboratory report may be used to establish eligibility.

[u] FSH will be measured for any suspected postmenopausal female subjects with at least 12 months of continuous spontaneous amenorrhea.

[v] A single blood sample will be collected for the G6PD activity test.

[redacted]

[x] On Days 3, 5, and 11, the following parameters will be measured: lactate dehydrogenase, total and direct bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase.

[y] Blood samples will be collected for PK analysis of VX-152, VX-661, M1-661, IVA, and M1-IVA. On Day 1, samples will be collected before dosing (0 hours) and at 1, 2, 4, and 6 hours after dosing (relative to morning dose). On Day 8, a predose sample will be collected before the morning dose of

Table 3-3 Study VX16-152-102: Schedule of Assessments for Part 2, Cohort 2B

Event/Assessment[a]	Screening	Run-in Period		Treatment Period[b]					Washout Period	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose[d]
	Days -56 to -29[e]	Day -28 (± 1 day)	Day -14[f] (± 1 day)	Day 1	Days 3 and 5[g] (or Days 4/6 or Days 3/6)[h]	Day 8 (± 1 day)	Day 11[g] (± 1 day)	Day 15 and Day 29 (± 1 day)	Day 43 (± 3 days)		
VX-661/IVA dosing[z]		Day -28 through Day 43									
VX-152 or placebo dosing[aa]				Day 1 through Day 29							
AEs, medications[bb], treatments and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit										

study drug (0 hours). On Day 15, samples will be collected before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing. On Day 29, a sample will be collected before the morning dose (0 hours). At ETT Visits, a single blood sample for PK analysis will only be collected from subjects who discontinued study drug after Day 1, but before Day 29.

[z] The last dose of VX-661/IVA will be the morning dose on Day 43.

[aa] The last dose of VX-152 or placebo will be the morning dose on Day 29.

[bb] Refer to Section 9.4 for details.

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List of Abbreviations

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransaminase
AUC_{0-12h}	area under the concentration versus time curve from time of dosing to 12 hours.
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator protein
C_{max}	maximum observed concentration
CPAP	clinical pharmacology analysis plan
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
[redacted]	[redacted]
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes/ears/nose/throat
ETT	early termination of treatment
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein (make italics)
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEF	forced expiratory flow
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
[redacted]	[redacted]
G6PD	glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
GLI	Global Lung Function Initiative
GPS	Global Patient Safety
HBE	human bronchial epithelial
ICF	informed consent form
ICH	International Conference on Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IPD	important protocol deviation
IRB	institutional review board
IVA	ivacaftor

Abbreviation	Term
IWRS	interactive web response system
LFT	liver function test
LLN	lower limit of normal
LUM	lumacaftor
max	maximum value
MCP	multiple comparisons procedure
MF	minimal function
min	minimum value
MMRM	mixed-effects model for repeated measures
N	total sample size (e.g., number of subjects treated)
OATP1B1	organic anion transporting polypeptide 1B1
OATP1B3	organic anion transporting polypeptide 1B3
P	probability
PCS	potentially clinically significant
PD	pharmacodynamic, pharmacodynamics
PE	physical examination
PK	pharmacokinetic, pharmacokinetics
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
q12h	every 12 hours
qd	daily
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
TC	triple combination
TE	treatment-emergent
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
Vertex	Vertex Pharmaceuticals Incorporated

5 INTRODUCTION

5.1 Background

Cystic fibrosis (CF) affects more than 70,000 children and adults worldwide[1] and is the most common fatal genetic disease in persons of European descent.[2] CF is caused by a defect in the gene encoding the CF transmembrane conductance regulator (CFTR), an ion channel that regulates the flow of chloride and other ions in epithelia of various tissues, including lungs, pancreas and other gastrointestinal organs, and sweat glands.[2] Decreased CFTR activity in people with CF results in multisystem pathology[3], beginning at birth. Despite progress in the treatment of CF with antibiotics and mucolytics, the median predicted survival age for a person with CF is approximately 40 years.[2,4] More effective treatments are needed for CF.

To address this medical need, Vertex Pharmaceuticals Incorporated is developing treatment regimens that include CFTR modulators to target the underlying cause of CF: the defective CFTR protein. Two types of CFTR modulators have been developed: potentiators, which increase the channel gating activity of the CFTR protein, and correctors, which increase the quantity of CFTR at the cell surface. Because potentiators can increase the activity of CFTR protein delivered to the cell surface by correctors, CFTR potentiators and correctors are complementary therapeutic approaches.

Ivacaftor (IVA; Kalydeco®), the first CFTR modulator developed by Vertex, is an orally administered CFTR potentiator that increases the channel-open probability of CFTR protein to enhance chloride transport. Globally, Kalydeco is indicated for the treatment of CF in patients as young as 2 years who have the *G551D* and certain other gating mutations as well as the *R117H* mutation in the *CFTR* gene depending on the country.[5]

Lumacaftor (LUM) and VX-661 are orally administered first-generation CFTR correctors developed by Vertex that act directly on CFTR to improve its cellular processing and trafficking, thereby increasing the quantity of functional F508del-CFTR protein at the cell surface. *F508del*, the most prevalent mutation in people with CF, occurs in about 83% of CF patients and results in a decreased quantity of CFTR protein at the cell surface. Orkambi™ (LUM/IVA combination therapy) is approved in the US, EU, Canada, and Australia for patients 12 years and older who are homozygous for *F508del*. Phase 3 studies of VX-661/IVA combination therapy are ongoing in populations that are homozygous or heterozygous for *F508del*.

VX-152 is a second-generation CFTR corrector that acts through a different site of the CFTR protein than LUM and VX-661. In vitro, VX-152 improves the processing and trafficking of F508del-CFTR, thereby increasing the quantity of functional F508del-CFTR protein at the cell surface. Consistent with different mechanisms of action, the effects of VX-152 and VX-661 are additive. The activity of the CFTR protein delivered to the cell surface by VX-152, alone or in combination with VX-661, is potentiated by IVA. In human bronchial epithelial (HBE) cells derived from CF patients homozygous for *F508del*, the triple combination (TC) of VX-152, VX-661, and IVA increased CFTR-mediated chloride transport more than the dual combinations (VX-152 and VX-661; VX-152 and IVA; VX-661 and IVA) or individual agents (VX-152; VX-661; IVA). These data, as well as the

nonclinical pharmacokinetic (PK) and safety profile, support the development of VX-152 in combination with other CFTR modulators for the treatment of CF.

5.2 Rationale for the Present Study

The present study is the first clinical study of VX-152 in subjects with CF and is designed to evaluate the safety, tolerability, pharmacodynamic (PD) effect, PK, and efficacy of VX-152 in TC with VX-661 and IVA.

VX-152 has been studied in vitro and in vivo, and the safety profile in the nonclinical toxicology studies supports clinical development of VX-152. [redacted]

Based on in vitro results and modeling of in vitro and in vivo data, there is the potential for clinical efficacy at a safe dose, providing the rational for the present study.

6 STUDY OBJECTIVES

6.1 Primary Objectives

- To evaluate the safety and tolerability of VX-152 in TC with VX-661 and IVA in adults with CF

6.2 Secondary Objectives

- To evaluate the PD effect of VX-152 in TC with VX-661 and IVA on CFTR function
- To evaluate the efficacy of VX-152 in TC with VX-661 and IVA
- To evaluate the PK of VX-152 when administered in TC with VX-661 and IVA
- To evaluate the PK of VX-661, IVA, and their respective metabolites when administered with VX-152

7 STUDY ENDPOINTS

7.1 Primary Endpoints

- Safety and tolerability assessments based on AEs, clinical laboratory values, standard 12-lead electrocardiograms (ECGs), vital signs, and pulse oximetry

7.2 Secondary Endpoints

- Absolute change in sweat chloride concentrations from baseline at Day 15 (Parts 1 and 2), and through Day 29 (Part 2, Cohort 2B only)
- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline at Day 15 (Parts 1 and 2), and through Day 29 (Part 2, Cohort 2B only)
- Relative change in $ppFEV_1$ from baseline at Day 15 (Parts 1 and 2), and through Day 29 (Part 2, Cohort 2B only)
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline at Day 15 (Parts 1 and 2), and at Day 29 (Part 2, Cohort 2B only)
- PK parameters of VX-152, VX-661, M1-661, IVA, and M1-IVA

[redacted]

8 STUDY DESIGN

8.1 Overview of Study Design

This is a Phase 2, 2-part, randomized, double-blind, placebo- and VX-661/IVA-controlled, parallel-group, multicenter study designed to evaluate the safety of VX-152 in TC with VX-661/IVA.

Up to approximately 72 subjects with CF are planned for enrollment: up to approximately 36 subjects in each of Part 1 (*F508del*/MF genotype) and in Part 2 (*F508del*/*F508del* genotype).

Parts 1 and 2 will enroll multiple cohorts, with each cohort evaluating 1 dose level of VX-152 as part of TC with VX-661/IVA (100 mg qd/150 mg q12h). Each cohort will enroll up to approximately 12 subjects in Part 1 and Part 2 Cohort 2A and up to approximately 24 subjects in Part 2 Cohort 2B. Subjects in all cohorts will be randomized 3:1 (active TC:comparator). Triple placebo will be the comparator in Part 1, and VX-661/IVA will be the comparator in Part 2.

Up to 3 cohorts are planned for Part 1 (Cohorts 1A, 1B, and 1C). Up to 2 cohorts are planned for Part 2 (Cohorts 2A and 2B). The doses of VX-152 planned for evaluation are 100 mg q12h in Cohort 1A, 200 mg q12h in Cohorts 1B and 2A, and 300 mg q12h in Cohorts 1C and 2B. The dose of VX-152 may be adjusted to be lower or the same as the dose level evaluated in the previous cohort.

