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VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 1/2 Study of VX-121 in Healthy Subjects and in Subjects With Cystic Fibrosis

Vertex Study Number: VX17-121-001

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2 PROTOCOL SYNOPSIS

Title

A Phase 1/2 Study of VX-121 in Healthy Subjects and in Subjects With Cystic Fibrosis

Clinical Phase and Clinical Study Type

Phase 1/2 safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy

Objectives

Primary Objectives

Part A: To evaluate the safety and tolerability of single ascending doses of VX-121 in healthy subjects

Part B: To evaluate the safety and tolerability of multiple ascending doses of VX-121 for 10 days in healthy subjects

Part C: To evaluate the safety and tolerability of multiple ascending doses of VX-121 administered in triple combination (TC) with tezacaftor (TEZ)/ivacaftor (IVA) for 14 days in healthy subjects

Part D: To evaluate the safety and tolerability of VX-121 in TC with TEZ/IVA in subjects with cystic fibrosis (CF)

Secondary Objectives

Part A

- To evaluate the PK of VX-121 after administration of single ascending doses of VX-121 in healthy subjects
- To evaluate the relative bioavailability (BA) of a tablet formulation of VX-121 relative to suspension in healthy subjects
- To evaluate the effect of milk on the PK of VX-121 after administration of suspension and tablet formulations

Part B

To evaluate the PK of VX-121 after administration of multiple ascending doses of VX-121 for 10 days in healthy subjects

Part C

- To evaluate the PK of VX-121 after administration of multiple ascending doses of VX-121 in TC with TEZ/IVA for 14 days in healthy subjects
- To evaluate the PK of TEZ, IVA, and their respective metabolites when administered in TC with VX-121 for 14 days in healthy subjects

Part D

- To evaluate the PK of VX-121 when administered in TC with TEZ/IVA in subjects with CF
- To evaluate the PK of TEZ, IVA, and their respective metabolites when administered in TC with VX-121 in subjects with CF
- To evaluate the PD effect of VX-121 in TC with TEZ/IVA in subjects with CF
- To evaluate the efficacy of VX-121 in TC with TEZ/IVA in subjects with CF

Endpoints

Primary Endpoint

Parts A, B, C, and D: Safety and tolerability, based on the assessment of adverse events (AEs), laboratory test results, standard 12-lead ECGs, vital signs, and spirometry (Part D only)

Secondary Endpoints

- **Parts A, B, C, and D:** PK parameter estimates of VX-121 derived from plasma concentration-time data
- **Parts C and D**: PK parameter estimates for TEZ and metabolites (M1-TEZ and M2-TEZ) and IVA and metabolites (M1-IVA and M6-IVA) derived from plasma concentration-time data
- **Part D**: Sweat chloride levels as a biomarker of PD effects
- **Part D**: Spirometry as preliminary evidence of efficacy

Number of Subjects

Approximately 132 subjects: 56 in Part A, 48 in Part B, 16 in Part C, and 12 in Part D

Study Population

Parts A, B, and C: Healthy male subjects and female subjects of non-childbearing potential between the ages of 18 and 55 years, inclusive

Part D: Male subjects and female subjects of non-childbearing potential with CF, heterozygous for *F508del* and a minimal *CFTR* function mutation that is not responsive to TEZ, IVA, or TEZ/IVA (F/MF genotypes), ages 18 and older

Investigational Drug

Parts A and B

Active substance: VX-121

Activity: CFTR corrector

Strength and route of administration:

Suspension: Drug substance will be reconstituted at various concentrations for oral administration

Tablet: 5-mg tablet for oral administration

Parts C and D

Active substance: VX-121

Activity: CFTR corrector

Strength and route of administration:

Suspension: Drug substance will be reconstituted at various concentrations for oral administration

Tablet: 5-mg tablet for oral administration

Active substance: TEZ (VX-661) and IVA (VX-770)

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

Strength and route of administration: 100-mg TEZ/150-mg IVA, film-coated fixed-dose combination (FDC) tablet for oral administration

Active substance: IVA (VX-770)

Activity: CFTR potentiator

Strength and route of administration: 150-mg film-coated tablet for oral administration

Study Duration

Excluding the Screening Period, the study duration for each subject is 9 to 12 days for Cohorts A1, A2, A4, A5, and A6, 18 to 20 days for Cohort A3, 26 to 28 days for Cohort A9, 18 to 21 days for Part B, 22 to 25 days for Part C, and

approximately 7 to 9 weeks for Part D.

Study Design

This is a 4-part, randomized, double-blind, placebo-controlled, single- and multiple-dose, first-in-human and first-in-patient dose escalation study of VX-121 that includes an evaluation of relative BA and the effect of milk on VX-121 exposure.

Parts A, B, and C (Healthy Subjects)

Approximately 7 cohorts are planned for Part A (A1 through A6 and A9), approximately 6 cohorts are planned for Part B, and approximately 2 cohorts are planned for Part C. Up to 2 additional cohorts each in Parts A, B, and C may be enrolled based on data from previous cohorts.

Approximately 8 subjects in each cohort (except Cohort A9) will be randomized 3:1 to receive VX-121 (or VX-121 in TC with TEZ/IVA in Part C) or placebo as a suspension, under fed conditions. All subjects in Cohort A3 will also receive an open-label dose of VX-121 to evaluate the effect of milk on a suspension formulation. Cohort A9 will enroll approximately 8 subjects who will receive open-label VX-121 to evaluate the BA of a tablet relative to suspension formulation and the effect of milk on the tablet formulation. The tablet formulation may then be used instead of the suspension in any remaining cohorts of the study if supported by preliminary PK data from Cohort A9. The existing restrictions on dairy consumption may be removed pending the results from Cohorts A3 and/or A9.

The decision to initiate successive cohorts and dose selection will be based on safety and tolerability data from preceding dose group(s) and available PK data from a minimum of 6 subjects (to ensure 4 subjects receiving active drug) in the preceding cohort.

Part A includes Cohorts A1 through A6, which are single-dose escalation cohorts. Up to 2 additional cohorts (Cohorts A7 and A8) may be enrolled based on data from previous cohorts. Cohort A9 is a single-dose cohort evaluating relative BA.

Cohorts A1 Through A6 (up to A8): VX-121 or placebo will be administered, on the morning of Day 1. The starting dose (Cohort A1) will be 10 mg. [redacted] Dosing will be staggered in Cohort A1 so that 2 subjects are dosed (1 with VX-121 and 1 with placebo) at least 24 hours before the remaining 6 subjects. Staggering at higher doses may be conducted if deemed necessary based on review of emerging safety data. The planned doses for Cohorts A1 through A6 are 10 mg, 20 mg, 5 mg, 40 mg, 60 mg, and up to 90 mg. Doses may be modified based on emerging data. If conducted, the dose(s) in Cohorts A7 or A8 may be a replicate of a dose evaluated in Cohorts A1 through A6 or may be increased above 90 mg, pending emerging safety, tolerability, and PK data from Cohorts A1 through A6.

Cohort A3: In addition to randomized study drug administration described above, after a washout of at least 8 days all subjects will receive an additional 5 mg single dose of open-label VX-121 suspension with milk.

Cohort A9 has an open-label, single sequence design in which subjects will receive a single dose of VX-121 on 3 dosing occasions with at least an 8-day washout between dosing occasions. VX-121 doses include a single oral dose of suspension, a single oral dose of tablet, and a single oral dose of tablet with milk (the planned dose is 10 mg for both formulations, but it will not exceed the highest dose that was safe and well tolerated in a previous Part A cohort).

Part B is a 6-cohort, multiple-dose escalation component (Cohorts B1 through B6). Up to 2 additional cohorts (Cohorts B7 and B8) may be conducted. Multiple oral

doses of VX-121 or placebo will be administered for 10 days once daily (qd).

The planned doses for Cohorts B1 through B4 are 10 mg qd, 20 mg qd, 40 mg qd, and 60 mg qd. Doses may be modified based on emerging data. The doses for Cohorts B5 and B6 are to be determined (TBD) based on emerging data.

Part B may be initiated while Part A is ongoing after review of safety, tolerability, and PK data. The total daily dose in the first Part B cohort (Cohort B1) will be at least 1 dose level below the highest Part A dose for which safety and tolerability results are available and supportive.

Part C is a 2-cohort, multiple-dose escalation of VX-121 administered in TC with TEZ/IVA for 14 days (Cohorts C1 and C2). Up to 2 additional cohorts (Cohorts C3 and C4) may be conducted.

The planned doses for Cohorts C1 and C2 are 10 mg qd and 20 mg qd. Doses may be modified based on emerging data. The dosage of TEZ/IVA will be TEZ 100 mg qd/IVA 150 mg q12h, which will be administered as TEZ 100 mg/IVA 150 mg FDC in the morning and IVA 150 mg in the evening.

Part C may be initiated while Parts A and B are ongoing after review of safety, tolerability, and PK data.

The total daily dose in the first Part C cohort (Cohort C1) will be at least 1 dose level below the highest total daily Part B dose for which safety and tolerability results are available and supportive. Dosing will be staggered in Cohort C1, with 2 of the 8 subjects receiving study drug (1 subject receiving VX-121 in TC with TEZ/IVA and 1 subject receiving triple placebo) at least 24 hours before the remaining 6 subjects. Staggering at higher doses may be conducted if deemed necessary based on review of emerging safety data.

Part D (Subjects With CF, F/MF Genotype)

Part D has a randomized, double-blind, placebo-controlled, parallel-group design. After completing the Screening Period, approximately 12 subjects will be randomized 3:1 to TC:placebo. Subjects will receive 4 weeks of treatment.

Screening in Part D will be initiated after the completion of Parts A, B, and C (cohorts needed for Part D dose selection only) through the Safety Follow-up Visit. The decision to proceed to Part D will be based on an evaluation of safety, tolerability, and PK data from completed cohorts in Parts A, B, and C. These data will be submitted to the IEC for approval before proceeding to screening for Part D. Based on preliminary data from Parts A, B, and C, the planned dose of 10 mg qd is predicted to provide an approximate $AUC_{0\text{-}24h}$ of 10 µg·h/mL, which is within the range of predicted efficacious exposure based on in vitro data. Based on emerging safety, tolerability, and PK data from Parts A, B, and C, the planned dose for Part D may be lowered to 5 mg qd. The total daily dose of VX-121 in Part D will be at least 1 dose level below the highest total daily dose tested in Part C. The dosage of TEZ/IVA in the TC will be TEZ 100 mg qd/IVA 150 mg q12h, which will be administered as TEZ 100 mg/IVA 150 mg FDC in the morning and IVA 150 mg in the evening.

Assessments

Safety

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

Pharmacokinetics

Blood samples will be collected from all subjects for the evaluation of plasma concentrations of VX-121, TEZ and metabolites (M1-TEZ and M2-TEZ), and IVA and metabolites (M1-IVA and M6-IVA).

Pharmacodynamics

Sweat chloride (Part D)

Efficacy

Spirometry (Part D)

Statistical Analyses

Eight subjects per dose cohort randomized 3:1 (active:placebo) is a typical sample size for first-in-human studies in healthy subjects and is considered sufficient to achieve the objectives of the study. Part D will enroll approximately 12 subjects with CF randomized 3:1 (active:placebo) and is considered sufficient to meet the objectives of the study. Only descriptive analyses will be provided for the safety data comprising AEs, clinical laboratory assessments, ECGs, vital signs, and spirometry (Part D only); no statistical hypothesis testing will be performed. The PK results for VX-121, TEZ and metabolites, and IVA and metabolites will be reported with descriptive statistics. The PD analysis of sweat chloride and efficacy analysis of spirometry will be performed using descriptive statistics and a mixed-effects model for repeated measures (MMRM).

Interim Analyses

An interim analysis (IA) may be performed for Parts A, B, and C after all subjects in Part C have completed the Safety Follow-up Visit.

3 SCHEDULE OF ASSESSMENTS

Schedules of assessments are shown in Table 3-1 through Table 3-7.

Table 3-1 Study VX17-121-001: Parts A, B, and C Screening

Event/Assessment	Screening Visit Day -28 to Day -2
Informed consent	X
Demographics	X
Medical history	X
Medications review[a]	X
Height, weight, BMI, and vital signs[b]	X
Full physical examination	X
Standard 12-lead ECG[c]	X
Serum FSH (postmenopausal female subjects only)	X
Serum β-hCG (all female subjects)	X
Serology (HBsAg, HCV, HIV-1, and HIV-2 Abs)	X
Serum chemistry	X
Hematology	X
Coagulation	X
Drug test (urine or blood), including cotinine	X
Alcohol test (urine, blood, or breath)	X
Urinalysis	X
Adverse events	Continuous from signing of informed consent form (ICF) through Safety Follow-up Visit

[a] All medications taken from 28 days before the first dose of study drug through the end of the study will be recorded.

[b] Weight and height will be measured with shoes off. Vital signs will be performed after the ECG, after the subject has been at rest for at least 5 minutes.

[c] A standard 12-lead ECG will be performed in the supine position after the subject has been at rest for at least 5 minutes. The ECG will be done before any other procedures that may affect heart rate, such as blood draws.

Table 3-2 Study VX17-121-001: Part A, Cohorts A1, A2, A4, A5, and A6, Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Study Day						Safety Follow-up (7 to 10 Days After Last Dose of Study Drug)[b]
	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	
Inpatient days	X	X	X	X	X	X[c]	
Outpatient visit							X
Randomization		X					
Weight[d]	X						
Standard 12-lead ECG[e]	X	X				X	X
Vital signs[f]	X	X	X	X	X	X	X
Full physical examination	X						X
Serum chemistry	X		X				X
Hematology	X		X				X
Blood for PK analysis[g]		X	X	X	X	X	X
Drug test (urine or blood), including cotinine	X						
Alcohol test (urine, blood, or breath)	X						
Urinalysis							X
Study drug administration[h]		X					
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit						
Medications review[i]	Continuous from signing of ICF through Safety Follow-up Visit						
Treatment and procedures review	Continuous from signing of ICF through Safety Follow-up Visit						

[a] On dosing days, assessments will be performed before dosing, unless noted otherwise.
[b] Additional PK samples and safety assessments may also be performed at the discretion of the investigator. See Section 9.1.1.4 for details.
[c] Subjects will be discharged from the CRU on Day 5 after completion of the study visit assessments.
[d] Weight will be measured with shoes off.
[e] Standard 12-lead ECGs will be performed in the supine position after the subject has been at rest for at least 5 minutes. The ECG will be done before any other procedures that may affect heart rate, such as blood draws. On Day 1, ECGs will be collected before dosing and approximately 1, 3, 5, and 6 hours (± 15 min) after dosing.
[f] Vital signs will be performed after the subject has been at rest for at least 5 minutes.
[g] Blood samples for PK assessments will be collected on Day 1 before dosing (0 hours), and at 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 (Day 2), 36 (Day 2), 48 (Day 3), 72 (Day 4), and 96 (Day 5) hours after dosing. Acceptable PK sampling windows are provided in Table 11-1. At the Safety Follow-up Visit, a single blood sample for PK analysis will be collected.
[h] Study drug will be administered in the fed state (Section 9.6.1).
[i] All medications taken from 28 days before the first dose of study drug through the end of the study will be recorded.