The actual number of cohorts enrolled in each part may be modified based on emerging safety and PK data. Blinded reviews of safety and available PK data will be conducted by the Vertex study team and lead investigator(s) on an ongoing basis.

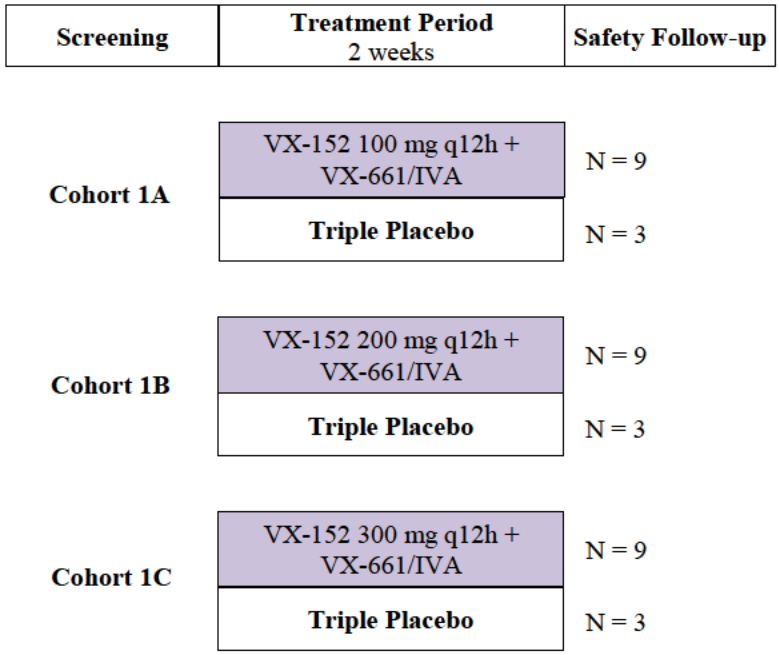
Cohorts will initiate dosing as follows:

- Cohort 1A will initiate dosing first.
- Cohorts 1B and 2A may initiate dosing if supported by blinded review of safety and available PK data after all subjects in Cohort 1A complete the Day 15 Visit.
- Cohorts 1C and 2B may initiate dosing if supported by blinded review of safety and available PK data after any of the following has occurred:
  - All subjects in Cohort 1B complete the Day 15 Visit.
  - All subjects in Cohort 2A complete the Day 15 Visit.
  - At least 12 subjects across Cohorts 1B and 2A complete the Day 15 Visit.

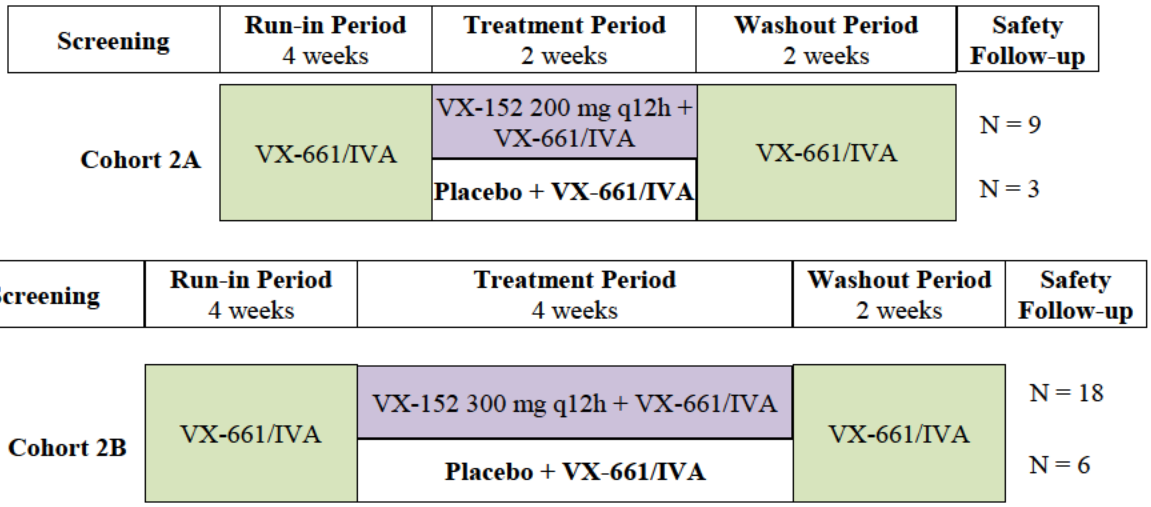
A schematic of the study design (including the doses of VX-152, VX-661, and IVA to be evaluated) is shown in Figure 8-1.

Figure 8-1 Schematic of the Study Design

Part 1: *F508del*/MF (up to ~12 subjects per cohort; randomized 3:1)



Part 2: *F508del*/*F508del* (up to ~12 subjects in Cohort 2A, up to ~24 subjects in Cohort 2b; randomized 3:1)



Notes: Schematic is not drawn to scale. The actual number of cohorts enrolled in each part may be modified based on emerging safety and PK data. The planned doses of VX-152 are shown in the figure but may be adjusted to be lower or the same as the dose level evaluated in the previous cohort. VX-661 will be administered 100 mg qd. IVA will be administered 150 mg q12h.

8.1.1 Screening

For Part 1, the Screening Period will occur within 28 days before the first dose of study drug in the Treatment Period. For Part 2, the Screening Period will occur within 28 days before the first dose of VX-661/IVA in the Run-in Period.

The assessments to be conducted are shown in Table 3-1, Table 3-2, and Table 3-3 and will be used to confirm that subjects meet the eligibility criteria for the study. The investigator (or an appropriate authorized designee) will obtain informed consent from each subject before any study procedure takes place.

The screening ophthalmologic examination does not have to be performed if there is documentation of an examination that met protocol criteria and was within 3 months before the date of informed consent (Section 11.7.6) or if there is documentation of bilateral lens removal for the subject.

8.1.1.1 Repetition of Screening Assessment(s)

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

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

If screening spirometry measurements fail to meet acceptability and repeatability criteria as specified by American Thoracic Society/European Respiratory Society guidelines,[6] repeat spirometry evaluation may be performed once.

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

8.1.1.2 Rescreening

Subjects may only be rescreened with the approval of the medical monitor. If a subject is rescreened, all screening assessments will be repeated except for *CFTR* genotyping, follicle-stimulating hormone (FSH) level (if serum FSH level was ≥40 mIU/mL during prior screening), G6PD activity test (if total bilirubin level was <2 × upper limit of normal [ULN] during prior screening), sweat chloride level, and the ophthalmologic examination (if documentation shows it was performed within the last 3 months). If a subject is rescreened, the new screening window will begin once the first rescreening assessment has been initiated.

8.1.1.3 Extension of Screening Period Window

A subject may have the Screening Period window extended by 2 weeks, without medical monitor approval, for the following reasons:

- Repetition of the Screening Period assessments (Section 8.1.1.1)
- To meet the eligibility criteria
- Scheduling of ophthalmologic examination (Section 11.7.6)
- Repetition of spirometry assessment if results are of poor quality

A subject may have the Screening Period window extended by 4 weeks, without medical monitor approval, for the following reason:

- For Part 1 subjects, washout of VX-661/IVA if enrolling from Study VX14-661-110 (Study 661-110)
- Operational or logistic delays

8.1.2 Run-in Period (Part 2)

The Run-in Period will have a total duration of 4 weeks and is designed to establish a reliable on-treatment (VX-661/IVA) baseline for the Treatment Period. The first dose of VX-661/IVA will be administered at the Day -28 Visit. The last dose of VX-661/IVA within the Run-in Period will be administered in the evening of Day -1 (1 day before the Day 1 Visit).

Study eligibility for Part 2 subjects will be confirmed before the first dose of VX-661/IVA in the Run-in Period (on Day -28).

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

8.1.3 Treatment Period

For Part 1, the Treatment Period will last approximately 2 weeks. For Part 2, the Treatment Period will last approximately 2 weeks for subjects in Cohort 2A and approximately 4 weeks for subjects in Cohort 2B.

Study visits during the Treatment Period will occur as shown in Table 3-1, Table 3-2, and Table 3-3. All visits should occur within the windows specified. Study drug administration details are provided in Section 10.2.

Subjects must meet both of the following criteria to continue into the Treatment Period:

- Must have stable CF disease (as judged by the investigator) and have remained on a stable CF medication regimen during the 28 days before the Day 1 Visit. (For example, subjects cannot have an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy [including antibiotics] for pulmonary disease within 28 days before the Day 1 Visit.)
- Must not have had an acute non-CF illness (e.g., gastroenteritis) within the 14 days before the Day 1 Visit.

If these criteria are not met, subjects may not be randomized and enter into the Treatment Period.

Randomization will occur before the first dose of study drug during the Treatment Period and will occur on Day 1 (or Day -1) after all criteria for entry into the Treatment Period have been confirmed. Study eligibility for Part 1 subjects will be confirmed before randomization.

For Part 2, subjects who prematurely discontinue VX-661/IVA during the Run-in Period will not be randomized or participate in the Treatment Period.

8.1.4 Washout Period (Part 2)

The Washout Period will last approximately 2 weeks and is designed to allow for the measurement of off-treatment effects. Subjects will continue to receive VX-661/IVA during the Washout Period.

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

8.1.5 Follow-up

The Safety Follow-up Visit assessments are listed in Table 3-1, Table 3-2, and Table 3-3. There will be an outpatient Safety Follow-up Visit occurring approximately 28 days after the last dose of study drug for subjects who complete study drug dosing and for subjects who prematurely discontinue study drug dosing.