Table 3-3 Study VX17-121-001: Part A, Cohort A3, Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Study Day																	Safety Follow-up (7 to 10 Days After Last Dose of Study Drug)[b]
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	
Inpatient days	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]	
Outpatient visit																		X
Randomization		X																
Weight[d]	X																	
Standard 12-lead ECG[e]	X	X							X	X							X	X
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full physical examination	X																	X
Serum chemistry	X		X								X							X
Hematology	X		X								X							X
Blood for PK analysis[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug test (urine or blood), including cotinine	X																	
Alcohol test (urine, blood, or breath)	X																	
Urinalysis																		X
Study drug administration		X[h]								X[i]								
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit																	
Medications review[j]	Continuous from signing of ICF through Safety Follow-up Visit																	
Treatment and procedures review	Continuous from signing of ICF through Safety Follow-up Visit																	

[a] On dosing days, assessments will be performed before dosing, unless noted otherwise.
[b] Additional PK samples and safety assessments may also be performed at the discretion of the investigator. See Section 9.1.1.4 for details.
[c] Subjects will be discharged from the CRU on Day 16 after completion of the study visit assessments.
[d] Weight will be measured with shoes off.
[e] Standard 12-lead ECGs will be performed in the supine position after the subject has been at rest for at least 5 minutes. The ECG will be done before any other procedures that may affect heart rate, such as blood draws. On Days 1 and 9, ECGs will be collected before dosing and approximately 1, 3, 5, and 6 hours (± 15 min) after dosing.
[f] Vital signs will be performed after the subject has been at rest for at least 5 minutes.
[g] Blood samples for PK assessments will be collected on Days 1 and 9 before dosing (0 hours), and at 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 (Days 2, 10), 36 (Days 2, 10), 48 (Days 3, 11), 72 (Days 4, 12), 96 (Days 5, 13), 120 (Days 6, 14), 144 (Days 7, 15), and 168 (Days 8, 16) hours after dosing. Acceptable PK sampling windows are provided in Table 11-1. At the Safety Follow-up Visit, a single blood sample for PK analysis will be collected.
[h] Subjects will be randomized 3:1 to receive VX-121 or placebo. Study drug will be administered in the fed state (Section 9.6.1).
[i] All subjects will receive open-label VX-121. Study drug will be administered in the fed state and with milk (Section 9.6.1).
[j] All medications taken from 28 days before the first dose of study drug through the end of the study will be recorded.

Table 3-4 Study VX17-121-001: Part A, Cohort A9, Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Study Day										Safety Follow-up (7 to 10 Days After Last Dose of Study Drug)[b]
	-1	1	2	3,4,5, 6,7,8	9	10	11,12,13, 14,15,16	17	18	19,20,21, 22,23,24	
Inpatient days	X	X	X	X	X	X	X	X	X	X[c]	
Outpatient visit											X
Weight[d]	X										
Standard 12-lead ECG[e]	X	X			X			X			X
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X
Full physical examination	X										X
Serum chemistry	X		X			X			X		X
Hematology	X		X			X			X		X
Blood for PK analysis[g]		X	X	X	X	X	X	X	X	X	X
Drug test (urine or blood), including cotinine	X										
Alcohol test (urine, blood, or breath)	X										
Urinalysis											X
Study drug adminstration[h]		X			X			X			
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit										
Medications review[i]	Continuous from signing of ICF through Safety Follow-up Visit										
Treatment and procedures review	Continuous from signing of ICF through Safety Follow-up Visit										

[a] On dosing days, assessments will be performed before dosing, unless noted otherwise.
[b] Additional PK samples and safety assessments may also be performed at the discretion of the investigator. See Section 9.1.1.4 for details.
[c] Subjects will be discharged from the CRU on Day 24 after completion of the study visit assessments.
[d] Weight will be measured with shoes off.
[e] Standard 12-lead ECGs will be performed in the supine position after the subject has been at rest for at least 5 minutes. The ECG will be done before any other procedures that may affect heart rate, such as blood draws. On Days 1, 9, and 17, ECGs will be collected before dosing and approximately 1, 3, 5, and 6 hours (± 15 min) after dosing.
[f] Vital signs will be performed after the subject has been at rest for at least 5 minutes.
[g] Blood samples for PK assessments will be collected on Days 1, 9, and 17 before dosing (0 hours), and at 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 (Days 2, 10, 18), 36 (Days 2, 10, 18), 48 (Days 3, 11, 19), 72 (Days 4, 12, 20), 96 (Days 5, 13, 21), 120 (Days 6, 14, 22), 144 (Days 7, 15, 23), and 168 (Days 8, 16, 24) hours after dosing. Acceptable PK sampling windows are provided in Table 11-1. At the Safety Follow-up Visit, a single blood sample for PK analysis will be collected.
[h] Study drug will be administered as a suspension in the fed state on the Day 1 Visit, as a tablet in the fed state on the Day 9 Visit, and as a tablet in the fed state and with milk on the Day 17 Visit (Section 9.6.1).
[i] All medications taken from 28 days before the first dose of study drug through the end of the study will be recorded.

Table 3-5 Study VX17-121-001: Part B, Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Study Day															Safety Follow-up (7 to 10 Days After Last Dose of Study Drug)[b]
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Inpatient days	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]	
Outpatient visits																X
Randomization		X														
Weight[d]	X										X					
Continuous ECGs[e]		X									X	X				
Standard 12-lead ECG[f]	X	X				X									X	X
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full physical examination	X															X
Serum chemistry	X		X			X					X					X
Hematology	X		X			X					X					X
4β-hydroxycholesterol	X										X					
Blood for PK analysis[h]		X	X (if qd)			X	X (if qd)	X	X	X	X	X	X	X	X	X
Drug test (urine or blood), including cotinine	X															
Alcohol test (urine, blood, or breath)	X															
Urinalysis																X

[a] On dosing days, assessments will be performed before dosing, unless noted otherwise.

[b] Additional PK samples and safety assessments may also be performed at the discretion of the investigator. See Section 9.1.1.4 for details.

[c] Subjects will be discharged from the CRU on Day 14 after completion of the study visit assessments.

[d] Weight will be measured with shoes off.

[e] Continuous ECGs will be extracted in up to 10 replicates on Day 1 before dosing at -60, -50, and -40 minutes, and on Day 10 before dosing (at -40 minutes) and at 1, 2, 4, 6, 8, 10, 12, and 24 hours (Day 11) after dosing. Subjects should be supine or semi-recumbent for at least 15 minutes before these time points.

[f] Standard 12-lead ECGs will be performed in the supine position after the subject has been at rest for at least 5 minutes. The ECG will be done before any other procedures that may affect heart rate, such as blood draws. On Days 1 and 5, ECGs will be collected before dosing and at approximately 1, 3, 5, and 6 hours (± 15 min) after dosing.

[g] Vital signs will be performed after the subject has been at rest for at least 5 minutes.

[h] Blood samples for PK assessments will be collected on Days 1 and 5 before dosing (0 hours), 1, 2, 3, 4, 5, 6, 8, and 12 hours after dosing (if qd dosing, blood samples will also be collected at 24 hours [on Day 2 and Day 6]). The 12- or 24-hour sample will be collected before the next administered dose. On Days 7, 8, and 9, a blood sample will be collected before dosing. On Day 10, blood samples for PK assessments will be collected before dosing (0 hours), 1, 2, 3, 4, 5, 6, 8, 10, 12, 24 (Day 11), 36 (Day 11), 48 (Day 12), 72 (Day 13), and 96 (Day 14) hours after dosing. The acceptable PK sampling windows are provided in Table 11-1. At the Safety Follow-up Visit, a single blood sample for PK analysis will be collected.

Table 3-5 Study VX17-121-001: Part B, Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Study Day															Safety Follow-up (7 to 10 Days After Last Dose of Study Drug)[b]
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Study drug administration[i]		X	X	X	X	X	X	X	X	X	X[i]					
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit															
Medications review[j]	Continuous from signing of ICF through Safety Follow-up Visit															
Treatment and procedures review	Continuous from signing of ICF through Safety Follow-up Visit															

[i] Study drug will be administered in the fed state (Section 9.6.1). The last dose of study drug will be administered on the morning of the Day 10 Visit.
[j] All medications taken from 28 days before the first dose of study drug through the end of the study will be recorded.

Table 3-6 Study VX17-121-001: Part C, Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Study Day																			Safety Follow-up (7 to 10 Days After Last Dose of Study Drug)[b]
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
Inpatient days	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]	
Outpatient visits																				X
Randomization		X																		
Weight[d]	X														X					
Standard 12-lead ECG[e]	X	X						X												X
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full physical examination	X																			X
Serum chemistry	X		X				X				X[g]				X					X
Hematology	X		X				X								X					X
Blood for PK analysis[h]		X	X	X	X	X		X	X		X		X		X	X	X	X	X	X
Drug test (urine or blood), including cotinine	X																			
Alcohol test (urine, blood, or breath)	X																			
Urinalysis	X																			X
Study drug administration[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X[i]					
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit																			

[a] On dosing days, assessments will be performed before dosing, unless noted otherwise, and will be performed relative to the morning dose only.

[b] Additional PK samples and safety assessments may also be performed at the discretion of the investigator. See Section 9.1.1.4 for details.

[c] Subjects will be discharged from the CRU on Day 18 after completion of the study visit assessments.

[d] Weight will be measured with shoes off.

[e] Standard 12-lead ECGs will be performed in the supine position after the subject has been at rest for at least 5 minutes. The ECG will be done before any other procedures that may affect heart rate, such as blood draws. On Days 1 and 7, ECGs will be collected before dosing and approximately 1, 3, 5, and 6 hours (± 15 min) after dosing.

[f] Vital signs will be performed after the subject has been at rest for at least 5 minutes.

[g] On Day 10, the following serum chemistry parameters will be measured: lactate dehydrogenase, total and direct bilirubin, alkaline phosphatase, aspartate transaminase, alanine transaminase, and gamma-glutamyl transferase.

[h] Blood samples for PK assessments of VX-121, TEZ and metabolites, and IVA and metabolites will be collected on Days 1 and 7 before dosing (0 hours) and at 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours after dosing. The 12-hour sample will be collected before the next administered dose. On Days 2, 3, 4, 5, 8, 10, and 12, blood samples will be collected before (morning) dosing. On Day 14, blood samples will be collected before dosing (0 hours), and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24 (Day 15), 36 (Day 15), 48 (Day 16), 72 (Day 17), and 96 (Day 18) hours after dosing. Acceptable PK sampling windows are provided in Table 11-1. At the Safety Follow-up Visit, a single blood sample for PK analysis will be collected.

[i] Study drug will be administered in the fed state (Section 9.6.1). The last dose of study drug will be administered on the morning of the Day 14 Visit.

Table 3-6 Study VX17-121-001: Part C, Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Study Day																		Safety Follow-up (7 to 10 Days After Last Dose of Study Drug)[b]
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
Medications review[j]	Continuous from signing of ICF through Safety Follow-up Visit																			
Treatment and procedures review	Continuous from signing of ICF through Safety Follow-up Visit																			

[j] All medications taken from 28 days before the first dose of study drug through the end of the study will be recorded.

Table 3-7 Study VX17-121-001: Part D, Screening, Treatment Period, and Safety Follow-up Visit

Event/Assessment[a]	Screening Visit[b]	Treatment Period[c]				ETT Visit[d]	Safety Follow-up 28 (± 7) Days After Last Dose of Study Drug
	Days -28 to -1	Day 1	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 29 (± 1 day)		
Outpatient visits	X	X	X	X	X	X	X
Informed consent	X						
Randomization[e]		X					
Demographics	X						
Medical history	X						
Weight[f]	X	X	X	X	X	X	X
Height[f]	X						
Vital signs[g]	X	X	X	X	X	X	X
Pulse oximetry[g]	X	X	X	X	X	X	X
Physical examination[h]	Complete	Abbreviated	Abbreviated	Abbreviated	Abbreviated	Abbreviated	Complete
Standard 12-lead ECG[i]	X	X	X	X	X	X	X
Sweat chloride[j,k]	X	X	X	X	X	X	X
Spirometry[l]	X	X	X	X	X	X	X
Urinalysis[j]	X	X	X	X	X	X	X
Serum β-hCG (all female subjects)	X						

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

[c] To qualify to continue into the Treatment Period, conditions for entry must be satisfied (Section 9.1.2.2).

[d] If the subject prematurely discontinues study drug, an ETT Visit should be scheduled as soon as possible after the decision to terminate study drug treatment. Additional PK samples and safety assessments may also be performed at the discretion of the investigator. See Section 9.1.2.4 for additional details.

[e] Randomization may occur on the previous day (Day -1) after all conditions for entering the Treatment Period have been confirmed (Section 9.1.2.2).

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

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

[h] Complete and abbreviated PEs are described in Section 11.7.3.

[i] Standard 12-lead ECGs will be performed in the supine position after the subject has been at rest for at least 5 minutes. The ECG will be done before any other procedures that may affect heart rate, such as blood draws. On Days 1 and 15, ECGs will be collected before dosing and 4 hours (± 1 hour) after dosing. ECGs collected on Day 1 before dosing will be performed in triplicate.

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

[k] Sweat chloride will be measured in all subjects. See Section 8.2.1 for information about the sweat chloride assessment for study eligibility.

[l] 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 3-7 Study VX17-121-001: Part D, Screening, Treatment Period, and Safety Follow-up Visit

Event/Assessment[a]	Screening Visit[b]	Treatment Period[c]				ETT Visit[d]	Safety Follow-up 28 (± 7) Days After Last Dose of Study Drug
	Days -28 to -1	Day 1	Day 8 (± 1 day)	Day 15 (± 1 day)	Day 29 (± 1 day)		
CFTR genotype[m]	X						
FSH[n]	X						
[redacted]							
Serum chemistry and hematology[j]	X	X	X	X	X	X	X
Coagulation[j]	X	X	X	X	X		X
PK sampling[p]		X	X	X	X	X	
Randomized study drug dosing[q]		Day 1 through Day 29					
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit						
Medications review[r]	Continuous from signing of ICF through Safety Follow-up Visit						
Treatment and procedures review	Continuous from signing of ICF through Safety Follow-up Visit						

[m] *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.

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

[redacted]

[p] Blood samples will be collected for PK analysis of VX-121, TEZ and metabolites, and IVA and metabolites. 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 Days 8 and 29, 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. Acceptable PK sampling windows are provided in Table 11-1. At the ETT Visit, a single blood sample for PK analysis will be collected.

[q] The last dose of study drug will be the morning dose on the Day 29 Visit.

[r] All medications taken from 28 days before the Screening Period through the end of the study will be recorded.

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the concentration versus time curve
$AUC_{0-\infty}$	AUC from the time of dosing extrapolated to infinity
AUC_{0-24h}	AUC from the time of dosing to 24 hours
β-hCG	beta-human chorionic gonadotropin
BA	bioavailability
BMI	body mass index
CD	compact disc
CF	cystic fibrosis
CFTR	*CF transmembrane conductance regulator gene*
CFTR	CF transmembrane conductance regulator protein
CI	confidence interval
Cl^-	chloride ion
C_{max}	maximum observed concentration
CMC	chemistry, manufacturing, and controls
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRO	clinical research organization
CRU	clinical research unit
CSR	clinical study report
CYP	cytochrome P450
[redacted]	[redacted]
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
E-R	exposure-response
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
F508del	CFTR protein lacking the phenylalanine normally found at position 508 of the wild-type protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
$FEF_{25\%-75\%}$	forced expiratory flow, midexpiratory phase
FEV_1	forced expiratory volume in 1 second
F/MF	*F508del*/minimal function
FPI	Formulation Preparation Instructions
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

Abbreviation	Definition
GI	gastrointestinal
GLI	Global Lung Function Initiative
GLP	Good Laboratory Practices
GPS	Global Patient Safety
HBE	human bronchial epithelial (cells)
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HED	human equivalent dose
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IA	interim analysis
ICF	informed consent form
ICH	International Council for Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IRB	institutional review board
IVA	ivacaftor
IWRS	interactive web response system
LFT	liver function test
LLN	lower limit of normal
LUM	lumacaftor
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal function
min	minimum value
MMRM	mixed-effects model for repeated measures
n	number of subjects
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
OATP	organic anion transporting polypeptide
P	probability
PD	pharmacodynamic, pharmacodynamics
PE	physical examination
PK	pharmacokinetic, pharmacokinetics
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
PR	PR interval
PT	Preferred Term
q12h	every 12 hours
QA	quality assurance
QC	quality control
qd	daily
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QTc	QT interval corrected
QTcB	QT interval corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
SAE	serious adverse event

Abbreviation	Definition
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SET	study execution team
SI	SI units (International System of Units)
SOC	System Organ Class
SUSAR	suspected, unexpected, serious adverse reaction
TBD	to be determined
TC	triple combination
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
ULN	upper limit of normal
US	United States
USA	United States of America
UV	ultraviolet
WHO-DD	World Health Organization-Drug Dictionary

5 INTRODUCTION

5.1 Background

Cystic fibrosis (CF) is an autosomal recessive, chronic disease with serious morbidities and frequent premature mortality. At present, there is no cure. CF affects more than 70,000 individuals worldwide.[1] Based on its prevalence, CF qualifies as an orphan disease.[2,3]

CF is caused by reduced quantity and/or function of the CFTR protein due to mutations in the *CFTR* gene. The CFTR protein is an epithelial chloride channel that aids in regulating salt and water absorption and secretion and pH balance in sweat glands and multiple organs, including the lungs, pancreas, and other gastrointestinal (GI) organs. Despite progress in the treatment of CF with antibiotics and mucolytics, the predicted median age of survival for a person with CF is approximately 40 years.[4,5] Progressive loss of lung function is the leading cause of mortality.[6]

There are more than 2000 variants described in the *CFTR* gene. The most commonly seen variants that are clearly associated with CF have been identified (312 to date), but many rare cases remain uncharacterized.[7]

Based on the understanding of the molecular defects caused by these *CFTR* mutations, 2 complementary approaches have been developed to address the decreased quantity and/or function of CFTR in order to enhance chloride transport in patients with CF. Correctors facilitate the cellular processing and trafficking to increase the quantity of CFTR at the cell surface. Potentiators increase the channel-open probability of the CFTR protein delivered to the cell surface to enhance ion transport. Depending on the *CFTR* genotype of the patient, both approaches may be required to ameliorate lung disease in patients with CF.

The therapeutic activity of CFTR correctors and potentiators has been established with products that were developed by Vertex and approved for the treatment of CF: ivacaftor (IVA) monotherapy (Kalydeco®), lumacaftor (LUM) in combination with IVA (Orkambi®), and tezacaftor (TEZ) in combination with IVA (Symdeko™). Kalydeco, Orkambi, and Symdeko are approved to treat CF in patients with specific *CFTR* genotypes. TEZ and LUM are first-generation CFTR correctors that improve the processing and trafficking of mutated CFTR protein, resulting in an increase in the quantity of protein at the cell surface. IVA increases the open-channel probability of the mutated CFTR protein that has been delivered to the cell surface, thereby enhancing total chloride transport. For the most common CF-causing mutation, *F508del*, the combined effect of either LUM and IVA or TEZ and IVA is increased quantity and function of F508del-CFTR at the cell surface.

VX-121 is a next-generation CFTR corrector. In vitro, VX-121 also improves the processing and trafficking of mutated CFTR, thereby increasing the quantity of functional protein at the cell surface. The effect of VX-121 was additive to the effect of TEZ. The CFTR protein delivered to the cell surface by VX-121 alone or in combination with TEZ (VX-121/TEZ) was potentiated by IVA. In human bronchial epithelial (HBE) cells derived from people homozygous for *F508del* and people heterozygous for *F508del* and a minimal function (MF) *CFTR* mutation (F/MF-HBE cells) and studied in vitro, the triple combination (TC) of VX-121, TEZ, and IVA (VX-121/TEZ/IVA) increased CFTR chloride transport more than the dual combination of VX-121 and either TEZ or IVA under most conditions studied (refer to VX-121 Investigator's Brochure).

5.2 Study Rationale

This is the first clinical study of VX-121 and it is designed to evaluate the safety, tolerability, and pharmacokinetics (PK) of VX-121 as monotherapy and in TC with TEZ/IVA in healthy subjects (Parts A, B, and C), as well as the safety, tolerability, PK, pharmacodynamics (PD), and efficacy of VX-121 in TC with TEZ/IVA in subjects with CF who are heterozygous for *F508del* and a MF *CFTR* mutation (F/MF genotype; Part D). Conducting the study in subjects with these genotypes investigates the effect of treating 1 responsive allele (*F508del*).

6 STUDY OBJECTIVES

6.1 Primary Objectives

Part A: To evaluate the safety and tolerability of single ascending doses of VX-121 in healthy subjects

Part B: To evaluate the safety and tolerability of multiple ascending doses of VX-121 for 10 days in healthy subjects

Part C: To evaluate the safety and tolerability of multiple ascending doses of VX-121 administered in TC with TEZ/IVA for 14 days in healthy subjects

Part D: To evaluate the safety and tolerability of VX-121 in TC with TEZ/IVA in subjects with CF

6.2 Secondary Objectives

Part A

- To evaluate the PK of VX-121 after administration of single ascending doses of VX-121 in healthy subjects
- To evaluate the relative bioavailability (BA) of a tablet formulation of VX-121 relative to suspension in healthy subjects
- To evaluate the effect of milk on the PK of VX-121 after administration of suspension and tablet formulations

Part B

To evaluate the PK of VX-121 after administration of multiple ascending doses of VX-121 for 10 days in healthy subjects

Part C

- To evaluate the PK of VX-121 after administration of multiple ascending doses of VX-121 in TC with TEZ/IVA for 14 days in healthy subjects
- To evaluate the PK of TEZ, IVA, and their respective metabolites when administered in TC with VX-121 for 14 days in healthy subjects

Part D

- To evaluate the PK of VX-121 when administered in TC with TEZ/IVA in subjects with CF
- To evaluate the PK of TEZ, IVA, and their respective metabolites when administered in TC with VX-121 in subjects with CF
- To evaluate the PD effect of VX-121 in TC with TEZ/IVA in subjects with CF
- To evaluate the efficacy of VX-121 in TC with TEZ/IVA in subjects with CF

7 STUDY ENDPOINTS

7.1 Primary Endpoint

Parts A, B, C, and D: Safety and tolerability, based on the assessment of adverse events (AEs), laboratory test results, standard 12-lead ECGs, vital signs, and spirometry (Part D only)

7.2 Secondary Endpoints

- **Parts A, B, C, and D:** PK parameter estimates of VX-121 derived from plasma concentration-time data
- **Parts C and D**: PK parameter estimates for TEZ and metabolites (M1-TEZ and M2-TEZ) and IVA and metabolites (M1-IVA and M6-IVA) derived from plasma concentration-time data
- **Part D**: Sweat chloride levels as a biomarker of PD effects
- **Part D**: Spirometry as preliminary evidence of efficacy

8 STUDY POPULATION

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

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible for the study.

8.1 Parts A, B, and C

8.1.1 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 (male subjects and female subjects of non-childbearing potential [as defined in Section 11.7.6.1]) will be between the ages of 18 and 55 years, inclusive, and healthy, as defined by no clinically relevant abnormalities identified by a detailed medical history, full physical examination (PE), including blood pressure and pulse rate measurement, standard 12-lead ECG, and clinical laboratory tests.
4. Female subjects must have a negative serum pregnancy test at the Screening Visit.
5. Body mass index (BMI) of 18.0 to 32.0 kg/m^2, inclusive, and a total body weight >50 kg.

8.1.2 Exclusion Criteria

1. History of any illness or any clinical condition that, in the opinion of the investigator or the subject's general practitioner, might confound the results of the study or pose an additional risk in administering study drug to the subject. This may include, but is not limited to, history of relevant drug or food allergies; history of cardiovascular or central nervous system disease; history or presence of clinically significant pathology; history of mental disease; and history of cancer.
2. History of febrile illness or other acute illness within 5 days before the first study drug dose.
3. Any condition possibly affecting drug absorption (e.g., gastrectomy, cholecystectomy, or other GI tract surgery, except appendectomy).
4. Standard 12-lead ECG demonstrating QTcF >450 msec at screening. If QTcF exceeds 450 msec, the ECG will be repeated 2 more times, and the average of the 3 QTcF values will be used to determine the subject's eligibility.
5. Blood donation (of approximately 1 pint [500 mL] or more) within 56 days before the first study drug dose or have had any significant loss of blood as determined by the investigator within 60 days before first study drug dose.
6. Use of restricted substances, activities, or devices within the specified duration before the first study drug dose, as defined in Table 9-2.
7. A screen positive for alcohol or drug substances listed in Section 11.7.2.
8. A screen positive for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or human immunodeficiency virus (HIV) 1 or 2 antibodies.
9. For Part A (Cohorts A3 and A9): a known or suspected lactose intolerance or milk allergy.
10. Subject, or 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 at that site.

8.2 Part D

8.2.1 Inclusion Criteria

1. Subject will sign and date an ICF.
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Subjects (male subjects and female subjects of non-childbearing potential [as defined in Section 11.7.6.1]) aged 18 years or older on the date of informed consent.
4. Female subjects must have a negative serum pregnancy test at the Screening Visit.
5. Body weight ≥35 kg.
6. Subjects must be able to produce a valid (quantity-sufficient) sweat sample at screening. If the initial screening collection results in insufficient sweat volume, then the sweat chloride collection may be repeated once.

Subjects must have a sweat chloride value ≥60 mmol/L at screening or documented in the form of a laboratory report in the subject's medical record. If the sweat chloride value cannot be determined from the screening test for a reason other than insufficient sweat volume (i.e., because of laboratory error, damaged specimen, or equipment malfunction), it is acceptable to use a sweat chloride value that was obtained in a Vertex-sponsored study before previous treatment with a CFTR modulator.

7. Confirmed diagnosis of CF as determined by the investigator.
8. Subjects must be heterozygous for *F508del* with a second *CFTR* allele carrying a mutation that is not responsive to TEZ, IVA, or TEZ/IVA therapy (Appendix A). 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 enrolled and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9).
9. Subjects must have a forced expiratory volume in 1 second (FEV_1) ≥40% and ≤90% of predicted normal for age, sex, and height (equations of the Global Lung Function Initiative [GLI])[8] at the Screening Visit. Spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria[9] for acceptability and repeatability.
10. Stable CF disease as judged by the investigator.
11. Willing to remain on a stable CF treatment regimen (other than protocol-specified changes in CFTR modulator regimen) through the Safety Follow-up Visit (Section 9.5.2).

8.2.2 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 clinically significant cirrhosis with or without portal hypertension.
3. Risk factors for Torsade de Pointes and other ventricular arrhythmias, 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. Any of the following abnormal laboratory values at screening:
   - Hemoglobin <10 g/dL
   - Total bilirubin ≥2 × ULN
   - Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (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

5. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for sinopulmonary disease within 28 days before the first dose of study drug.
6. 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, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
   - The subject has not had a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent.
   - The subject has had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent 1 within the 6 months before the date of informed consent.
7. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug.
8. Standard 12-lead ECG demonstrating QTcF >450 msec at screening. If QTcF exceeds 450 msec, the ECG will be repeated 2 more times, and the average of the 3 QTcF values will be used to determine the subject's eligibility.
9. History of solid organ or hematological transplantation.
10. History of alcohol or drug abuse in the past year, including, but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator.
11. Ongoing or prior participation in a study of an investigational treatment with the exception of the following:
    - Ongoing or prior participation in an investigational study of a Vertex CFTR modulator, including VX-661, VX-440, VX-152, VX-659, and VX-445. A washout period of 28 days must elapse before Day 1.
    - 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.
12. Use of prohibited medications as defined in Table 9-3, within the specified window before the first dose of study drug.
13. Subject, or 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 at that site. However, an adult (aged 18 years or older) who is a relative of a study staff member may be enrolled in the study provided that
    - the adult lives independently of and does not reside with the study staff member, and

- the adult participates in the study at a site other than the site at which the family member is employed.