The following subjects will not have a Safety Follow-up Visit:

- Part 2 subjects who do not meet the criteria to enter the Treatment Period (Section 8.1.3), and re-enter Study 661-110
- Part 2 subjects in Cohort 2A who complete the Day 29 Visit and re-enter Study 661-110
- Part 2 subjects in Cohort 2B who complete the Day 43 Visit and re-enter Study 661-110

All other subjects will have a Safety Follow-up Visit.

8.1.6 Early Termination of Treatment

If a subject prematurely discontinues treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the decision to terminate study drug treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 days after their last dose of study drug. The assessments performed at the Safety Follow-up Visit are listed in Table 3-1, Table 3-2, and Table 3-3.

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

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

8.1.7 Independent Data Monitoring Committee

This study will be monitored by an external independent data monitoring committee (IDMC), which will conduct periodic reviews of safety data from all parts of the study (Section 12.3.6.2). Procedural details of the IDMC structure and function, frequency of meetings, and data planned for review will be included in the IDMC Charter. The IDMC Charter will be finalized before the first subject is screened.

8.2 Rationale for Study Design and Study Drug Regimens

8.2.1 Study Design

This Phase 2 study is the first clinical study of VX-152 in subjects with CF. It is designed to evaluate the safety of VX-152 in TC with VX-661/IVA and to establish proof-of-concept in 2 populations of subjects defined by *CFTR* genotype: subjects heterozygous for the *F508del-CFTR* mutation with a second *CFTR* mutation not expected to respond to VX-661/IVA (*F508del*/minimal function [MF]) (Part 1) and subjects homozygous for *F508del* (*F508del*/*F508del*) (Part 2).

Based on in vitro data, TC is predicted to provide clinically relevant improvements in chloride transport in both populations, though the magnitude of response may not be the same in these populations. The subjects will be evaluated by genotype in separate cohorts in Parts 1 and 2, based on the potential for differences in the magnitude of treatment response among these genotype categories. PD will be evaluated through the assessment of sweat chloride, and efficacy will be evaluated through the assessment of spirometry and patient reported outcomes. Part 1 of the study will also obtain information regarding the exposure-response relationship (Section 12.1.2.1).

Placebo is the comparator in Part 1, as efficacy has not been established for a corrector, potentiator, or corrector/potentiator combination in subjects with *F508del*/MF genotypes. VX-661/IVA is the comparator in Part 2, based on the potential for benefit demonstrated for VX-661/IVA in subjects with the *F508del*/*F508del* genotype in Study VX11-661-101.[7] Part 2 will have a 4-week run-in period to establish a reliable on-treatment (VX-661/IVA) baseline for comparison to the Treatment Period, when subjects will additionally receive VX-152 or placebo. Off-treatment effects will also be measured at the Safety Follow-up Visit in Part 1 and at the end of the Washout Period in Part 2.

8.2.2 Study Drug Dose and Duration

Part 1 will evaluate up to 3 dose levels of VX-152 (100, 200, and 300 mg q12h) in TC with VX-661/IVA in subjects with the *F508del*/MF genotype. [redacted]

The dose escalation of VX-152 is no more than 2-fold. [redacted]

Up to 3 dose levels of VX-152 will be evaluated as part of the TC in Part 1 to provide a range of doses and exposures that will enable dose-response and exposure-response analyses for PD (Section 12.1.2.1). Dose- and exposure-response information obtained from Part 1 (*F508del*/MF genotype) is expected to be applicable to other populations with an *F508del* mutation, including *F508del*/*F508del* genotypes, based on similar in vitro potency for the TC in HBE cells with 1 or 2 copies of *F508del*.[8]

The dose of VX-661 and IVA (100 mg qd and 150 mg q12h) in the TC are the same doses currently under evaluation in Phase 3 studies of VX-661/IVA. These doses of VX-661 and IVA are appropriate for evaluation in the TC based on in vitro experiments with VX-152 which evaluated similar levels of VX-661 and IVA exposure after correction for protein-binding.

[redacted] In Studies VX06-770-101 and VX11-661-101, improvements in sweat chloride and ppFEV$_1$ were observed as rapidly as 3 to 7 days after the start of dosing, with most of the effect observed within 14 days. Given the increased in vitro response of the TC relative to VX-661/IVA, it is expected that the 2-week treatment duration will be sufficient to observe differences between treatment arms with respect to efficacy and PD endpoints. In addition, based on previous clinical experience, 2 weeks is sufficient for VX-152, VX-661, and IVA to reach steady-state levels of exposure. The 4-week treatment duration in Part 2 Cohort 2B will provide additional safety data for the TC.

8.2.3 Rationale for Study Assessments

[redacted]

The PD and efficacy assessments are widely accepted and generally recognized as reliable, accurate, and relevant to the study of patients in CF. All assessments were routinely measured in the registration studies of IVA (Kalydeco) or LUM/IVA combination therapy (Orkambi).

9 STUDY POPULATION

Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects are randomized (Part 1) or receive VX-661/IVA in the Run-in Period on Day -28 (Part 2).

9.1 Inclusion Criteria

1. Subject will sign and date an informed consent form (ICF).
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Subjects will be aged 18 years or older on the date of informed consent.
4. Body weight ≥35 kg.
5. Sweat chloride value ≥60 mmol/L from test results obtained during screening. If the value cannot be determined from the screening test, a sweat chloride value documented in the subject's medical record may be used to establish eligibility. (It is acceptable to use a sweat chloride value that was obtained before previous treatment with IVA, LUM/IVA, or an investigational CFTR modulator).
6. Subjects must have an eligible *CFTR* genotype as noted below. If the screening *CFTR* genotype result is not received before randomization (Part 1) or before Day -28 (Part 2), a previous *CFTR* genotype laboratory report may be used to establish eligibility.
   Note: Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.5).
   - Part 1: Heterozygous for *F508del* with a second *CFTR* allele carrying an MF mutation that is not likely to respond to VX-661 and/or IVA therapy (Appendix A)
   - Part 2: Homozygous for *F508del*
7. Subjects must have an FEV_1 ≥40% and ≤90% of predicted normal for age, sex, and height (equations of the Global Lung Function Initiative [GLI])[9] at the Screening Visit. Spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria[6] for acceptability and repeatability.
8. Stable CF disease as judged by the investigator.
9. Willing to remain on a stable CF medication regimen through the planned end of treatment or, if applicable, the Safety Follow-up Visit.

9.2 Exclusion Criteria

1. History of any comorbidity that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject.
2. History of cirrhosis with portal hypertension.

3. Risk factors for Torsade de Pointes, including but not limited to, history of any of the following: familial long QT syndrome, chronic hypokalemia, heart failure, left ventricular hypertrophy, chronic bradycardia, myocardial infarction, cardiomyopathy, history of arrhythmia (ventricular or atrial fibrillation), obesity, acute neurologic events (subarachnoid hemorrhage, intracranial hemorrhage, cerebrovascular accident, or intracranial trauma), or autonomic neuropathy.
4. History of hemolysis.
5. G6PD deficiency, defined as G6PD activity less than the lower limit of normal (LLN) or 70% of the mean of the LLN and the ULN, whichever is greater.
6. Any of the following abnormal laboratory values at screening:
   - Hemoglobin <10 g/dL
   - Total bilirubin ≥2 × ULN
   - AST, ALT, gamma-glutamyl transpeptidase (GGT), or alkaline phosphatase (ALP) ≥3 × ULN
   - Abnormal renal function defined as glomerular filtration rate ≤50 mL/min/1.73 m^2 (calculated by the Modification of Diet in Renal Disease Study Equation)[10,11] for subjects ≥18 years of age
7. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before the first dose of study drug (Day 1 for Part 1, Day -28 for Part 2).
8. Lung infection with organisms associated with a more rapid decline in pulmonary status (e.g., *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*). For subjects who have had a history of a positive culture in the past, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
   - The subject has had 2 respiratory tract cultures negative for these organisms within the past 12 months, with no subsequent positive cultures.
   - These 2 respiratory tract cultures were separated by at least 3 months, and 1 of them was obtained within the past 6 months.
9. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug (Day 1 for Part 1, Day -28 for Part 2).
10. A standard digital ECG demonstrating QTc >450 msec at screening. If QTc exceeds 450 msec for the screening ECG, the ECG should be repeated 2 more times during the Screening Period, and the subject will be excluded if the average of the 3 QTc values is >450 msec.
11. History of solid organ or hematological transplantation.

12. History or evidence of cataract or lens opacity determined to be clinically significant by the ophthalmologist or optometrist, based on the ophthalmologic examination during the Screening Period. If there is documentation of an examination meeting protocol criteria that was conducted within 3 months before the date of informed consent then the ophthalmologic examination does not need to be repeated during the Screening Period. This criterion does not apply to subjects with documentation of bilateral lens removal, and the ophthalmologic examination is not required for these subjects at screening.
13. History of alcohol or drug abuse in the past year, including but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator.
14. Ongoing or prior participation in an investigational drug study with the exception of the following:
    - Ongoing or prior participation in an investigational study of VX-661/IVA, IVA, LUM/IVA, or other CFTR modulator. For Part 1, a washout period of 28 days must elapse before Day 1. Subjects participating in Study 661-110 may have the Part 1 Screening Period extended by 4 weeks (Section 8.1.1.3). For Part 2, a washout period before Day -28 is not required, and subjects participating in Study 661-110 will transition directly from their prior treatment to the VX-661/IVA Run-in Period providing that they meet eligibility criteria. For both parts, subjects participating in Study 661-110 may have their screening assessments performed while continuing to participate in Study 661-110.
    - For prospective subjects with ongoing or prior participation in all other interventional studies, a washout period of 28 days or 5 terminal half-lives, whichever is longer, must elapse before screening. The duration of the elapsed time may be longer if required by local regulations.
    - Ongoing participation in a noninterventional study (including observational studies and studies requiring assessments without administration of study drug or assignment to other interventions) is permitted.
15. Use of commercially available CFTR modulator (e.g., Kalydeco, Orkambi) within 14 days before screening (Part 1 only).
16. Use of restricted medications as defined in Table 9-1, within the specified window before the first dose of study drug (Day 1 in Part 1, Day -28 in Part 2).
17. Pregnant or nursing females: Females of childbearing potential must have a negative pregnancy test at screening and Day 1.
18. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study. An adult (aged 18 years or older) who is a relative of a study staff member may be randomized in the study provided that
    - the adult lives independently of and does not reside with the study staff member, and
    - the adult participates in the study at a site other than the site at which the family member is employed.