9 STUDY IMPLEMENTATION

9.1 Study Design

This is a 4-part, randomized, double-blind, placebo-controlled, single- and multiple-dose, first-in-human and first-in-patient dose escalation study of VX-121 that includes an evaluation of relative BA and the effect of milk on VX-121 exposure.

9.1.1 Parts A, B, and C (Healthy Subjects)

A schematic of the study design for Parts A, B, and C is shown in Table 9-1. Up to 2 additional cohorts each in Parts A (Cohorts A7 and A8), B, and C may be enrolled based on data from previous cohorts; these cohorts will follow the corresponding schedule of assessments.

There is no prespecified ratio of males to females, but reasonable effort will be made to enroll females of non-childbearing potential in all dosing cohorts. Subjects will be allowed to participate in up to 2 cohorts (subjects may enroll in 2 cohorts in Part A or 1 cohort in Part A and 1 cohort in either Part B or Part C; see Section 9.1.1.1).

The decision to initiate successive cohorts and dose selection will be based on safety and tolerability data from preceding dose group(s) and available PK data from all subjects in the preceding cohort (minimum of 6 subjects to ensure 4 subjects receiving active drug). Refer to Section 9.7.1 for dose escalation criteria and Section 9.8.1 for stopping rules.

Subjects will receive VX-121 as a suspension, under fed conditions. The tablet formulation may be used instead of the suspension in any remaining cohorts of the study if supported by preliminary PK data from Cohort A9. The existing restrictions on dairy consumption (Section 9.4.1) may be removed pending the results from Cohorts A3 and/or A9.

Staggered Dosing in Cohorts A1 and C1

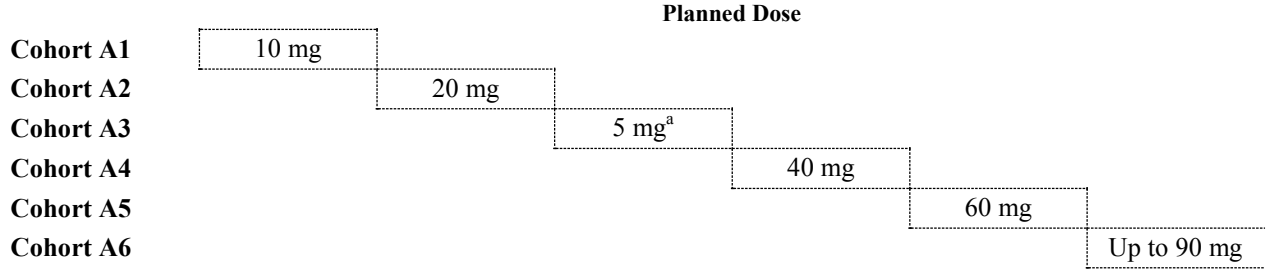
Dosing in the first cohort of Parts A and C (Cohorts A1 and C1) will initiate with staggered dosing in 2 subjects (1 active, 1 placebo) followed by a minimum 24-hour observation before dosing of the remaining subjects in the cohort (Section 9.3.1). Staggering at higher doses may be conducted if deemed necessary based on review of emerging safety data.

Cohort A9

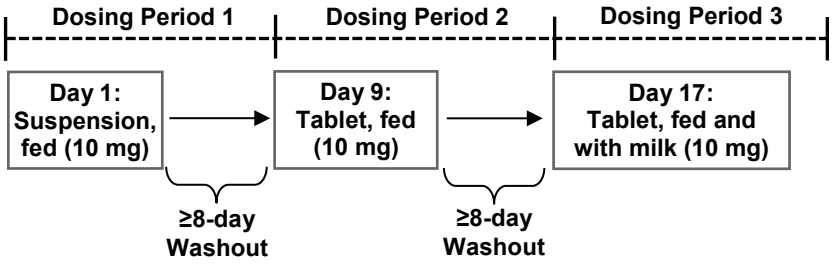
Cohort A9 will not be initiated until all documentation required to support administration of the VX-121 tablet has been submitted to and approved by the competent authority (IRB/IEC, as applicable).

Table 9-1 Study Design for Parts A, B, and C

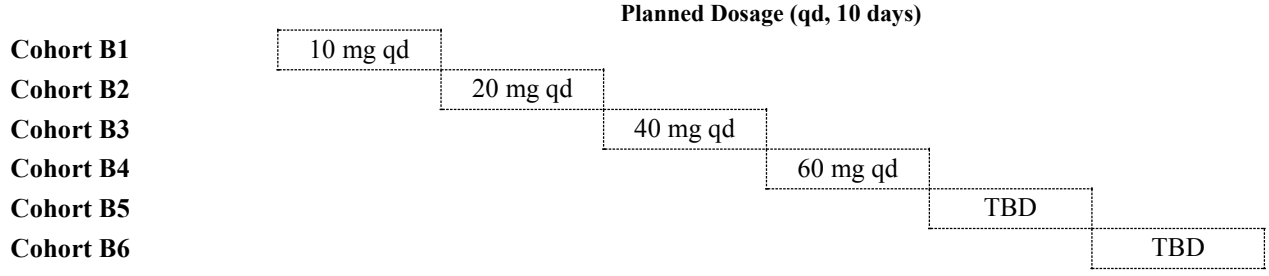
Part A: Single-dose escalation of VX-121
Approximately 8 subjects per cohort, randomized 3:1 (VX-121:placebo) except for Cohort A9



Cohort A9 (Approximately 8 subjects, open-label VX-121, single sequence)[b]



Part B: Multiple-dose escalation of VX-121
Approximately 8 subjects per cohort, randomized 3:1 (VX-121:placebo)



Part C: Multiple-dose escalation of VX-121 in TC with TEZ/IVA[c]
Approximately 8 subjects per cohort, randomized 3:1 (VX-121/TEZ/IVA:triple placebo)

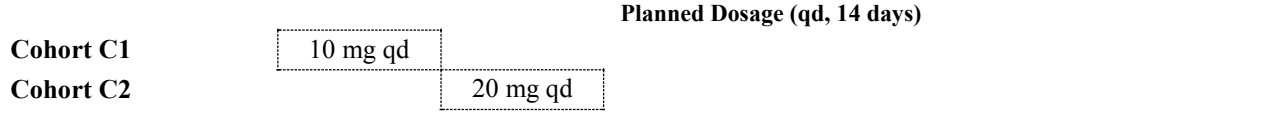


Table 9-1 Study Design for Parts A, B, and C

Notes: In Part A, planned doses are shown; any cohort may be initiated at a lower or higher dose level than the planned dose based on emerging safety, tolerability, and PK data. No dose increment will be expected to yield greater than a 3-fold increase (Cohorts A1 through A3) or a 2-fold increase (all other Part A cohorts and Part B cohorts) in exposure from the preceding dose level. Dose escalation criteria and predefined stopping criteria are described in Section 9.7.1 and Section 9.8.1.

[a] In addition to randomized study drug administration depicted above, after a washout of at least 8 days all subjects will receive an additional 5 mg single dose of open-label VX-121 suspension with milk to evaluate the effect of milk on VX-121 exposure.

[b] Subjects will receive a single dose of VX-121 on 3 dosing occasions with at least an 8-day washout between dosing occasions. VX-121 doses include a single oral dose of suspension, a single oral dose of tablet to evaluate the relative BA of the tablet, and a single oral dose of tablet with milk to evaluate the effect of milk on VX-121 exposure (the planned dose is 10 mg for both formulations, but it will not exceed the highest dose that was safe and well tolerated in a previous Part A cohort).

[c] The dosage of TEZ/IVA will be TEZ 100 mg qd/IVA 150 mg q12h, which will be administered as TEZ 100-mg/IVA 150-mg FDC in the morning and IVA 150 mg in the evening.

9.1.1.1 Screening

Screening Visit assessments are listed in Table 3-1.

Screening will occur within 28 days before administration of study drug. If the time between screening and dosing exceeds 28 days as a result of unexpected operational delays (e.g., delayed drug shipment), then subjects do not require rescreening if the Day -1 laboratory results meet the eligibility criteria.

Subjects will be instructed on the study restrictions (Section 9.4).

A subject who qualified but did not enroll for an earlier cohort may be used in a subsequent cohort with no required rescreening if the Day -1 laboratory results meet the eligibility criteria and if all other screening data were obtained within 28 days before administration of study drug.

Individual subjects may enroll in up to 2 cohorts (either 2 cohorts in Part A or 1 cohort in Part A and 1 cohort in either Part B or Part C) if at least 21 days has elapsed between the last dose of study drug in the first cohort in which they participate and the first dose of study drug in the next cohort. All screening assessments must be completed again and eligibility confirmed for participation in the next cohort.

Subjects who do not meet the eligibility criteria may not be rescreened, with the following exceptions, all of which require principal investigator approval:

- Subjects who met all eligibility criteria but had an intercurrent illness (e.g., upper respiratory infection with fever) in the 14 days before the first study drug dose that was properly evaluated and which resolved fully
- Subjects who met all eligibility criteria but were not able to obtain required documentation within the allotted screening window
- Subjects who met all eligibility criteria but transiently (for personal reasons) are unable to commit to all study procedures

- Subjects who met all eligibility criteria but are not randomized for administrative reasons (e.g., study drug is not available at the study site)
- If applicable, subjects who were screened under a prior version of the protocol and did not meet any exclusion criterion, with the exception of a criterion that was updated in a subsequent version of the protocol

Repetition of any screening assessment that did not meet eligibility criteria is not permitted, unless there is clear evidence of a laboratory error or a damaged specimen (e.g., hemolysis of sample).

The medical monitor should be notified of any decisions made regarding rescreening or retesting.

9.1.1.2 Treatment Period

Subjects will be admitted on Day -1 and will remain in the clinical research unit (CRU) for the duration of the Treatment Period.

Treatment Period assessments are listed in Table 3-2 (Cohorts A1 through A6 [up to A8]), Table 3-3 (Cohort A3), Table 3-4 (Cohort A9), Table 3-5 (Part B), and Table 3-6 (Part C).

The treatment periods for Part A, B, and C will be conducted as described in Section 9.1.1. Dosing details are given in Section 9.6.1.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the medical monitor (or authorized designee) will be notified, and the subject will be asked to remain in the CRU until such abnormalities resolve. If the subject is unable or unwilling to remain in the CRU, the medical monitor (or authorized designee) will be notified, and the investigator will make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

9.1.1.3 Follow-up

Subjects will have a Safety Follow-up Visit 7 to 10 days after the last study drug dose. Safety Follow-up Visit assessments are listed in Table 3-2 (Cohorts A1 through A6 [up to A8]), Table 3-3 (Cohort A3), Table 3-4 (Cohort A9), Table 3-5 (Part B), and Table 3-6 (Part C).

9.1.1.4 Early Discontinuation

Subjects who prematurely discontinue study drug dosing will be asked to return to the CRU for a Safety Follow-up Visit. Safety Follow-up Visit assessments are listed in Table 3-2 (Cohorts A1 through A6 [up to A8]), Table 3-3 (Cohort A3), Table 3-4 (Cohort A9), Table 3-5 (Part B), and Table 3-6 (Part C).

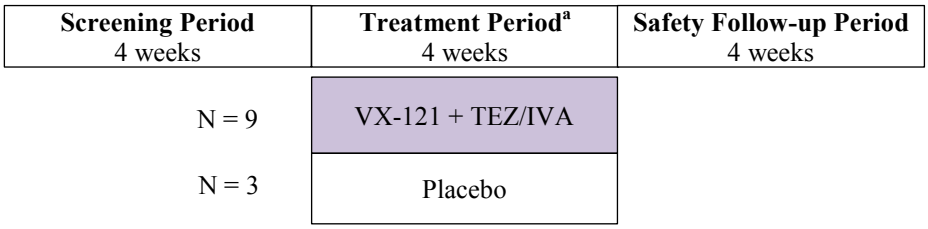
Subjects who discontinue from study drug dosing for any reason (except withdrawal of consent) will have a final PK blood sample drawn as soon as possible after the decision to discontinue study drug is made. Additional safety assessments may also be performed at the discretion of the investigator, including possible consultation with a specialist consultant. The Vertex medical monitor will be informed about these additional assessments, and any additional data collected (e.g., as the result of an outside consultation) will be considered part of the study record to provide the most complete safety profile of the study drug.

9.1.2 Part D (Subjects With CF)

A schematic of the study design for Part D is shown in Figure 9-1, which has a randomized, double-blind, placebo-controlled, parallel-group design. After completing the Screening Period, approximately 12 subjects will be randomized 3:1 to TC:placebo.

Screening in Part D will be initiated after the completion of Parts A, B, and C (cohorts needed for Part D dose selection only) through the Safety Follow-up Visit. The decision to proceed to Part D will be based on an evaluation of safety, tolerability, and PK data from completed cohorts in Parts A, B, and C. These data will be submitted to the IEC for approval before proceeding to screening for Part D. Refer to Section 9.3.2 for additional details.

Figure 9-1 Schematic of Study Design for Part D



[a] The planned VX-121 dose for Part D is 10 mg qd. This dose is predicted to provide an approximate $AUC_{0\text{-}24h}$ of 10 µg·h/mL, which is within the predicted efficacious exposure range based on in vitro data. Based on emerging safety, tolerability, and PK data from Parts A, B, and C, the planned dose for Part D may be lowered to 5 mg qd. The total daily dose of VX-121 in Part D will be at least 1 dose level below the highest total daily dose tested in Part C. The dosage of TEZ/IVA in the TC will be TEZ 100 mg qd/IVA 150 mg q12h, which will be administered as TEZ 100 mg/IVA 150 mg FDC in the morning and IVA 150 mg in the evening.

9.1.2.1 Screening

Screening Visit assessments are shown in Table 3-7.

The Screening Period will occur within 28 days before the first dose of study drug. The site investigator (or designee) will confirm and document study eligibility before randomization.

9.1.2.1.1 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, damaged specimen (e.g., hemolysis of sample), or equipment malfunction, collection of a repeat sample for the appropriate laboratory test or assessment is permitted.
- Exclusionary liver function test (LFT) levels may be retested once within 14 days of the original screening date. The Vertex medical monitor should be made aware of the repeat testing.
- Assessments required for eligibility may be repeated if permitted, as described in Section 8.2.