9.3 Prohibited Medications

Medications that are prohibited in this study (Screening Period through the Safety Follow-up Visit) are shown in Table 9-1. VX-152, VX-661, and IVA are metabolized extensively via cytochrome P450 (CYP) 3A4. VX-152 is also metabolized by CYP2C9. Therefore, the use of moderate and strong inducers of CYP3A or CYP2C9 and strong and moderate inhibitors of CYP3A, which have the potential to alter the exposure of VX-152, VX-661, or IVA, will be restricted in this study. VX-152 was shown in vitro to be an inhibitor of the hepatic transporters organic anion transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3). Therefore, sensitive substrates of OATP1B1/1B3, such as HMG Co-A Reductase Inhibitors (i.e., "statins"), are also restricted during the study.

A non-exhaustive list of study prohibitions and cautions for medication will be provided in the Study Reference Manual.

Table 9-1 Study Restrictions

	Timing of Restriction	
Medication	**Start of Restriction**	**End of Restriction**
Moderate and strong CYP3A or CYP2C9 inducers	None allowed within 14 days before the first dose of the study drug on Day 1 (Part 1) or Day -28 (Part 2)	None allowed through the Safety Follow-up Visit
Moderate and strong CYP3A inhibitors (except ciprofloxacin)	None allowed within 14 days before the first dose of the study drug on Day 1 (Part 1) or Day -28 (Part 2)	None allowed through the Safety Follow-up Visit
Sensitive OATP1B1/1B3 substrates	None allowed within 14 days before the first dose of VX-152 or placebo on Day 1	None allowed until after last dose of VX-152 or placebo
Commercially available CFTR modulators (e.g., Kalydeco, Orkambi)	Part 1: None allowed within 14 days before screening Part 2: None allowed from the start of the Run-in Period	Part 1: None allowed through the Safety Follow-up Visit Part 2: None allowed through the end of the Washout Period

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

9.4 Prior and Concomitant Medications

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

- Subjects must remain on a stable medication (and supplement) regimen for their CF from 28 days before Day 1 through the Safety Follow-up Visit. Stable medication regimen is defined as the current medication regimen for CF that subjects have been following for at least 28 days before Day 1. Subjects must not initiate long-term treatment with new medication from 28 days before Day 1 through the Safety Follow-up Visit unless discussed and approved by the 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 cycle onto and off an inhaled antibiotic should continue on their prior schedule. The timing of the first dose of study drug on Day 1 should be synchronized as closely as possible (and not more than ± 3 days) to the first day in the cycle onto the inhaled antibiotic.
    - Subjects who alternate between 2 different inhaled antibiotics should remain on the same cycling schedule during the study. The timing of the first dose of study drug on Day 1 should be synchronized as closely as possible (and not more than ± 3 days) to the first day in the cycle onto 1 of the inhaled antibiotics.
- Subjects may receive doses of prednisone of up to 10 mg/day or equivalent (chronically) or prednisone 60 mg qd for up to 5 days without prior approval of the medical monitor.
- Information about bronchodilator use during the study will be collected and documented. Subjects who are using a bronchodilator must have their spirometry assessments performed according to the guidelines provided in Section 11.6.1.

9.5 Removal of Subjects

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

Subjects who have been randomized and whose screening *CFTR* genotype does not confirm study eligibility must be discontinued from the study, even if a previous *CFTR* genotype laboratory report was used to establish eligibility.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome.

The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a Safety Follow-up Visit, if applicable (see Section 8.1.6), and follow up with the subject regarding any unresolved AEs.

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

9.6 Replacement of Subjects

Subjects who withdraw or are withdrawn before the first dose of study drug on Day 1 may be replaced.

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

10 STUDY DRUG ADMINISTRATION AND MANAGEMENT

Study drug refers to VX-152, VX-661/IVA, IVA, and their matching placebos.

10.1 Preparation and Dispensing

Study drug may be dispensed only under the supervision of the investigator or an authorized designee and only for administration to the study subjects.

10.2 Administration

Study drug will be administered orally. Subjects will receive the same number of tablets each day to maintain the blind. Additional information is provided in the Pharmacy Manual.

Study drug will be administered with a fat-containing meal or snack, such as a standard "CF" high-fat, high-calorie meal or snack or a standard meal, according to the following guidelines:

1. It is recommended that the dose be taken within 30 minutes of the start of the meal or snack.
2. Study drug will be administered q12h (± 2 hours). For each subject, all doses of study drugs will be taken at approximately the same time each day. For example, the morning dose could be taken at 08:00 every morning and the evening dose could be taken at 20:00 every evening throughout the study.
3. The date, amount taken, and time of study drug administration, including whether food was taken with each dose, will be recorded for the 2 doses before PK sample collection and the dose received on the morning of PK sample collection.
4. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. The meal or snack will be provided by the site for the morning dose of study drug.

5. If a subject's scheduled visit is to occur in the afternoon, the following guidelines must be used:
    - If the dose in the clinic will be within 6 hours of the subject's scheduled morning dose, the subject should withhold their morning dose of study drug and the morning dose will be administered in the clinic.
    - If the dose in the clinic will be more than 6 hours after the subject's scheduled morning dose, the subject should take the morning dose at home and the evening dose will be administered in the clinic. In this event, all assessments will be collected relative to the evening dose.
6. 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.

10.2.1 Missed Doses

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

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

10.3 Method of Assigning Subjects to Treatment Groups

Approximately 12 subjects (Part 1 and Part 2, Cohort 1A) and approximately 24 subjects (Part 2, Cohort 2B) will be randomized in the ratio 3:1 to TC versus comparator in each cohort. An interactive web response system (IWRS) will be used to assign subjects to treatment. The randomization code list will be produced by Vertex Biostatistics or a qualified randomization vendor.

10.4 Study Drug Interruption and Stopping Rules

Subjects with new treatment-emergent ALT or AST elevations of >3 × ULN, or total bilirubin >2 × ULN, must be followed closely, including confirmatory testing performed by the central laboratory within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT, AST, and bilirubin levels, as clinically indicated.

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

Study drug administration **must be interrupted** immediately (prior to confirmatory testing), and the medical monitor must be notified, if any of the following criteria are 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
- Indirect bilirubin >2 × ULN (defined as ULN for total bilirubin minus ULN for direct bilirubin)

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

Study drug administration **must be discontinued**, if confirmatory testing results obtained after study drug interruption meet any of the following criteria:

- 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
- Indirect bilirubin >2 × ULN (defined as ULN for total bilirubin minus ULN for direct bilirubin), in association with decreased haptoglobin

If an alternative, reversible cause of transaminase elevation and/or increased bilirubin or clinical jaundice has been identified, study drug administration may be resumed once transaminases or bilirubin return to baseline or are ≤2 × ULN, whichever is higher. Approval of the medical monitor is required before resumption of study drug.

All subjects in whom treatment is discontinued for elevated transaminases and/or bilirubin should have these levels monitored closely until levels normalize or return to baseline.

10.5 Packaging and Labeling

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

10.6 Study Drug Supply, Storage, and Handling

VX-152 (100 mg) and matching placebo will be supplied as tablets of similar size and appearance containing 100 mg VX-152 and 0 mg VX-152, respectively.

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

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

Blister cards must be stored under conditions noted in Table 10-1 and in the Pharmacy Manual. The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for via the drug accountability forms as instructed by Vertex.

Table 10-1 Study Drug

Drug Name	Strength/Formulation/ Route	Dosage	Storage Condition
VX-152	100-mg tablet, oral	100, 200, or 300 mg q12h (planned)	≤25°C (77°F) with excursions to 30°C (86°F)
VX-152-matching placebo	0-mg tablet, oral	0 mg q12h	≤25°C (77°F) with excursions to 30°C (86°F)
VX-661/IVA fixed-dose	100-mg/150-mg tablet; oral	100 mg/150 mg qd (morning dose)	≤25°C (77°F) with excursions to 30°C (86°F)
VX-661/IVA-matching placebo	0-mg/0-mg tablet; oral	0 mg/0 mg qd (morning dose)	≤25°C (77°F) with excursions to 30°C (86°F)
IVA	150-mg tablet, oral	150 mg qd (evening dose) 150 mg q12h	≤25°C (77°F) with excursions to 30°C (86°F)
IVA-matching placebo	0-mg tablet, oral	0 mg qd (evening dose) 0 mg q12h	≤25°C (77°F) with excursions to 30°C (86°F)

10.7 Drug Accountability

The pharmacist or designated study site staff will maintain information regarding the dates and amounts of study drug received; study drug dispensed to the subjects; and study drug returned by the subjects. Subjects will be instructed to return all used 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.

10.8 Disposal, Return, or Retention of Unused Drug

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

10.9 Compliance

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

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

10.10 Blinding and Unblinding

This will be a double-blind study.

10.10.1 Blinding

All subjects, site personnel (including the investigator, the site monitor, and the study team), and the Vertex study team will be blinded to the treatment codes with the exception of the following:

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of the subject and her fetus in the event of a pregnancy
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy serious adverse event (SAE) processing and reporting regulations
- Unblinded statistician preparing the final (production) randomization list who is not part of the study team
- Vertex IWRS Manager
- Vertex Clinical Supply Chain
- IDMC
- Vendor performing the interim analyses and preparing the unblinded analysis for the ongoing reviews of efficacy and safety data, and a limited Vertex team not involved in the conduct of the study
- Vendor analyzing PK samples and Vertex Bioanalytical staff (non-study team) reviewing raw data from vendor
- Vertex Modeling and Simulations personnel or vendor conducting the population PK and PK/PD analyses
- Vertex medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time

Sweat Chloride and Spirometry Blinding: During the conduct of the study, the Vertex study team will not have access to the spirometry results after the morning dose on Day 1. Furthermore, sites, subjects, and their parents/caregivers/companions should not be informed of their study-related sweat chloride and spirometry results during the Treatment Period regardless of whether the subject has prematurely discontinued treatment.

A limited Vertex team not involved in the conduct of the study will be unblinded to results of the interim analyses and will have access to safety, efficacy, and PD data for the purpose of conducting ongoing reviews of safety and efficacy data for planning and enabling clinical development, regulatory, and chemistry, manufacturing, and controls (CMC) decisions.

The Vertex study team and lead investigator(s) will also conduct blinded reviews of all available safety and PK data after all subjects within a cohort complete the Day 15 Visit to make decisions about dose selection for potential subsequent cohorts.

When an interim analysis is performed after all subjects in 1 part have completed the Safety Follow-up Visit, results from that part will be unblinded for full review by the Vertex study team.

10.10.2 Unblinding

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

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

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

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

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

definitions or criteria for SAEs, and if so, submit an SAE report to Vertex GPS or designee, per Section 13.1.2.

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

11 ASSESSMENTS

11.1 Timing of Assessments

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

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

1. Vital signs and pulse oximetry
2. Standard 12-lead ECG recordings
3. Sweat chloride, spirometry
4. Safety laboratory assessments (including all blood draws)
5. PK sampling

11.2 Subject and Disease Characteristics

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

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

11.3 Pharmacokinetics

11.3.1 Blood Sampling

Blood samples will be collected as shown in Table 3-1, Table 3-2, and Table 3-3 for the determination of plasma concentrations of VX-152, VX-661, M1-661, IVA, and M1-IVA.

[redacted]

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.

Table 11-1 Acceptable Pharmacokinetic Sampling Windows

Sampling Time	Time From Scheduled Sampling Allowed
Predose	-60 minutes
From 0.25 up to ≤8 hours after study drug dosing	± 15 minutes

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

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

Plasma concentration samples collected from subjects treated with placebo will not be routinely analyzed.

11.3.2 Processing and Handling of Pharmacokinetic Samples

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

11.3.3 Bioanalysis

Samples will be analyzed using 1 or more validated analytical methods in compliance with Vertex or designee standard operating procedures. A description of the assay and validation data will be provided in separate reports.

11.4 Pharmacodynamics

11.4.1 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 3-1, Table 3-2, and Table 3-3, using an approved collection device. At each time point, 2 samples will be collected, 1 from each arm (left and right). 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 with the exception of the screening values. Specific instructions for collection, handling, processing, and shipping of sweat chloride samples to the central laboratory will be provided separately.

Subjects and their parents/caregivers/companions should not be informed of their study-related sweat chloride results during the Treatment Period, regardless of whether the subject prematurely discontinues treatment.

[redacted]

11.6 Efficacy

11.6.1 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines/European Respiratory Society Guidelines[6] at the time points noted in Table 3-1, Table 3-2, and Table 3-3 and according to the additional guidelines that follow.

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

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

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 the morning dose of study drugs at approximately the same time at each visit. Postdose spirometry assessments will be performed as noted in Table 3-1, Table 3-2, and Table 3-3.

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 assessment is pre-bronchodilator but, on a subsequent visit, the subject forgets to withhold bronchodilator use, a post-bronchodilator spirometry assessment will be obtained for that visit only, and the visit will not be rescheduled.
- If, on Day 1, the subject forgets to withhold his/her dose of bronchodilator, spirometry should be performed post-bronchodilator, and all subsequent spirometric measurements (according to the schedule of assessments detailed in Table 3-1, Table 3-2, and Table 3-3) should be performed post-bronchodilator.

- Each spirometry assessment will be recorded in the source documents as pre- or post-bronchodilator.

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

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

Subjects and their parents/caregivers/companions should not be informed of their study-related spirometry results during the Treatment Period, regardless of whether the subject prematurely discontinues treatment.

The measured spirometric values listed below will be converted to percent predicted values using the standards of GLI.[9]

- FEV_1 (L)

[redacted]

[redacted]

[redacted]

11.6.2 Height and Weight

Height and weight will be measured with shoes off at time points noted in Table 3-1, Table 3-2, and Table 3-3.

11.6.3 Cystic Fibrosis Questionnaire-Revised

Subjects will be asked to complete the CFQ-R in their native language, if validated translations are available.[12,13] The CFQ-R will be completed before any other study assessments are performed at the visits noted in Table 3-1 (Part 1) , Table 3-2 (Part 2, Cohort 2A), and Table 3-3 (Part 2, Cohort 2B). Subjects will complete the Adolescent/Adult version of the questionnaire themselves at all visits. The questionnaires provide information about demographics; general quality of life, school, work, or daily activities; and symptom difficulties (pertaining to CF). Copies of the CFQ-R used in this study will be provided in the Study Reference Manual. Validated translations of the CFQ-R, if available, will be provided for participating centers in non-English-speaking countries.[14,15]

11.7 Safety

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

11.7.1 Adverse Events

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

11.7.2 Clinical Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected as shown in Table 3-1, Table 3-2, and Table 3-3. Fasting is not required. Blood and urine samples will be analyzed at a central laboratory, with the exception of the urine pregnancy tests which will be performed and analyzed at the site. Laboratory test results that are abnormal and considered clinically significant will be reported as AEs.

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

Table 11-2 Safety Laboratory Test Panels

Serum Chemistry	Hematology[a]	Urinalysis[b]
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen	Erythrocytes	Nitrite
Creatinine	Mean corpuscular hemoglobin	Urobilinogen
Sodium	Mean corpuscular hemoglobin concentration	Urine protein
Potassium	Mean corpuscular volume	pH
Calcium	Reticulocytes	Urine blood
Chloride	Platelets	Specific gravity
Magnesium	Leukocytes	Urine ketones
Bicarbonate	Differential (absolute and percent):	Urine bilirubin
Inorganic phosphate	Eosinophils	Urine glucose
Total bilirubin	Basophils	
Direct bilirubin	Neutrophils	
Alkaline phosphatase	Lymphocytes	
Aspartate aminotransferase	Monocytes	
Alanine aminotransferase	**Coagulation Studies**	
Lactate dehydrogenase	Activated partial thromboplastin time	
Gamma-glutamyl transpeptidase	Prothrombin time	
Total protein	Prothrombin time International Normalized Ratio	
Albumin		
Amylase		
Lipase		
Haptoglobin[c]		

[a] Blood smears will be saved for future evaluation, if needed.
[b] If urine is positive for leukocyte esterase, nitrite, protein, or blood, microscopic examination of urine will be performed for leukocytes, erythrocytes, crystals, bacteria, and casts.
[c] Haptoglobin will be analyzed only if there is evidence of possible hemolysis.

Pregnancy (β-human chorionic gonadotropin) Tests for Females of Childbearing Potential:
Serum samples will be obtained as specified in Table 3-1, Table 3-2, and Table 3-3 and analyzed at the central laboratory. Urine pregnancy tests will be performed at the site as specified in Table 3-1, Table 3-2, and Table 3-3. The urine pregnancy test on Day 1 must be negative before the first dose of study drug. Additional urine pregnancy tests may be required according to local regulations and/or requirements.

Follicle-stimulating Hormone (Screening Period only): Blood sample for FSH will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be within the postmenopausal reference range of the performing laboratory to be considered postmenopausal.

CFTR genotype (Screening Period only): *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used to establish eligibility. Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.5).

G6PD Activity Test (Screening Period only): A single blood sample will be collected for the G6PD activity test, which will be performed in an established laboratory that runs the assay routinely. The use of a local laboratory that routinely runs quantitative G6PD activity assays is acceptable as an alternative to the central laboratory.

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

For purposes of study conduct, the central laboratory must be used for all laboratory tests with the exception of the G6PD activity test. 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 Physical Examinations and Vital Signs

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, and Table 3-3). 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 complete PE includes a review of the following systems: head/neck/thyroid; eyes/ears/nose/throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. After screening, any clinically significant abnormal findings in PEs will be reported as AEs.

The abbreviated PE will include an assessment of the following body systems: EENT, cardiovascular system, respiratory system, abdomen, and skin.

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 position.

11.7.4 Pulse Oximetry

Arterial oxygen saturation by pulse oximetry will be measured at visits specified in Table 3-1, Table 3-2, and Table 3-3. This will be assessed following a 5-minute rest (seated) and before study drug dosing. At visits when study drug is taken at the site, pulse oximetry will be collected before the morning dose. This is a noninvasive measure of oxygen delivery to the tissues and has been correlated with clinical status and lung function.

11.7.5 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout according to the Schedule of Assessments (Table 3-1, Table 3-2, and Table 3-3). 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 seated 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 (HR), such as blood draws.

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

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

11.7.6 Ophthalmologic Examination

Subjects will undergo an ophthalmologic examination performed by a licensed ophthalmologist or optometrist as noted in Table 3-1, Table 3-2, and Table 3-3, 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 before randomization. This examination does not have to be performed if there is documentation of an examination that met protocol criteria and was within 3 months before the date of informed consent or if there is documentation of bilateral lens removal for the subject.