If screening spirometry measurements fail to meet acceptability and repeatability criteria as specified by American Thoracic Society/European Respiratory Society guidelines,[9] 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.

9.1.2.1.2 Rescreening

Subjects may be rescreened only once. 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), and sweat chloride level. If a subject is rescreened, the new screening window will begin once the first rescreening assessment has been initiated.

9.1.2.1.3 Extension of Screening Period Window

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

- Repetition of the Screening Period assessments (Section 9.1.2.1.1)
- Unexpected operational or logistic delays, or to meet the eligibility criteria
- Repetition of spirometry assessment if results are of poor quality

9.1.2.2 Treatment Period

The Treatment Period will last approximately 4 weeks. Subjects will be evaluated as outpatients.

Study visits during the Treatment Period will occur as shown in Table 3-7. All visits will occur within the windows specified. Study drug administration details are provided in Section 9.6.2.

Subjects must meet both of the following conditions to qualify 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 first dose of study drug in the Treatment Period.)
- Must not have had an acute non-CF illness (e.g., gastroenteritis) within the 14 days before the first dose of study drug in the Treatment Period.

If these conditions 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 the Day 1 Visit (or Day -1) after conditions for entry into the Treatment Period have been confirmed.

9.1.2.3 Follow-up

Subjects will have a Safety Follow-up Visit approximately 28 days after the last study drug dose. Safety Follow-up Visit assessments are listed in Table 3-7.

9.1.2.4 Early Termination of Treatment

If the subject prematurely discontinues study drug, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the subject decides to terminate study drug. Subjects who prematurely discontinue study drug 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 3-7.

Subjects who discontinue from study drug dosing for any reason (except withdrawal of consent) will have a final PK blood sample drawn as soon as possible after the decision to discontinue study drug is made. Additional safety assessments may also be performed at the discretion of the investigator, including possible consultation with a specialist consultant. The Vertex medical monitor will be informed about these additional assessments, and any additional data collected (e.g., as the result of an outside consultation) will be considered part of the study record to provide the most complete safety profile of the study drug.

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

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

9.2 Method of Assigning Subjects to Treatment Groups

A randomization list for each part will be produced by Vertex Biostatistics or a qualified randomization vendor. The Vertex study biostatistician will review and approve the dummy randomization list. The final randomization list will be reviewed and approved by a designated unblinded biostatistician who is not a member of the study execution team (SET).

Parts A, B, and C

Subjects will be assigned a unique subject number (unique to subject and cohort). Only subjects who have completed screening assessments and are eligible for participation in the study will be randomized to receive active study drug or placebo during the Treatment Period. A list identifying subjects by their subject number will be maintained in the study file at the CRU.

Part D

Subjects will be assigned a unique subject number. Only subjects who have completed screening assessments and are eligible for participation in the study (and qualify to enter the Treatment Period) will be randomized to receive active study drug or placebo during the Treatment Period.

An interactive web response system (IWRS) will be used to assign subjects to treatment.

9.3 Rationale for Study Design and Study Drug Regimens

9.3.1 Study Design

Parts A, B, and C

Parts A (except Cohort A9) and B have a dose-escalation design, with each subject participating in only 1 cohort (unless at least 21 days has elapsed before participation in another cohort), to avoid PK and/or PD carryover effects.

Part C will evaluate the safety, tolerability, and PK of VX-121 administered in TC with TEZ/IVA because VX-121 is being developed for use in this TC for the treatment of CF. It will also include an evaluation of the PK of TEZ and metabolites, and IVA and metabolites, following administration of VX-121 in TC with TEZ/IVA.

Parts A, B, and C (except Cohort A9) will be randomized, double-blind, and placebo-controlled to avoid bias in the collection and evaluation of safety and tolerability data during their conduct. Subjects will be randomized 3:1 to receive either active study drugs or placebo. Placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related or simply related to the study conditions.

Predictive models suggest that the solubility of VX-121 may decrease in the presence of calcium-rich food such as milk and milk products, reducing the absorption and systemic exposure of VX-121. Therefore, in addition to randomized study drug administration described above, after a washout of at least 8 days all subjects in Cohort A3 will receive a single dose of open-label VX-121 suspension with milk to evaluate the effect of milk on VX-121 exposure.

Staggered Dosing in Cohorts A1 and C1

Dosing in the first cohort of Parts A and C (Cohorts A1 and C1) will initiate with staggered dosing in 2 subjects (1 active, 1 placebo) followed by a minimum 24-hour observation before dosing of the remaining subjects in the cohort. Staggering at higher doses may be conducted if deemed necessary based on review of emerging safety data.

Staggered dosing is proposed for Part A because this is the first time VX-121 will be administered to humans. In addition, staggered dosing is proposed for Part C because it is the first time VX-121 will be administered in TC with TEZ/IVA in humans. Staggered dosing for Part B is not considered necessary, because the total daily dose to be evaluated in the first cohort (Cohort B1) will be at least 1 dose level below the highest Part A dose for which safety, tolerability, and PK results are available and supportive. Therefore, the relative risk to subjects dosed in Cohort B1 is less than that of subjects in Cohorts A1 and C1.

Cohort A9

Cohort A9 will not be initiated until all documentation required to support administration of the VX-121 tablet has been submitted to and approved by the competent authority (IRB/IEC, as applicable).

Subjects in Cohort A9 will receive 3 single doses of VX-121 to evaluate the BA of a tablet (with calcium restrictions) relative to the suspension formulation (with calcium restrictions) and the effect of milk on the tablet formulation. Each dosing occasion will be separated by at least 8 days. Based on preliminary clinical data, the interval between dosing occasions is considered adequate to minimize any potential for carryover.

Part D

Part D will evaluate the safety, tolerability, PK, PD, and efficacy of VX-121 administered in TC with TEZ/IVA in subjects with CF who are heterozygous for *F508del* and a MF *CFTR* mutation (F/MF genotype).

Efficacy has not been established for a corrector, potentiator, or any corrector/potentiator combination in subjects with F/MF genotypes. Because there is no effective treatment for this

population, a placebo arm will be included as the control treatment to assess whether any observed effects are treatment-related or simply related to the study conditions.

9.3.2 Study Drug Dose and Duration

VX-121 Starting Dose

[redacted] Using the lowest of the HED values (1.6 mg/kg), assuming a 60-kg human subject, and applying a default safety factor of 10, the maximum recommended safe starting dose is estimated to be approximately 10 mg/day. The selected starting dose of 10 mg for Cohort A1 [redacted]

Part A VX-121 Dose Escalation

The planned dose escalation scheme for Part A is shown in Table 9-1. Dose escalation criteria for Part A (including the data that will be reviewed before initiating successive cohorts) are presented in Section 9.7.1. Stopping rules are presented in Section 9.8.1. Dose escalation may be adjusted upward or downward based on emerging safety, tolerability, and PK data.

For Cohorts A2 and A3 only, PK data will be available from the "lagging" cohort before escalation (i.e., Cohort A1 PK results may not be available before escalation to Cohort A2, but Cohort A1 PK data will be available before escalation to Cohort A3). Availability of lagging PK is appropriate for the lower dose cohorts because the projected exposure at these relatively low doses are not expected to approach or exceed the exposure cap based on nonclinical NOEL/NOAELs.

Cohort A9 VX-121 Dose Selection

The planned oral dose of VX-121 administered in Cohort A9 as suspension and tablet is 10 mg for both formulations. The oral dose will not exceed a dose shown to be safe and well tolerated in a previous Part A cohort.

Part B VX-121 Starting Dose and Dose Escalation

The planned dose escalation scheme for Part B is shown in Table 9-1. The starting dose in Part B will be selected based on the safety, tolerability, and PK data in Part A. Cohort B1 will begin after evaluation of safety, tolerability, and PK data from at least 1 dose level above the corresponding daily dose from Part A to sufficiently establish the safety, tolerability and exposure of the study drug after multiple doses.

Initiation of successive cohorts and dose selection will be based on safety, tolerability, and PK data described in Section 9.7.1. PK data through Day 5 is sufficient to predict steady-state exposures for the next cohort.

Part C VX-121 Starting Dose and Dose Escalation

The planned dose escalation scheme for Part C is shown in Table 9-1. The starting dose in Part C will be selected based on the safety, tolerability, and PK data in Parts A and B. The total daily dose in the first Part C cohort (Cohort C1) will be at least 1 dose level below the highest total daily Part B dose for which safety and tolerability results are available and supportive.

Parts B and C Treatment Duration

The durations of dosing in Part B (10 days) and Part C (14 days) are standard durations for multiple-dosing in first-in-human studies and are of sufficient length for an early assessment of safety and tolerability and for assessment of steady-state PK. Given that the starting dose in Part C will be at least 1 dose level below the highest Part B dose (Section 9.7.1), the cumulative exposure in Part C is predicted to be lower than in Part B provided dose-proportional PK and no drug-drug interactions that significantly impact VX-121 exposure are observed.

TEZ and IVA Doses

The doses of TEZ and IVA are the same as those evaluated in Phase 3 studies of TEZ/IVA combination therapy (TEZ: 100 mg qd; IVA: 150 mg q12h). These doses of TEZ and IVA are appropriate for evaluation in the TC based on in vitro experiments with VX-121 that evaluated similar levels of TEZ and IVA exposure after correction for protein-binding.

Part D VX-121 Dose Selection

Screening in Part D will be initiated after the completion of Parts A, B, and C (cohorts needed for Part D dose selection only) through the Safety Follow-up Visit. The decision to proceed to Part D will be based on an evaluation of safety, tolerability, and PK data from completed cohorts in Parts A, B, and C. These data will be submitted to the IEC for approval before proceeding to screening for Part D. Based on preliminary data from Parts A, B, and C, the planned dose of 10 mg qd is predicted to provide an approximate $AUC_{0\text{-}24h}$ of 10 µg·h/mL, which is within the range of predicted efficacious exposure based on in vitro data (refer to VX-121 Investigator's Brochure). Based on emerging safety, tolerability, and PK data from Parts A, B, and C, the planned dose for Part D may be lowered to 5 mg qd. The total daily dose of VX-121 in Part D will be at least 1 dose level below the highest total daily dose tested in Part C; as Part C may not include all total daily dose levels tested in Part B, Part D may include a total daily dose that has not been tested in Part C but is at least 1 dose level below the highest total daily dose tested in Part C. The 4-week treatment duration is considered appropriate for initial evaluation of safety, tolerability, and PK of the TC in subjects with CF.

Administration of VX-121, TEZ, and IVA With Food

Oral doses of VX-121, TEZ, and IVA will be administered under fed conditions. This is consistent with how VX-121, TEZ, and IVA were administered in nonclinical studies, including the GLP toxicity studies. In humans, a positive food effect has been established for IVA, and is predicted for VX-121.

9.3.3 Rationale for Study Assessments

The majority of safety and PK assessments are standard parameters for Phase 1 clinical studies. Rationales for other safety, PK, PD, and efficacy assessments are listed below.

4β-hydroxycholesterol

4β-hydroxycholesterol is an endogenous marker for CYP3A activity.[12] Evaluation of 4β-hydroxycholesterol is being used increasingly to assess potential clinical CYP3A induction. In Part B, comparison of 4β-hydroxycholesterol on the Day 10 Visit (predose) relative to baseline (Day-1 predose) will be used to evaluate potential induction of CYP3A by VX-121.

Spirometry

Mild post-dose declines in lung function have been observed after the initial dose with another CFTR corrector not included in the current study (LUM).[13] Although nonclinical toxicity results do not indicate a risk of lung function declines for VX-121, lung function, as assessed by spirometry, will be included in Part D to assess for post-dose declines in spirometric indices. In addition, lung function, as assessed by spirometry, will be evaluated for preliminary evidence of efficacy.

Sweat chloride test and *CFTR* genotyping

The sweat chloride test is a standard diagnostic tool for CF and is a biomarker of CFTR activity in patients with CF. Based on the mechanism of action of VX-121, the sweat chloride test will be included as a measure of the PD effect of VX-121 and the TC on CFTR activity. Sweat chloride levels will be measured in subjects with CF receiving VX-121 TC or placebo in Part D. Sweat chloride levels will be measured at visits before study drug administration, at visits during the Treatment Period (when study drug exposures are expected to be at steady-state), and at Safety Follow-up Visit (to evaluate off-treatment effects of study drug).

Continuous ECG monitoring

Continuous ECG monitoring will be performed in all Part B subjects for later extraction and high-precision QTc analysis of 10 ECG replicate measurements. It has been demonstrated that evaluation of QTc in early phase clinical studies with a robust dose range can be used to evaluate a potential exposure-response (E-R) relationship for QTc, which may be used to replace the thorough QTc study for new drugs.[14] The ECGs collected by continuous monitoring may or may not be analyzed for the purpose of E-R modeling, based on future development decisions for VX-121. If analyzed, results of the high-precision QTc analysis and E-R modeling will not be included in the clinical study report (CSR), but will be included in a separate report.

9.4 Study Restrictions

9.4.1 Parts A, B, and C

Study restrictions are summarized in Table 9-2.

Table 9-2 Parts A, B, and C: Study Restrictions

Restricted Medication/Food/Activity[a]	Timing of Restriction	
	From (minimum)	To
Depo-Provera®	6 months before first study drug dose	Completion of Safety Follow-up Visit assessments
Tobacco- or nicotine-containing product	45 days before first study drug dose	Completion of Safety Follow-up Visit assessments

Table 9-2 Parts A, B, and C: Study Restrictions

Restricted Medication/Food/Activity[a]	Timing of Restriction	
	From (minimum)	To
Other investigational drugs or devices	30 days before first study drug dose, 5 half-lives before first study drug dose, or time determined by local requirements, whichever is longest	Completion of Safety Follow-up Visit assessments
VX-121	21 days before first study drug dose	First study drug dose
Hormonal methods of contraception (oral, vaginal, or patch) or hormonal replacement therapies	28 days before first study drug dose	Completion of Safety Follow-up Visit assessments
Prescription medications	14 days or 5 half-lives (whichever is longer) before first study drug dose	Completion of Safety Follow-up Visit assessments
Nonprescription medications	14 days or 5 half-lives (whichever is longer) before first study drug dose. Occasional, limited ibuprofen (≤800 mg/day) and acetaminophen at doses of ≤2 g/day is allowed for pain.	Completion of Safety Follow-up Visit assessments
Herbal and dietary supplements	14 days before first study drug dose	Completion of Safety Follow-up Visit assessments
Grapefruit or grapefruit juice, apple or orange juice, vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats	72 hours before first study drug dose	Until last PK sample is taken
Milk, milk products (e.g., yogurt, cheese, cream), calcium supplemented foods (e.g., orange juice, juices fortified with added calcium), other calcium-rich foods (e.g., spinach, kale, bok choy, watercress, broccoli, sardines, okra, almonds), and drugs such as antacids[b]	4 hours before each study drug dose	4 hours after each study drug dose (except when VX-121 will be administered in presence of milk)
Alcohol	Not more than 28 units per week for males and 21 units per week for females (where 1 unit is equal to half a pint of beer or one 25 ml measure of spirits; a small [125 ml] glass of wine has 1.4 units) within 6 months before the Screening Visit, and none from 48 hours before admission to the CRU.	Completion of Safety Follow-up Visit Assessments
Caffeine	24 hours before first study drug dose	Until last PK sample is taken

Table 9-2 Parts A, B, and C: Study Restrictions

Restricted Medication/Food/Activity[a]	Timing of Restriction	
	From (minimum)	To
Strenuous exercise (e.g., heavy lifting, weight training, and aerobics)	96 hours before first clinical laboratory testing	Completion of Safety Follow-up assessments

[a] See Section 9.5.1 for guidance on concomitant medications.
[b] The restrictions on dairy consumption may be removed pending the results from Cohorts A3 and/or A9.