If a cataract or lens opacity is identified and determined to be clinically significant by the ophthalmologist or optometrist at the screening examination, the subject must not be randomized. If a cataract or lens opacity is identified and determined to be clinically significant by the ophthalmologist or optometrist after dosing, the subject will be notified. After discussion with the principal investigator, and in collaboration with the 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 Visit. If the subject continues study drug treatment, more frequent ophthalmologic monitoring should be considered.

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

In addition, at screening, the following history will be obtained and documented 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 Contraception and Pregnancy

The effects of VX-152 monotherapy or in dual or triple combination with VX-661 and IVA on conception, pregnancy, and lactation in humans are not known. VX-152, VX-661, and IVA did not show any genotoxic potential in a standard battery of in vitro (Ames test, chromosomal aberration or micronucleus in cultured mammalian cells) and in vivo (rodent micronucleus) studies. VX-152, VX-661, and IVA were each found to be nonteratogenic in reproductive toxicology studies in rats and rabbits.[5,7,16,17,18,19,20]

11.7.7.1 Contraception

Study participation requires compliance with the contraception guidelines outlined below.

Contraception requirement 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. True abstinence must be practiced from the Screening Visit through 90 days after the last dose of study drug.
- If the male is infertile (e.g., bilateral orchiectomy). If a male subject is assumed to have complete bilateral absence of the vas deferens, infertility must be documented before the first dose of study drug (e.g., examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound).

- If the female is of non-childbearing potential. To be considered of non-childbearing potential, the female must meet at least 1 of the following criteria:
  - Postmenopausal: Amenorrheic for at least 12 consecutive months and a serum FSH level within the laboratory's reference range for postmenopausal females.
  - Documented hysterectomy or bilateral oophorectomy/salpingo-oophorectomy.

  Note: All other females (including females with tubal ligations and females who do not have a documented bilateral oophorectomy) will be considered to be of childbearing potential.
- Same sex relationships

For subjects for whom the contraception requirement is not waived, study participation requires a commitment from the subject that at least 1 acceptable method of contraception is used as a couple. Acceptable methods of contraception are listed in Table 11-3.

Table 11-3 Acceptable Methods of Contraception

	Male Subjects and Their Female (Non-study) Partners	Female Subjects and Their Male (Non-study) Partners
Vasectomy 6 months or more previously, with a documented negative postvasectomy semen analysis for sperm	Yes	Yes
Bilateral tubal ligation performed at least 6 months previously.	Yes	Yes
Male or female condom with or without spermicide[a]	Yes	Yes
Female barrier contraception (such as diaphragm, cervical cap, or sponge) with spermicide	Yes	Yes
Continuous use of an intrauterine device for at least 90 days before the first dose of study drug.		
Hormone-releasing	Yes	No[b]
Non-hormone releasing	Yes	Yes
Hormonal contraceptives, if successfully used for at least 60 days before the first dose of study drug.	Yes	No[b]

Note: At least 1 acceptable method of contraception must be used by couples not exempt from the contraception requirement. Methods of contraception must 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. Additional contraception requirements may need to be followed according to local regulations and/or requirements.

[a] A female condom cannot be used with a male condom due to risk of tearing.

[b] Hormone-releasing intrauterine devices and hormonal contraceptives are not considered an acceptable method in female study subjects; however, female subjects are not required to discontinue their use of hormone-releasing intrauterine devices or hormonal contraceptives.

Additional notes:

- 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), or is otherwise already pregnant before the male subject's first dose of study drug, must be compliant with the contraception requirements. In this scenario, the male subject and his female partner must commit to using a male condom (to ensure there is no exposure of the fetus to study drug) for the duration of the study and until 90 days after the last dose of study drug.
- Female subjects should not nurse a child from the start of study drug dosing through 90 days following the last dose of study drug.
- Unique situations that may not fall within the above specifications should be discussed with the medical monitor.

11.7.7.2 Pregnancy

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

If a female subject or the female partner of a male subject becomes pregnant while participating in the study, study drug will be permanently discontinued immediately. The investigator will 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 confirmed to be on active drug, the subject or partner will be followed until the end of the pregnancy and the infant will be followed for 1 year after the birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE.

12 STATISTICAL AND ANALYTICAL PLANS

12.1 Sample Size and Power

12.1.1 Primary Objectives

The primary objective of the study is the evaluation of safety and tolerability of VX-152 in TC with VX-661/IVA. The sample size calculations described below are deemed adequate to evaluate the safety objective of the study, based on clinical and statistical considerations.

12.1.1.1 Safety and Tolerability

The primary safety endpoint is the incidence of AEs. Up to approximately 72 subjects are planned to be enrolled in the study with up to 36 subjects receiving VX-152 in TC with VX-661/IVA for 2 weeks (Part 1 and Part 2, Cohort 2A), and 18 subjects receiving VX-152 in TC with VX-661/IVA for 4 weeks (Part 1 and Part 2, Cohort 2B). The sample size for each treatment group in Parts 1 and 2 will provide sufficient data for a descriptive analysis of AEs. Table 12-1 provides the probability of observing an AE in at least 1 subject based on a sample size of 9 or 18 subjects subjects per TC treatment group and AE incidences ranging from 5% to 15%. The probability calculations are based on a binomial model using the probability calculator in the PASS software package (Version 11.0).

Table 12-1 Probability of Observing an Adverse Event

	Number of Subjects in TC Treatment Group [a]	
AE Incidences[a]	**9**	**18**
5%	37%	60%
10%	61%	85%
15%	77%	95%

[a] AE incidences are based on 2 weeks of treatment in 9 subjects for Part 1 and Part 2 (Cohort 1A), and 4 weeks of treatment in 18 subjects for Part 2, Cohort 2B.

12.1.2 Secondary Objectives

The secondary objectives of the study include the evaluation of the PD effect of VX-152 in TC with VX-661/IVA on sweat chloride concentrations, and the evaluation of the efficacy of VX-152 in TC with VX-661/IVA.

12.1.2.1 Pharmacodynamic Effect

The absolute change from baseline at Day 15 in sweat chloride concentrations is a secondary endpoint used to evaluate the PD objective of the study. In Part 1, a test for a decreasing dose-response trend between placebo and the TC dose groups will be performed using a multiple comparisons procedure (MCP). The procedure consists of testing the null hypothesis of a non-decreasing dose-response trend versus a decreasing trend using the 1-sided maximum *t*-statistic that controls the type I error at alpha = 5%. The procedure requires a family of candidate dose-response models to be prespecified, that covers the range of plausible and diverse dose-response profiles.

The candidate models that best describe the expected decreasing dose-response profile of the TC groups compared to placebo include a linear model, a maximum effect (E_{max}) model, and a sigmoid E_{max} model. The contrasts (i.e., linear combinations of the treatment group means at Day 15) selected to perform the MCP and that capture the shape of these candidate models are described in Table 12-2 below.

Table 12-2 Contrast Coefficients for the Multiple Comparisons Procedure in Part 1

Candidate Model	Placebo	Cohort 1A Dose	Cohort 1B Dose	Cohort 1C Dose
Linear	3.0	1.0	-1.0	-3.0
E_{max}	3.0	-1.0	-1.0	-1.0
Sigmoid E_{max}	1.0	1.0	-1.0	-1.0

Note: Contrast coefficients are presented for 2 TC dose groups and placebo.

Table 12-3 provides the power to detect a dose-response trend with the MCP procedure for 3 different expected dose-response profiles with 9 subjects assigned to placebo, 9 subjects assigned to TC in Cohort 1A, 9 subjects assigned to TC in Cohort 1B, and 9 subjects assigned to TC in Cohort 1C for a total sample size of 36 subjects in Part 1 (based on 5000 simulations for each profile using the R software package MCPMod [Version 1.0-8]).

Table 12-3 Power to Detect a Decreasing Dose-response Trend Based on Change From Baseline in Sweat Chloride in Part 1

	Mean Change From Baseline in Sweat Chloride				
Candidate Model	Placebo	Cohort 1A Dose	Cohort 1B Dose	Cohort 1C Dose	Power
Linear	0	-12	-16	-20	94%
E_{max}	0	-20	-20	-20	98%
Sigmoid E_{max}	0	0	-20	-20	>99%

Note: A 1-sided maximum *t*-statistic with a sample size of 36 subjects in Part 1 assigned to TC in Cohort 1C, TC in Cohort 1B, TC in Cohort 1A, and placebo at a ratio 1:1:1:1 was used for power calculations. An SD change from baseline in sweat chloride of 13 mmol/L was used for power calculations.

Table 12-4 provides the power to reject the null within-group hypothesis of no decrease in the mean absolute change from baseline for sweat chloride at Day 15 for the TC treatment groups in Parts 1 and 2 with a sample size of 9 or 18 subjects per treatment group. The power calculations are based on a 1-sided 1-sample *t*-test at alpha = 5% using the software package PASS (Version 11.0), assuming a mean change of -10 to -20 mmol/L and an SD of 13 mmol/L in the absolute change from baseline for sweat chloride.

Table 12-4 Power for Within-group Decrease for Mean Absolute Change From Baseline in Sweat Chloride

Mean Absolute Change From Baseline in Sweat Chloride (mmol/L)	Number of Subjects per Treatment Group[a]	
	9	18
-10	68%	93%
-15	93%	>99%
-20	>99%	>99%

Note: An SD of 13 mmol/L for the absolute change from baseline in sweat chloride was used for power calculations.

[a] Applies to Parts 1 and 2.

12.1.2.2 Efficacy

The absolute change from baseline in $ppFEV_1$ at Day 15 is a secondary endpoint used to evaluate the efficacy objective of the study. Table 12-5 provides the power to reject the null within-group hypothesis of no increase in the mean absolute change from baseline for $ppFEV_1$ at Day 15, for the TC treatment groups in Parts 1 and 2 with a sample size of 9 or 18 subjects per treatment group. The power calculations are based on a 1-sided 1-sample *t*-test at alpha = 5% using the software package PASS (Version 11.0), assuming an absolute mean change of 3 to 7 percentage points and an SD of 8 percentage points in the absolute change from baseline for $ppFEV_1$.