9.4.1.1 Activity

In Part B, subjects will be confined for the first 4 hours after dosing on the Day 10 Visit during continuous ECG monitoring, except to use the bathroom. After this time, if the equipment setup allows, subjects may be ambulatory during the telemetry (Holter monitor) period, but will not engage in strenuous activities. If ECG equipment does not allow ambulation, appropriate accommodations will be made by the study site to facilitate continuous monitoring (i.e., bedside urinals will be provided to accommodate subjects' excretory needs).

9.4.2 Part D

9.4.2.1 Prohibited Medications

Prohibited medications are shown in Table 9-3. VX-121, TEZ, and IVA are metabolized extensively via CYP3A. Therefore, use of moderate and strong inducers or inhibitors of CYP3A, which have the potential to alter the exposure of VX-121, TEZ, or IVA, will be prohibited. VX-121 is a potential inhibitor of the hepatic transporter organic anion transporting polypeptide 1B1 (OATP1B1). Therefore, sensitive substrates of OATP1B1, such as HMG-Co-A Reductase Inhibitors ("statins") will be prohibited.

A non-exhaustive list of study prohibitions and cautions for medication will be provided in the Study Reference Manual. Food restrictions, including potential dairy restrictions, will also be specified in the Study Reference Manual.

Table 9-3 Part D: Prohibited Medications

Medication[a]	Timing of Restriction	
	Start of Restriction	End of Restriction
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of study drug	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 study drug	None allowed through the Safety Follow-up Visit
CFTR modulators other than study drug (e.g., Kalydeco, Orkambi, TEZ/IVA)	None allowed within 28 days before the first dose of study drug	None allowed through the Safety Follow-up Visit
Sensitive OATP1B1 substrates	None allowed within 14 days before the first dose of the study drug	None allowed through the Safety Follow-up Visit

Note: The use of prohibited medication by subjects with medical needs will be addressed on a case-by-case basis with the medical monitor.
[a] See Section 9.5.2 for guidance on concomitant medications.

9.4.3 Parts A, B, C, and D

9.4.3.1 Exposure to Sunlight

Subjects will take appropriate measures to minimize exposure to UV radiation (e.g., sunlight, tanning booths) from the Day 1 Visit through the Safety Follow-up Visit.

9.5 Prior and Concomitant Medications

9.5.1 Parts A, B, and C

- Subjects will abstain from medication as described in Table 9-2.
- All medications taken from 28 days before the first dose of study drug through the end of the study will be recorded with indication, route of administration, and start and stop dates of administration. All subjects will be questioned about medications at each clinic visit.

9.5.2 Part D

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 be documented only in the subjects' source documents.

- Subjects must remain on a stable CF medication (and supplement) regimen (other than protocol-specified changes in CFTR modulator regimen) for their CF from 28 days before the Day 1 Visit through the Safety Follow-up Visit. Stable CF medication regimen is defined as the current medication regimen for CF that subjects have been following for at least 28 days before the Day 1 Visit. Subjects must not initiate long-term treatment with new medication from 28 days before the Day 1 Visit through the Safety Follow-up Visit unless discussed and approved by the medical monitor. Guidelines for stable CF 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 the Day 1 Visit 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 the Day 1 Visit 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 or prednisolone of up to 10 mg/day or equivalent (chronically), or prednisone or prednisolone 60 mg/day 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 11.7.5.

9.6 Administration

9.6.1 Parts A, B, and C

For all dosing occasions, study drug will be administered under supervision of the investigator or authorized designee. VX-121 and matching placebo will be administered as a suspension or tablets. TEZ and IVA and their matching placebos will be administered as tablets.

Study drug will be administered according to the following guidelines:

- Study drug will be administered after baseline vital signs and ECGs are performed.
- Study drug should be given to subjects within each Treatment Period, at approximately the same time (± 30 minutes) on each dosing occasion.
- Administration of VX-121 suspension will be followed by 240 mL of water or milk (in addition to randomized study drug administration depicted in Table 9-1, subjects in Cohort A3 will receive an additional single dose of VX-121 suspension with milk; all other suspension administration will be with water). Water will be used and consumed as needed to rinse suspension from the dosing vial when administration of VX-121 is followed by milk. A taste-masking agent will be given to subjects before and after study drug dosing. Additional details will be provided in the Pharmacy Manual, Formulation Preparation Instructions (FPI), and the ICF.
- When multiple study drugs are being administered, study drugs will be administered at the same time.
- When VX-121, TEZ, and IVA are administered as tablets, subjects will swallow the study drugs whole, followed by 240 mL of water. Subjects may take additional water, as needed, to swallow tablets.
- To standardize the conditions on PK sampling days, all subjects will be required to refrain from lying down (except when required for study procedures), eating, and drinking beverages other than water during the first 4 hours after dosing. In Part A and on days of intensive PK sampling in Parts B and C, water and clear liquids may be consumed without restriction beginning 1 hour after the morning dose.

Parts A, B, and C

The meals (described below) given at the time of drug dosing (breakfast in Parts A, B, and C) will not contain any milk or milk products (e.g., yogurt, cheese) or other calcium-rich foods. These restrictions on dairy consumption (Section 9.4.1) may be removed pending the results from Cohorts A3 and/or A9.

Part A

Part A, Cohorts A1 Through A6 (up to A8): Single Ascending Dose Escalation

All cohorts in Part A will be dosed under fed conditions.

Subjects must abstain from all food and drink (except water) at least 8 hours before the start of the standard breakfast. A standard breakfast, containing approximately 20 g of fat, will be served to subjects 30 minutes before dosing. Subjects must complete the entire meal in 30 minutes or less; study drug will be administered 30 minutes after the start of the meal. Food will not be permitted for at least 4 hours after dosing. Water (including clear liquids) may be consumed without restriction beginning 1 hour after dosing.

Lunch will be provided approximately 4 to 5 hours after dosing. Dinner will be provided approximately 9 to 10 hours after dosing.

An afternoon and/or evening snack will be permitted.

Part A, Cohort A3: Effect of Milk

In addition to the above instructions for dosing under fed conditions, on Day 9 (open-label VX-121 suspension, fed state and with milk), administration of the VX-121 suspension will be followed by a glass of skim milk (240 mL). Water will be consumed with dosing as needed to rinse suspension from the dosing vial. Refer to the FPI for additional information.

Part A, Cohort A9: Relative Bioavailability and Effect of Milk

On the Day 1, 9, and 17 Visits (fed state), subjects must abstain from all food and drink (except water) at least 8 hours before the start of the standard breakfast. A standard breakfast, containing approximately 20 g of fat, will be served to subjects 30 minutes before dosing. Subjects must complete the entire meal in 30 minutes or less; study drug will be administered 30 minutes after the start of the meal. Food will not be permitted for at least 4 hours after dosing. Water (including clear liquids) may be consumed without restriction beginning 1 hour after dosing. On Day 17 (tablet, fed state and with milk), administration of the VX-121 tablet will occur with a glass of skim milk (240 mL) instead of water.

Lunch will be provided approximately 4 to 5 hours after dosing. Dinner will be provided approximately 9 to 10 hours after dosing.

An evening snack will be permitted.

Part B

All cohorts in Part B will be dosed under fed conditions.

On all days of study drug administration, a standard breakfast (containing approximately 20 g of fat) will be served 30 minutes before morning dosing. Subjects must complete the entire meal in 30 minutes or less; study drug will be administered 30 minutes after the start of the meal.

On days of intensive PK sampling, subjects must abstain from all food and drink (except water) at least 8 hours before the start of the standard breakfast. Food will not be permitted for at least 4 hours after the morning dose but water and other clear liquids may be consumed without restriction beginning 1 hour after the morning dose.

Part C

All doses of VX-121, TEZ, and IVA will be administered under fed conditions, consistent with the dosing recommendations for TEZ/IVA.

Subjects will be given a standardized meal (standard breakfast containing approximately 20 g of fat; standard dinner containing approximately 30 to 60 g of fat) 30 minutes (for breakfast) or

45 minutes (for dinner) before all doses of study drug on the Day 1 to 14 Visits. Subjects must complete the meal within 30 minutes (for breakfast) or 45 minutes (for dinner); study drug will be administered 30 minutes (for breakfast) or 45 minutes (for dinner) after the start of the meal.

On days of intensive PK sampling, subjects must abstain from all food and drink (except water) at least 8 hours before the start of the standard breakfast. Food will not be permitted for at least 4 hours after the morning doses but water and clear liquids may be consumed without restriction beginning 1 hour after the morning dose.

9.6.2 Part D

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. Food restrictions, including potential dairy restrictions, will be specified in the Study Reference 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 after the start of the meal or snack.
2. Study drug or placebo will be administered q12h or qd (± 2 hours). VX-121 and TEZ will be administered qd and IVA will be administered q12h. 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 the 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.
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.

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.

9.7 Dose Escalation Criteria

9.7.1 Parts A, B, and C

The decision to initiate successive cohorts and dose selection will be based on safety and tolerability data from preceding dose group(s) and available PK data from a minimum of 6 subjects (to ensure 4 subjects receiving active drug) in the preceding cohort. The investigator, Vertex medical monitor, and Vertex Global Patient Safety (GPS) physician will conduct a blinded evaluation of all safety data on an ongoing basis, and all Grade 3 or higher laboratory abnormalities or AEs (Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials) will be evaluated to determine if dosing/dose escalation should be continued. A safety report, which includes available PK data and justification for selection of the dose, will be prepared by the investigator for the proposed dose escalation.

Part A: The planned dose escalation scheme for Part A is shown in Table 9-1. Doses may be adjusted upward or downward based on safety, tolerability, and available PK data from preceding dose group(s). No dose increment will be expected to yield greater than a 3-fold increase (Cohorts A1 through A3) or a 2-fold increase (all other Part A cohorts) in exposure from the preceding dose level. Dose escalation will be stopped when the predefined stopping criteria is met (see Section 9.8.1).

Cohort A2 initiation will be based on safety data (through ≥48 hours postdose) from Cohort A1. Cohort A3 initiation and dose selection will be based on safety data (through ≥48 hours postdose) from Cohort A2 and PK data (through ≥24 hours postdose) from Cohort A1 (i.e., lagging PK). For all other Part A cohorts, initiation and dose selection will be based on safety data (through ≥48 hours postdose) and PK data (through ≥24 hours postdose) from the previous cohort.

If conducted, the dose(s) in Cohorts A7 or A8 may be a replicate of a dose evaluated in Cohorts A1 through A6 or may be increased above 90 mg, pending emerging safety, tolerability, and PK data from Cohorts A1 through A6.

Part B: Part B may be initiated while Part A is ongoing after review of safety, tolerability, and PK data. The starting daily dose (Cohort B1) will be at least 1 dose level below the highest Part A dose for which safety and tolerability results are supportive.

The decision to initiate successive cohorts and dose selection will be based on safety data through the Day 10 Visit and PK data as available through the Day 5 Visit from the previous cohort. Doses may be adjusted upward or downward based on safety, tolerability, and PK data from preceding dose group(s). No dose increment will be expected to yield greater than a 2-fold

increase in exposure from the preceding dose level. The highest daily dose of VX-121 in Part B will not exceed the highest Part A dose for which safety and tolerability results are supportive. Stopping rules are presented in Section 9.8.1.

Part C: Part C may be initiated while Parts A and B are ongoing after review of safety, tolerability, and PK data. The starting dose (Cohort C1) will be at least 1 dose level below the highest Part B dose for which safety and tolerability results are supportive.

The decision to initiate successive cohorts and dose selection will be based on safety data through the Day 14 Visit and PK data as available through the Day 7 Visit from the previous cohort. The highest dose of VX-121 in Part C will not exceed the highest Part B dose for which safety and tolerability results are supportive.

9.7.2 Part D

Part D is a single cohort part; dose escalation criteria are not applicable.

9.8 Stopping Rules

9.8.1 Parts A, B, and C

Stopping Rules for Cohorts

In Parts A and B, dose escalation will be stopped if the mean $AUC_{0-\infty}$ (single-dose escalation) or AUC_{0-24h} (multiple-dose escalation) of the next dose is predicted to exceed an AUC of 356 µg·h/mL or the C_{max} is predicted to exceed 21 µg/mL [redacted] Dose escalation will also consider individual subject exposure and potential outliers. Exposures in male and female rats were higher than the dog at the NOAEL in the rat 28-day GLP toxicity study.

If a serious adverse event (SAE) occurs that is considered related or possibly related to study drug, or if 2 severe (or greater) AEs occur that are considered related or possibly related to study drug, then the study will be halted (dosing of study drug in all study subjects will be halted). Occurrence of such events will trigger an internal safety review, including discussion between the investigator and medical monitor, and notification to regulatory authorities and ethics committees, if applicable. If the sponsor decides it is appropriate to restart the study, dosing of study drug will be resumed only after approval of a substantial amendment to the Clinical Trial Authorization.

9.8.2 Part D

The medical monitor should be notified of a discontinuation of study drug or an interruption of study drug that lasts >72 hours for any reason and of the resumption of study drug after such interruption.

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) 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

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 subsequent ALT or AST values confirm the initial elevation that satisfied the interruption rule (above), and no convincing alternative etiology (e.g., acetaminophen use, viral hepatitis, alcohol ingestion) is identified, regardless of whether transaminase levels have improved.

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.

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. Regardless of the duration of interruption, the medical monitor should be notified prior to resumption of study drug. Upon resumption of study drug, transaminases and bilirubin should be assessed weekly until the Safety Follow-up Visit. If a protocol-defined transaminase or bilirubin elevation interruption threshold recurs with rechallenge with the study drug (with confirmation of the initial elevation by repeat testing within 48 to 72 hours), then the study drug must be permanently discontinued, regardless of the presumed etiology.

9.8.3 Parts A, B, C, and D

Individuals who develop AEs will be monitored closely; consideration should be given to the need for additional safety assessments and possible consultation (e.g., with a dermatologist, GI specialist, or other specialist consultant). Any additional data collected (e.g. as a result of an outside consultation) will be considered part of the study record to provide the most complete safety profile of the study drug.

9.9 Removal of Subjects

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

- Pregnancy
- Unacceptable toxicity

Subjects who are withdrawn from study drug dosing will complete assessments as described in Sections 9.1.1.4 and 9.1.2.4 and may have additional PK samples collected as deemed appropriate by the investigator in consultation with the Vertex medical monitor. Consideration should be given to the need for additional safety assessments as described in Sections 9.1.1.4 and 9.1.2.4. The investigator will use clinical judgment to determine whether assessments after study drug discontinuation should occur while the subject remains confined in the clinical unit or can be completed as outpatient visits.

In Part D, 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) (Part D only), request that the subject return for a Safety Follow-up Visit, if applicable (see Sections 9.1.1.3 and 9.1.2.3), and follow up with the subject regarding any unresolved AEs.

If the subject withdraws consent for the study, no further evaluations should be performed, and no additional data should be collected. Vertex may retain and continue using the study data and samples after the study is over, and may use the samples and information in the development of the study compound, and for other drugs and diagnostics, in publications and presentations, and for education purposes. If the subject withdraws from the study, the study data and samples collected will remain part of the study. A subject will not be able to request the withdrawal of his/her information from the study data. A subject may request destruction of the samples collected from him/her during the study as long as those samples can be identified as his/her samples.

Stopping rules are presented in Section 9.8.

9.10 Replacement of Subjects

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

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

10 STUDY DRUG INFORMATION AND MANAGEMENT

Study drug refers to VX-121, TEZ/IVA (VX-661/VX-770), IVA, and their matching placebos.

10.1 Preparation and Dispensing

Parts A, B, and C

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

When administered as a suspension, drug substance will be reconstituted and then dispensed into individual dosing containers, when appropriate, by 2 operators, 1 of whom is a qualified pharmacist. Details of dose preparation will be given in the FPI.

Tablets will be dispensed at the CRU to individual dosing containers by 2 operators, 1 of whom is a qualified pharmacist, and following national and local laws and regulations.

Part D

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 Packaging and Labeling

Vertex will supply the VX-121 drug substance and tablets, TEZ/IVA fixed-dose combination (FDC) tablets, IVA tablets, and all matching placebos. Study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing will be included in the Pharmacy Manual.

10.3 Study Drug Supply, Storage, and Handling

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

VX-121 drug substance and matching placebo will be provided to the site and will be compounded as a suspension. Refer to the Pharmacy Manual for storage and handling conditions for bulk and unit dose suspensions.

VX-121 and matching placebo will be supplied as tablets of similar size and appearance containing 5 mg VX-121 and 0 mg VX-121, respectively.

TEZ/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 TEZ/150 mg IVA and 0 mg TEZ/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.

All study drugs will be stored in accordance with the drug label or the Pharmacy Manual.

10.4 Drug Accountability

The pharmacist or designated study site staff will maintain information regarding the dates and amounts of (1) study drug received; (2) study drug dispensed to the subjects; and (3) study drug returned by the subjects (Part D only). Subjects will be instructed to return all used and unused materials associated with the study drug to the site (Part D only). 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.

10.5 Disposal, Return, or Retention of Unused Drug

The study site staff or pharmacy personnel will retain all materials returned by the subjects (Part D only) 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.

10.6 Compliance

10.6.1 Parts A, B, and C

All doses will be administered under the direct supervision of the investigator or designee. A hand-and-mouth check will be done after each dose administration in the CRU to ensure 100% study treatment compliance.

10.6.2 Part D

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.

10.7 Blinding and Unblinding

This will be a double-blind study, with the exception of Cohort A9, which will be open-label.

10.7.1 Blinding

10.7.1.1 Parts A, B, and C

Blinding of subject treatment assignments will be maintained until database lock. The packaging and labeling of study drug will be done to ensure that treatment assignments are blinded within each cohort in all parts of the study.

During the conduct of the study, all study personnel will be blinded to subject treatment assignments except for

- the unblinded site monitor;
- designated clinical research organization (CRO) performing the PK bioanalysis;
- Bioanalytical CRO analyzing PK samples and Vertex Bioanalytical personnel who are not members of the SET but review raw data from the Bioanalytical CRO. The Vertex Bioanalytical SET member will continue to be blinded;

- vendor preparing the unblinded statistical and PK/PD analysis of continuous ECG data collected in Part B;
- the unblinded biostatistician preparing the randomization list as well as an unblinded quality control (QC) biostatistician;
- the dispensing contracted pharmacist;
- the pharmacy QC/quality assurance (QA) personnel, as applicable; and
- Vertex GPS and Regulatory Affairs, when required to satisfy regulatory reporting requirements.

The Vertex medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time.

A limited Vertex team, which may include members of the Vertex SET, may be unblinded to individual subject treatment assignments for the purposes of review of PD, PK/PD, and/or safety data. No unblinded data or results of unblinded analyses will be shared with the CRU or with blinded Vertex personnel. All instances of unblinding by Vertex personnel will be documented.

Bioanalytical results (i.e., concentrations of VX-121) will be reported by the Bioanalytical CRO using masked IDs for PK analysis.

10.7.1.2 Part D

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 or the male subject's partner and her fetus in the event of a pregnancy
- Vertex GPS and Regulatory Affairs personnel to satisfy SAE processing and reporting regulations
- Unblinded statistician preparing the final (production) randomization list who is not part of the study team
- Vertex IWRS Manager
- Vertex Clinical Supply Chain
- Vendor preparing the unblinded analysis for the ongoing reviews of data by a limited Vertex team (see below)
- Bioanalytical CRO analyzing PK samples and Vertex Bioanalytical personnel who are not members of the SET but review raw data from the Bioanalytical CRO. The Vertex Bioanalytical SET member will continue to be blinded.
- 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 the Day 1 Visit.
- Sites, 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 has prematurely discontinued treatment.
- 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 has prematurely discontinued treatment.

A limited Vertex team will be unblinded and have access to safety, PD, and efficacy data for the purpose of conducting ongoing data reviews for planning and enabling clinical development, regulatory, and chemistry, manufacturing, and controls (CMC) decisions.

Refer to Section 12.3.5.1 for details regarding interim analyses (IAs).

10.7.2 Unblinding

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

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

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), 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 a 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 schedule of assessments is shown in Table 3-1 through Table 3-7.

11.2 Subject and Disease Characteristics

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

11.3 Pharmacokinetics

11.3.1 Blood Sampling

Blood samples will be collected from all subjects for the evaluation of plasma concentrations of VX-121, TEZ and metabolites (M1-TEZ and M2-TEZ), and IVA and metabolites (M1-IVA and M6-IVA). [redacted]

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

Based on emergent data, the number of sampling points for VX-121 plasma may be reduced and/or time points may be modified. Actual sampling times may change upon agreement of the clinical pharmacologist and investigator. 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.

Table 11-1 Acceptable Pharmacokinetic Sampling Windows

Part	Sampling Time	Time From Scheduled Sampling Allowed
Parts A, B, and C	Predose	Within 30 minutes before dosing
	From 0.25 up to ≤12 hours after study drug dosing	± 5 minutes
	From >12 up to ≤24 hours after study drug dosing	± 10 minutes
	From >24 up to ≤48 hours after study drug dosing	± 20 minutes
	From >48 up to ≤168 hours after study drug dosing	± 30 minutes
Part D	Predose	Within 60 minutes before dosing
	From 1 up to ≤8 hours after study drug dosing	± 15 minutes

Samples collected outside of these acceptable windows will be considered protocol deviations.

For each visit with a PK blood draw, a record of study drug administration will be collected as described in Section 9.6. The collection date and exact time that each PK blood sample is drawn will also be recorded.

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.

11.3.3 Bioanalysis

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

[redacted]

11.4 Pharmacodynamics

11.4.1 Sweat Chloride (Part D)

Collection of sweat samples will be performed in Part D using the Macroduct® (Wescor, Logan, UT) collection device.

At each time point, 2 samples will be collected, 1 from each arm (left and right). Additionally, sweat collections will be performed on any single day during screening. Collection of sweat chloride will not overlap with any other study assessments.

Sweat samples will be sent to a central laboratory for analysis of sweat chloride concentrations. Sweat chloride results for individual subjects will not be disclosed to the study sites.

Specific instructions for collection, handling, processing, and shipping of sweat chloride samples to the central laboratory will be provided separately.

[redacted]

11.6 Efficacy

11.6.1 Spirometry (Part D)

Refer to Section 11.7.5.

11.7 Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, ECGs, PEs, and spirometry (Part D).

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 CRF completion guidelines for investigators as well as training will be provided.

11.7.2 Clinical Laboratory Assessments

In Parts A, B, and C, blood and urine samples will be analyzed at a local laboratory. In Part D, blood and urine samples will be analyzed at a central laboratory.

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

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

Table 11-2 Safety Laboratory Test Panels

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

Note: In Part D, glomerular filtration rate will be calculated by the Modification of Diet in Renal Disease Study Equation for subjects ≥18 years of age (Section 8.2.2).

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

[b] If blood urea nitrogen cannot be collected, urea may be substituted.

[c] In Parts A, B, and C, coagulation will only be assessed at screening.

Other Clinical Laboratory Assessments as Described in Section 3:

Serum Pregnancy (β-human chorionic gonadotropin) Tests for All Female Subjects: For Parts A, B, and C, serum samples will be analyzed at the local laboratory. For Part D, serum samples will be analyzed at the central laboratory for all female subjects.

FSH: Blood samples 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.

Serology (Parts A, B, and C): HBsAg, HCV antibody, and HIV-1 and HIV-2 antibodies will be tested for.

Drug and Alcohol Screening (Parts A, B, and C): Opiates, methadone, cannabinoids, cocaine, amphetamines/methamphetamines, barbiturates, benzodiazepines, cotinine, and alcohol levels will be assessed by a blood or urine test; alcohol breath tests are acceptable alternatives for alcohol testing. Subjects may undergo random urine drug screen and alcohol testing if deemed appropriate by the investigator. Drug screen result must be negative for all subjects to receive study drug.

CFTR Genotype (Part D): *CFTR* genotyping will be performed for all subjects (Section 8.2.1).

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

In Part D, for purposes of study conduct, the central laboratory must be used for all laboratory tests. 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. At other visits, symptom-directed PEs and symptom-directed vital sign assessments can be performed at the discretion of the investigator or healthcare provider.

A PE includes a review of the following systems: head/neck/thyroid; eyes, ears, nose, and 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, skin, and abdomen.

Vital signs include blood pressure (systolic and diastolic), temperature, pulse rate, respiration rate, and pulse oximetry (Part D only). The subject will be instructed to rest for at least 5 minutes before vital signs are assessed.

11.7.4 Electrocardiograms

11.7.4.1 Safety ECGs

Standard 12-lead ECGs will be performed using a machine with printout. 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 ECG will be done before any other procedures that may affect heart rate, such as blood draws.
- The subject will be instructed to rest for at least 5 minutes before having an ECG.
- The test should be performed in the supine position

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.

Study sites should use QTcF unless they receive approval in advance from the medical monitor to use QTcB.

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 >60 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 (>60 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.

11.7.4.2 Continuous ECGs for Cardiodynamic Assessment (Part B)

In Part B, continuous ECGs will be obtained as noted in Table 3-5 using a Global Instrumentation (Manlius, NY, USA) M12R ECG continuous 12-lead digital recorder, supplied by iCardiac Technologies. The continuous 12-lead digital ECG data will be stored onto Secure Digital memory cards. ECGs to be used in the analyses will be selected by predetermined time points as defined in Table 3-5, and will be read centrally by ERT. At each protocol-specified time point, 10 ECG replicates will be extracted from a 5-minute "ECG window" (typically, the last 5 minutes of the 15-minute period when the subject is maintained in a supine or semi-recumbent quiet position).

The following principles will be followed in ERT's core laboratory:

- ECG analysts are blinded to the subject, visit, and treatment allocation
- Baseline and on-treatment ECGs for a particular subject will be over-read on the same lead and will be analyzed by the same reader.
- The primary analysis lead is lead II. If lead II is not analyzable, then the primary lead of analysis will be changed to another lead for the entire subject data set.

The ECG data collected by continuous monitoring may or may not be analyzed, or the analysis may be restricted initially to 1 or more cohorts. The decision to analyze the ECG data will be based on future development decisions for VX-121.

11.7.5 Spirometry (Part D Only)

Spirometry will be performed according to the American Thoracic Society Guidelines/European Respiratory Society Guidelines.[9]

Spirometry will be performed as outlined below:

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 3-7.

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 Visit 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 the Day 1 Visit, 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 3-7) 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.

11.7.6 Contraception and Pregnancy

The effects of VX-121 monotherapy or in TC with TEZ and IVA on conception, pregnancy, and lactation in humans are not known. VX-121, TEZ, and IVA did not show 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.

11.7.6.1 Contraception

Study participation requires compliance with the contraception guidelines outlined below:

- There are no contraceptive requirements for female subjects. Only females of non-childbearing potential will be enrolled (Section 8). 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

  Notes: All other females (including females with tubal ligations) are considered to be of childbearing potential and are not eligible for the study. Female subjects must have a negative serum pregnancy test at the Screening Visit in order to be eligible for the study.
- There are no contraceptive requirements for males subjects with female partners of non-childbearing potential (as defined above).
- For male subjects with female partners of childbearing potential, study participation requires the male subject to use a condom to avoid exposure of a potential embryo or fetus to study drug via the seminal fluid. In addition, study participation requires a commitment from the subject that at least 1 acceptable method of contraception will be used as a couple. Refer to Table 11-3 for more details.