Table 12-5 Power for Within-group Increase for Mean Absolute Change From Baseline in $ppFEV_1$

Mean Absolute Change From Baseline in $ppFEV_1$	Number of Subjects per Treatment Group[a]	
	9	18
3%	27%	45%
5%	53%	82%
7%	77%	97%

Note: An SD of 8 percentage points for the absolute change from baseline in $ppFEV_1$ was used for power calculations.

[a] Applies to Parts 1 and 2.

12.2 Analysis Sets

The following analysis sets are defined: All Subjects Set, Full Analysis Set, and Safety Set. Additional analysis sets related to the Run-in Period will be defined in the statistical analysis plan (SAP), as appropriate.

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

The **Full Analysis Set (FAS)** will include all randomized subjects who carry the intended *CFTR* allele mutation and have received at least 1 dose of study drug in the Treatment Period. The FAS will be used to summarize subject demographics and baseline characteristics, and for all PD and efficacy analyses, unless otherwise specified.

The **Safety Set** will include all subjects who received at least 1 dose of study drug in the Treatment Period. The Safety Set will be used for all safety analyses, unless otherwise specified.

12.3 Statistical Analysis

This section presents a summary of the planned statistical analyses of the primary PD and efficacy endpoints of the study. Statistical analysis details will be provided in the SAP and clinical pharmacologic analysis details will be provided in the clinical pharmacology analysis plan (CPAP). Both plans will be finalized before the clinical data lock and unblinding of the study.

12.3.1 General Considerations

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, standard error (SE), median, minimum value (min), and maximum value (max). The precision of the measurement for each continuous variable will be specified in the SAP. Unless otherwise specified, minimum and maximum values will be reported with the same precision as the units of the raw data. The mean, median, SD, and SE will be reported to 1 additional decimal place. Any values that require a transformation to standard units (metric or International System [SI]) will be converted with the appropriate precision.

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

The **baseline** value, unless otherwise specified, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the Treatment Period (i.e., Day 1). For ECG, baseline will be defined as the average of the most recent triplicate pretreatment measurements before the first dose of study drug in the Treatment Period (i.e., Day 1).

Absolute change from baseline will be calculated as postbaseline value – baseline value.

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

The Treatment-emergent (TE) Period will include the time from the first dose in the Treatment Period to the Safety Follow-up Visit or 28 days after the last dose of the study drug for subjects who do not complete the Safety Follow-up Visit. Additional TE periods related to the Run-in period will be defined in the SAP, as appropriate.

There will be no multiplicity adjustment for performing multiple hypothesis tests.

The rules for handling missing data due to treatment or study discontinuation will be described in the SAP.

All data will be summarized for Parts 1 and 2, separately, unless specified otherwise.

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

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

12.3.2.2 Demographics and Baseline Characteristics

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

The following demographics and baseline characteristics will be summarized overall and by treatment group for the FAS and will include (but are not limited to): sex, race, age, baseline weight, baseline height, baseline body mass index (BMI), baseline ppFEV$_1$, and baseline sweat chloride.

No statistical tests will be performed to evaluate baseline imbalance between treatment groups.

12.3.2.3 Prior and Concomitant Medications

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

- **Prior medication:** any medication that started before initial dosing of study drug, regardless of when it ended
- **Concomitant medication:** medication continued or newly received during the TE Period
- **Post-treatment medication:** medication continued or newly received after the TE Period

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

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

Additional classifications of concomitant medications related to the Run-in Period will be defined in the SAP, as appropriate.

12.3.2.4 Study Drug Exposure and Compliance

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

Dosing compliance based on number of tablets taken, will be summarized for the FAS, and will be derived as 100 × [(total number of tablets dispensed) – (total number of tablets returned)]/ (total number of tablets planned to be taken per day × duration of study drug exposure in days).

Dosing compliance based on study drug exposure, will be derived as 100 × [1 - (total number of days of study drug interruption) / (duration of study drug exposure in days)].

12.3.2.5 Important Protocol Deviations

An important protocol deviation (IPD) is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. The rules for identifying an IPD will be described in the SAP.

All IPDs will be provided in an individual subject data listing.

12.3.3 Efficacy Analysis

A secondary objective of the study is the evaluation of the efficacy of VX-152 in TC with VX-661/IVA in Parts 1 and 2.

12.3.3.1 Analysis of Primary Efficacy Variables

The primary efficacy variable is the absolute change from baseline for $ppFEV_1$ at Day 15. The analysis will be performed using a mixed-effects model for repeated measures (MMRM) with change from baseline for $ppFEV_1$ as the dependent variable. The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects, with the baseline $ppFEV_1$ value as a covariate. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the F test for fixed effects will be estimated using the Kenward-Roger approximation. A compound symmetry covariance structure will be used to model the within-subject errors. Conditional on the fixed effects, missing data due to treatment or study discontinuation will be assumed to be missing at random.

Descriptive analyses of the change from baseline will be performed for all treatment groups. Adjusted means and 2-sided 95% confidence intervals of the treatment effect at Day 15, with 1-sided *P* values for all within-group and between-group comparisons, will be estimated within MMRM using LSMeans via PROC MIXED in SAS in both parts.

[redacted]

There will be no multiplicity adjustment for performing multiple hypothesis tests.

12.3.3.2 Analysis of Secondary Efficacy Variables

The secondary efficacy variables include:

- Absolute change from baseline for $ppFEV_1$ through Day 29 (Part 2, Cohort 2B only).
- Relative change in $ppFEV_1$ from baseline at Day 15 (Part 1 and Part 2), and through Day 29 (Part 2, Cohort 2B only)
- Absolute change in the CFQ-R respiratory domain score from baseline at Day 15 (Part 1 and Part 2), and at Day 29 (Part 2, Cohort 2B only)

Details of the analysis will be provided in the SAP.

[redacted]

12.3.4 Pharmacodynamic Analysis

A secondary objective of the study is the evaluation of the PD effect of VX-152 in TC with VX-661/IVA on sweat chloride concentrations.

12.3.4.1 Pharmacodynamic Effect at Day 15

The absolute change in sweat chloride from baseline at Day 15 is a secondary endpoint used to evaluate the PD objective of the study. In Part 1, the test to detect a decreasing dose-response trend between placebo and the TC dose groups will be performed using the MCP procedure with the prespecified comparisons (contrasts) of the treatment group means within a linear MMRM framework. The model will include the absolute change from baseline for sweat chloride as the dependent variable, with treatment group, visit, and treatment-by-visit interaction as fixed effects, and the baseline sweat chloride value as a covariate. The test will be performed using the 1-sided maximum *t*-statistic of the individual *t*-statistics for the multiple prespecified contrasts at alpha = 5%, based on the treatment group means at Day 15.

Further, adjusted means and 2-sided 95% confidence intervals of the treatment effect at Day 15, with 1-sided *P* values for all within-group and between-group comparisons, will be estimated within MMRM, in both parts.

Additional details of the analysis will be provided in the SAP.

12.3.4.2 Pharmacodynamic Effect through Day 29 (Part 2, Cohort 2B only)

The absolute change in sweat chloride from baseline through Day 29 (Part 2, Cohort 2B only) is also a secondary endpoint used to evaluate the PD objective of the study. The adjusted mean and 2-sided 95% confidence interval of the average treatment effect through Day 29 for the within-group and between-group comparisons in Part 2, Cohort 2B will be estimated within MMRM.

12.3.5 Safety Analysis

The primary objective of the study is the evaluation of safety and tolerability. All safety analyses will be based on data from the TE Period for all subjects in the Safety Set.

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

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

All safety data will be summarized by treatment group and overall, for each Part. In addition, safety data will also be summarized separately for Part 2, Cohort 2B.

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

12.3.5.1 Adverse Events

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

- Pretreatment AE: any AE that started before the first dose of study drug
- TEAE: any AE that increased in severity or that was newly developed at or after the first dose of study drug through the end of the TE Period
- Post-treatment AE: any AE that increased in severity or that was newly developed beyond the TE Period

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

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

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

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

relationship level in the relationship summaries. In addition, a listing containing individual subject level AE data for all deaths and other serious and significant AEs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

12.3.5.2 Clinical Laboratory Assessments

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

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE Period will be summarized overall and by treatment group for each Part. The threshold analysis criterion shift from baseline 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 and the serum pregnancy test will be listed in individual subject data listings only. In addition, a listing containing individual subject hematology, chemistry, and coagulation values outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled visits.

12.3.5.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided overall and by treatment group for each Part, at each scheduled visit and time point, as applicable, for the following ECG interval measurements (in ms): RR, PR, QT, and QT corrected for HR (QTcF), QRS duration, and HR (beats per minute).

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

Additional ECG analyses will be described in the SAP.

12.3.5.4 Vital Signs

For the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized overall and by treatment group at each scheduled visit. The following vital signs parameters will be summarized: systolic and diastolic blood pressure (mm Hg), body temperature (°C), HR (beats per minute), and respiratory rate (breaths per minute).

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE Period will be summarized overall and by treatment group for each Part. The threshold analysis criteria will be provided in the SAP.

Additional vital signs analyses will be described in the SAP.

12.3.5.5 Pulse Oximetry

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

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

12.3.5.6 Physical Examination

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

12.3.5.7 Other Safety Analysis

Not applicable.

12.3.6 Interim and IDMC Analyses

12.3.6.1 Interim Analysis

Interim analyses for each cohort may be performed after all subjects in the cohort have completed the Day 15 Visit. The results of these analyses will be reviewed by a limited Vertex team. When an interim analysis is performed after all subjects in 1 part have completed the Safety Follow-up Visit, results from that part will be unblinded for full review by the Vertex study team.

12.3.6.2 IDMC Analysis

The safety of the TC will be monitored by an external, IDMC to ensure the safety of the subjects in the study.

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

12.4 Clinical Pharmacology Analysis

12.4.1 Pharmacokinetic Analysis

The PK analysis of VX-152, VX-661 and metabolite M1-661, and IVA and metabolite M1-IVA will be performed using nonlinear mixed effects modeling. Standard noncompartmental analysis may also be performed as data allow. Descriptive statistics will be used to summarize PK parameter values for all analytes.

A detailed description of the planned PK analysis will be presented in the CPAP.

12.4.2 Pharmacokinetic/Pharmacodynamic Analyses

PD assessments to be included in PK/PD analyses may include sweat chloride, $ppFEV_1$, as well as other secondary endpoints such as [redacted] CFQ-R. Comparison between postdose and predose values will be performed and expressed as a change from baseline.

A sequential approach will be used to perform the population PK/PD analysis. The Bayesian estimates of individual PK parameters from the final population PK model will be used to simulate PK profiles for each subject. The simulated VX-152, VX-661, IVA, or metabolite plasma concentrations will be used in the potential pharmacological response models to describe changes in each endpoint from baseline. Fixed- and random-effect parameter estimates and the associated asymptotic SEs will be estimated. Descriptive statistics will be used to summarize Bayesian estimates of individual PK/PD parameters obtained from the population PK/PD model.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

13.1.1.2 Clinically Significant Assessments

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

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

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

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

A laboratory value that is Grade 4 will not automatically be an SAE. A Grade 4 laboratory value will be an SAE if the subject's clinical status 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
    - the ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (see Section 8.1.6).

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

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

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed August 2015). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." In considering the severity of an AE in a pediatric subject, the investigator will consider that reference ranges for pediatric clinical laboratory parameters may differ from those given in the CTCAE. The severity of an AE that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

Classification	Definition
Mild (Grade 1)	Mild level of discomfort and does not interfere with regular activities
Moderate (Grade 2)	Moderate level of discomfort and significantly interferes with regular activities
Severe (Grade 3)	Significant level of discomfort and prevents regular activities
Life-threatening (Grade 4)	Any adverse drug event 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 reappeared 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.

AE: adverse event

13.1.1.7 Adverse Event Outcome

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

Table 13-4 Classifications for Outcome of an AE

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

AE: adverse event

13.1.1.8 Treatment Given

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

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

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

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

If a subject has a hospitalization or procedure (e.g., surgery) for an event or condition that occurred before the subject signed the ICF, and the hospitalization or procedure was planned before the subject signed the ICF, the hospitalization or procedure 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 through the Safety Follow-up Visit, regardless of causality, will be reported by the investigator to Vertex GPS. In addition, all SAEs that occur after the Safety Follow-up Visit and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours**.

SAEs will be recorded on the Vertex Organized Safety Information Collection Form (hereafter referred to as the "SAE Form") using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the investigator for relationship to the investigational study drug(s) and possible etiologies. On the SAE Form, relationship to study drug(s) will be assessed only as related (includes possibly related) or not related (includes unlikely related), and severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the event to resolution and report to Vertex the outcome of the event using the SAE Form.

13.1.2.3 Reporting Serious Adverse Events

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

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (preferred choice)

Fax: [redacted]

Contact Telephone: [redacted]

13.1.2.4 Expedited Reporting and Investigator Safety Letters

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

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

13.2.3 Investigator Compliance

No modifications to the protocol will be made without the approval of both the investigator and Vertex. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (i.e., efficacy assessments) will require IRB/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 the protocol will be fully documented in the source documentation and in a protocol deviation log.

13.2.4 Access to Records

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

13.2.5 Subject Privacy

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

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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4 Cystic Fibrosis Foundation. Patient Registry: 2014 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation; 2015.

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6 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.

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APPENDIX A *CFTR* Mutations That Are Predicted to Result in a CFTR Protein With Minimal Function (Part 1)

Per the study eligibility criteria, heterozygous *F508del-CFTR* subjects in Part 1 must have a second *CFTR* allele containing a mutation that is predicted to result in a CFTR protein with minimal function and not likely to respond to VX-661 and/or ivacaftor (IVA) therapy. These *CFTR* mutations were defined using 3 major sources:

- biological plausibility for the mutation to respond (i.e., mutation class)
- evidence of clinical severity on a population basis (per CFTR2 patient registry; accessed on 15 February 2016)
    - average sweat chloride >86 mmol/L, and
    - prevalence of pancreatic insufficiency (PI) >50%
- in vitro testing
    - mutations resulting in baseline chloride transport <10% of wild-type CFTR were considered minimal function
    - mutations resulting in chloride transport <10% of wild-type CFTR following the addition of VX-661 and/or IVA were considered nonresponsive

The clinical severity criteria (average sweat chloride >86 mmol/L and %PI >50%) do not apply to the individual subjects to be enrolled in this study, but were used to classify the mutation status on a population level.

The list below represents acceptable mutations; however, this list may not include every eligible mutation, and investigators should contact the medical monitor regarding other mutations that may also meet study eligibility criteria.

CFTR Mutations Eligible for VX15-152-101, Part 1

Criteria	Mutation				
Truncation mutations • %PI >50% and/or $SwCl^-$ >86 mmol/L • no full-length protein	S4X	C276X	G542X	R792X	E1104X
	G27X	Q290X	G550X	E822X	R1158X
	Q39X	G330X	Q552X	W846X	R1162X
	W57X	W401X	R553X	Y849X	S1196X
	E60X	Q414X	E585X	R851X	W1204X
	R75X	S434X	G673X	Q890X	L1254X
	E92X	S466X	Q685X	S912X	S1255X
	Q98X	S489X	R709X	Y913X	W1282X
	Y122X	Q493X	K710X	W1089X	Q1313X
	E193X	W496X	L732X	Y1092X	E1371X
	L218X	C524X	R764X	W1098X	Q1382X
	Q220X	Q525X	R785X	R1102X	Q1411X

CFTR Mutations Eligible for VX15-152-101, Part 1

Criteria	Mutation				
Splice mutations • %PI >50% and/or $SwCl^-$ >86 mmol/L • no or little mature mRNA	185+1G→T	711+5G→A	1717-8G→A	2622+1G→A	3121-1G→A
	296+1G→A	712-1G→T	1717-1G→A	2790-1G→C	3500-2A→G
	405+1G→A	1248+1G→A	1811+1G→C	3040G→C (G970R)	3600+2insT
	405+3A→C	1249-1G→A	1811+1.6kbA→G		3850-1G→A
	406-1G→A	1341+1G→A	1812-1G→A	3120G→A	4005+1G→A
	621+1G→T	1525-2A→G	1898+1G→A	3120+1G→A	4374+1G→T
	711+1G→T	1525-1G→A	1898+1G→C	3121-2A→G	
Small (≤3 nucleotide) insertion/deletion (ins/del) frameshift mutations • %PI >50% and/or $SwCl^-$ >86 mmol/L • garbled and/or truncated protein	182delT	1119delA	1782delA	2732insA	3876delA
	306insA	1138insG	1824delA	2869insG	3878delG
	365-366insT	1154insTC	2043delG	2896insAG	3905insT
	394delTT	1161delC	2143delT	2942insT	4016insT
	442delA	1213delT	2183AA→G [a]	2957delT	4021dupT
	444delA	1259insA	2184delA	3007delG	4040delA
	457TAT→G	1288insTA	2184insA	3028delA	4279insA
	541delC	1471delA	2307insA	3171delC	4326delTC
	574delA	1497delGG	2347delG	3659delC	
	663delT	1548delG	2585delT	3737delA	
	935delA	1609del CA	2594delGT	3791delC	
	1078delT	1677delTA	2711delT	3821delT	
Non-small (>3 nucleotide) insertion/deletion (ins/del) frameshift mutations • %PI >50% and/or $SwCl^-$ >86 mmol/L • garbled and/or truncated protein	CFTRdele2,3	1461ins4	2991del32		
	CFTRdele22,23	1924del7	3667ins4		
	124del23bp	2055del9→A	4010del4		
	852del22	2105-2117del13insAGAAA	4209TGTT→AA		
	991del5	2721del11			
Class II, III, IV mutations not responsive to IVA alone or in combination with VX-661 or LUM • %PI >50% and/or $SwCl^-$ >86 mmol/L AND • Not responsive in vitro to IVA alone or in combination with VX-661 or LUM	A46D [b]	V520F	Y569D [b]		
	G85E	A559T [b]	L1065P		
	R347P	R560T	R1066C		
	L467P [b]	R560S	M1101K		
	I507del	A561E	N1303K		

CFTR: cystic fibrosis transmembrane conductance regulator; IVA: ivacaftor; LUM: lumacaftor; $SwCl^-$: sweat chloride; PI: pancreatic insufficiency

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 February 2016.

%PI: percentage of *F508del-CFTR* heterozygous patients in the CFTR2 patient registry who are pancreatic insufficient; $SwCl^-$: mean sweat chloride of *F508del-CFTR* heterozygous patients in the CFTR2 patient registry

[a] Also known as 2183delAA→G.

[redacted]

15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX16-152-102	Version #: 3.0	Version Date: 14 April 2017
Study Title: A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety of VX-152 Combination Therapy in Adults With Cystic Fibrosis		

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

[redacted]

15.2 Investigator Signature Page

Protocol #: VX16-152-102	Version #: 3.0	Version Date: 14 April 2017
Study Title: A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety of VX-152 Combination Therapy in Adults With Cystic Fibrosis		

I have read Protocol VX16-152-102, Version 3.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-152, VX-661, and ivacaftor, and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date