Table 11-3 Contraceptive Requirements

Male subjects and their female (non-study) partners of childbearing potential[a]	Male subjects must use a condom with or without spermicide.[a] In addition, at least 1 of the following acceptable methods must be used as a couple: • Vasectomy performed at least 6 months previously, with a documented negative postvasectomy semen analysis for sperm. • Bilateral tubal occlusion (e.g., ligation) performed at least 6 months previously. • Continuous use of an intrauterine device for at least 90 days before the first dose of study drug, throughout study drug treatment, and until 7 days after the last dose of study drug. • Hormonal contraceptives, if successfully used for at least 60 days before the first dose of study drug, throughout study drug treatment, and until 7 days after the last dose of study drug.

Note: There are no contraception requirements for female subjects (who will be of non-childbearing potential) and male subjects with female partners of non-childbearing potential.

[a] Male subjects must use a condom to avoid exposure of the female partner (and a potential embryo or fetus) to study drug via the seminal fluid. Condom must be used during the period starting from the first dose of study drug until 7 days after the last dose of study drug.

Additional notes:

- Male subjects must not donate sperm during the period starting from the first dose of study drug until 90 days after the last dose of study drug.
- For male subjects with a female partner of childbearing potential, the couple should not plan to become pregnant during the study or within 90 days after the last dose of study drug, with the exception of couples who plan to become pregnant by artificial insemination using sperm banked by the male subject before the first dose of study drug or sperm from another source.

11.7.6.2 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 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

This section presents a summary of the planned safety analyses and clinical pharmacology for this study. Safety statistical analysis details will be provided in the statistical analysis plan (SAP) for this study, and clinical pharmacologic analysis details will be provided in the clinical pharmacology analysis plan (CPAP), both of which will be finalized before clinical database lock.

Final analyses will take place after all subjects have completed the study, all data have been entered in the clinical study database, and the database has been locked.

12.1 Sample Size and Power

No formal sample size calculations have been performed. The number of subjects participating in each cohort of Parts A, B, and C is typical for first-in-human studies in healthy subjects and is considered sufficient to achieve the objectives of the study. Approximately 12 subjects in Part D is considered sufficient to meet the objectives of the study for this early assessment in subjects with CF.

12.2 Analysis Sets

12.2.1 All Subjects Set

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

12.2.2 Full Analysis Set (Part D Only)

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 for all PD and efficacy analyses in which subjects will be analyzed according to their randomized treatment group, unless otherwise specified.

12.2.3 Safety Set

The Safety Set will include all subjects who received at least 1 dose of study drug. All safety, demographics, baseline characteristics, study drug exposure, and concomitant medications will be summarized for the Safety Set.

12.2.4 Pharmacokinetic Set

The PK Set will include all subjects who received at least 1 dose of study drug and for whom the primary PK data are considered sufficient and interpretable. The PK Set will be used to summarize PK plasma data.

12.3 Statistical Analysis

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

12.3.1 General Considerations

Only descriptive analyses will be performed; no statistical hypothesis testing will be done. Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, SE, median, minimum value, and maximum value. Categorical variables will be summarized using counts and percentages.

All individual subject data for subjects who were randomized or received at least 1 dose of study drug will be presented in individual subject data listings.

For Parts A, B, and C, the **Treatment-emergent (TE) Period** will be from the first dose date of study drug to (1) the Safety Follow-up Visit for subjects who have a Safety Follow-up Visit, or (2) 7 days after the last dose of study drug for subjects who do not have a Safety Follow-up Visit.

For Part D, the **TE Period** will be from first dose date of study drug to 28 days after the last dose date of study drug.

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 Safety Set, included in the FAS, completing Treatment Period, completing the Safety Follow-up Visit, and discontinuing study with a breakdown of the reasons for discontinuation) will be summarized for the All Subjects Set.

12.3.2.2 Demographics and Baseline Characteristics

Demographic and other baseline characteristics will include, but are not limited to age, sex, race, weight, height, BMI, medical history, baseline safety parameters, and baseline sweat chloride. These characteristics will be summarized for the Safety Set. No statistical tests will be done to evaluate baseline imbalances between groups.

12.3.2.3 Prior and Concomitant Medications

Medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) and presented in 2 parts:

1. Prior medication: Medication that started before the first dose of study drug, regardless of when dosing of the medication ended
2. Concomitant medication: Medication received at or after the first dose of study drug, medication that was received before initial dosing and continued after initial dosing of study drug, or medication with missing stop date

If a medication start date is on or after the date of initial dosing of the study drug, then the medication will be summarized as concomitant medication regardless of whether the medication end date is missing or not. If a medication end date is before the date of initial dosing of the study drug, then the medication will be summarized as prior medication regardless of whether the medication start date is missing or not. Note that medication that started before initial dosing of the study drug and continued after initial dosing will be summarized as prior medication and separately as concomitant medication.

Prior medications will be listed only. Concomitant medications will be summarized using preferred name.

12.3.2.4 Study Drug Exposure

Exposure to study drug in Parts C and D (i.e., duration of treatment) will be summarized for the Safety Set in terms of duration of treatment a subject received (in days), defined as the last day minus the first day of study drug plus 1.

Duration of treatment will be summarized by means of descriptive summary statistics for Parts C and D only.

Dosing administration will be presented in an individual subject data listing for all parts.

12.3.3 Efficacy Analysis

12.3.3.1 Spirometry (Part D Only)

The following parameters of FEV_1 (L), forced vital capacity (FVC) (L), FEV_1/FVC (ratio), and forced expiratory flow, midexpiratory phase ($FEF_{25\%-75\%}$) (L/s) will be summarized using descriptive statistics for the FAS.

In addition, a mixed-effects model for repeated measures (MMRM) with change from baseline for percent predicted forced expiratory volume in 1 second ($ppFEV_1$) as the dependent variable will be performed for the FAS. The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects. 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 VX-121 TC and placebo. Adjusted means and 2-sided 95% CIs of the treatment effect through Day 29 (averaged over Day 15 and 29), with *P* values for all within-group comparisons, will be estimated within MMRM.

12.3.4 Safety Analysis

Safety is the primary objective of this study. The overall safety profile of VX-121 will be assessed in terms of the following primary (safety) endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (including coagulation studies)
- ECG outcomes

- Vital signs
- Spirometry (Part D only)

Safety analyses will be based on the Safety Set. No statistical hypothesis testing will be conducted.

For safety variables, the baseline value will be defined as the most recent non-missing measurement collected before the initial administration of study drug.

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

12.3.4.1 Adverse Events

AEs will be coded according to MedDRA. The number and percentage of subjects experiencing an AE will be summarized by the MedDRA System Organ Class (SOC) and Preferred Term (PT). AEs will be classified as pretreatment or treatment-emergent.

Pretreatment AEs are defined as AEs that were reported or worsened after signing the ICF up to the start of study drug dosing.

TEAEs during the Treatment Period are defined as any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug through the end of the TE Period for the Treatment Period.

Only TEAEs will be summarized in tables. All summaries of TEAEs will be presented by the severity of the AE and relationship to the study drug. Some rules that will apply to the summarization of AEs are (1) a subject with multiple occurrences of the same AE or a continuing AE will be counted only once; (2) only the maximum severity level will be presented in the severity summary; and (3) only the worst relationship level will be presented in the relationship summary.

AEs leading to death, other SAEs, dose interruption, and permanent discontinuation will be listed separately. All AEs through the Safety Follow-up Visit will be listed in an individual subject data listing, including pretreatment AEs.

12.3.4.2 Clinical Laboratory Assessments

All statistical analyses of laboratory values will be performed using SI units. Observed and change from baseline values for hematology and clinical chemistry results will be summarized at each scheduled time point. Urinalysis results will be listed only in individual subject data listings. These results will not be summarized. Clinically significant abnormal laboratory findings will be reported as AEs.

12.3.4.3 Electrocardiogram

A summary of raw values and change from baseline values will be provided at each scheduled visit for the following ECG measurements: PR, QT, QRS, and QTc intervals and heart rate. In addition, the number and percentage of subjects by maximum on-treatment value of QT/QTc intervals, categorized as ≤450 msec, >450 msec and ≤480 msec, >480 msec and ≤500 msec, and >500 msec, as well as maximum on-treatment change from baseline value of QT/QTc intervals, categorized as ≤0 msec, >0 and ≤30 msec, >30 and ≤60 msec, and >60 msec, will be provided. Clinically significant abnormal findings will be reported as AEs.

12.3.4.3.1 Cardiodynamic ECG Assessment (Part B)

If it is determined that the continuous ECG data will be analyzed, a separate analysis plan will be created for the evaluation of the continuous ECG data, including the Cardiodynamic ECG Assessment and Concentration-QTc Analysis.

12.3.4.4 Vital Signs

The following vital signs will be summarized at each scheduled time point: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), and respiratory rate (breaths per minute). Clinically significant abnormal findings in vital signs will be reported as AEs.

12.3.4.5 Physical Examination

PE results will be presented in individual subject data listings only. Clinically relevant results identified after screening will be reported as AEs.

[redacted]

12.3.5 Interim and IDMC Analyses

12.3.5.1 Interim Analysis

An IA of the continuous ECG data may be performed after all subjects in Part B have completed the Safety Follow-up Visit (see Section 12.3.4.3.1). These results will be reviewed by a small unblinded Vertex team.

An IA may be performed for Parts A, B, and C after all subjects in Part C have completed the Safety Follow-up Visit.

12.3.5.2 IDMC Analysis

Not applicable

12.4 Clinical Pharmacology Analysis

A detailed analysis plan that addresses the PK objectives of the study will be presented in the CPAP.

12.4.1 Pharmacokinetic Analysis

The PK parameters of VX-121, TEZ and metabolites, and IVA and metabolites will be estimated using standard noncompartmental analysis methods. The analysis of PK results for all analytes will be based on the PK Set and will be described using descriptive statistics. Further details of the PK analyses will be provided in the CPAP.

12.4.2 Pharmacodynamic Analysis (Part D Only)

The sweat chloride assessment will be performed in Part D to evaluate the effect of VX-121 on sweat chloride levels. The analysis of sweat chloride data will be based on the FAS and will be summarized using descriptive statistics.

In addition, the same MMRM model as for $ppFEV_1$ will be used to analyze the change from baseline for sweat chloride. Adjusted means and 2-sided 95% CIs of the treatment effect through Day 29 (averaged over Day 15 and 29), with *P* values for all within-group comparisons, will be estimated within MMRM.

12.4.3 Pharmacokinetic/Pharmacodynamic Analyses (Part D Only)

Correlations between sweat chloride results and PK parameters may be analyzed.

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 in Parts A, B, and C who do not have a Safety Follow-up Visit, 10 days after the last dose of study drug
- For enrolled subjects in Part D 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 9.1.2.4)

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

13.1.1.4.1 Parts A, B, and C

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007, Center for Biologics Evaluation and Research, http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775.htm (Accessed November 2017). The severity of an AE that does not appear in this scale 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

13.1.1.4.2 Part D

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed November 2017). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." The severity of an AE that does not appear in the CTCAE will be determined according to the definitions in Table 13-2.

Table 13-2 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 13-3.

Table 13-3 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).

Table 13-3 Classifications for AE Causality

Classification	Definition

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 13-4.

Table 13-4 Classifications for Study Drug Action Taken With Regard to an AE

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

13.1.1.7 Adverse Event Outcome

An AE will be followed until the investigator has determined and provided the final outcome. The outcome will be classified according to the categories shown in Table 13-5.

Table 13-5 Classifications for Outcome of an AE

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

13.1.1.8 Treatment Given

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

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

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

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

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

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

13.1.2.2 Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent and assent (where applicable) through the Safety Follow-up Visit, regardless of causality, will be reported by the investigator to Vertex GPS. In addition, all SAEs that occur after the Safety Follow-up Visit and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours**.

SAEs will be recorded on the Vertex Organized Safety Information Collection Form (hereafter referred to as the "SAE Form") using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the investigator for relationship to the investigational study drug(s) and possible etiologies. On the SAE Form, relationship to study drug(s) will be assessed only as related (includes possibly related) or not related (includes unlikely related), and

severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the event to resolution and report to Vertex the outcome of the event using the SAE Form.

13.1.2.3 Reporting Serious Adverse Events

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

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (preferred choice)

Fax: [redacted]

For questions, 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, IECs, and participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable. In addition, Vertex, or authorized designee, will be responsible for the submission of safety letters to central IECs.

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

13.2 Administrative Requirements

13.2.1 Ethical Considerations

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

13.2.2 Subject Information and Informed Consent

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

13.2.3 Investigator Compliance

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

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

Parts A, B, and C

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all data provided to Vertex, 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 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.

Part D

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.

Parts A, B, C, and D

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

13.2.6 Record Retention

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

13.2.7 Study Termination

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

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

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

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

13.2.8 End of Study

The end of study is defined as the last scheduled visit (or contact) of the last subject in the study.

13.3 Data Quality Assurance

Parts A, B, and C

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. Vertex will provide, or assess and approve, any electronic data capture (EDC) tools.

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. Data collected during the study, including results from screening, will be recorded in a data capture system for each enrolled subject. Each subject's set of captured data records, once complete, will be signed and dated by the investigator.

Part D

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 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

Parts A, B, and C

Monitoring and auditing procedures developed or approved by Vertex will be followed to comply with GCP guidelines. On-site checking of the data captured for the study/SAE Forms for completeness and clarity, 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 data captured for the study/SAE Forms and source documents. The study site monitor will ensure that the investigation is conducted according to the protocol design and regulatory requirements.

Part D

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

Parts A, B, and C

Sites will use an EDC tool to record data for each enrolled subject.

It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported. 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, including the dates and details of study procedures, AEs, other observations, and subject status.

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 data reported to Vertex, including any changes made, to endorse the final submitted data for the subjects for whom the investigator is responsible.

Part D

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 compact disc (CD) or other electronic media will be placed in the investigator's study file.

13.6 Publications and Clinical Study Report

[redacted]

[redacted]

13.6.2 Clinical Study Report

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

14 REFERENCE

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APPENDIX A Eligible MF *CFTR* Mutations

"MF" mutations are a subset of minimal function mutations that are non-responsive to TEZ, IVA, or TEZ/IVA. A mutation is considered an MF mutation if it meets at least 1 of the following 2 criteria:

(1) biological plausibility of no translated protein (genetic sequence predicts the complete absence of CFTR protein), or

(2) in vitro testing that supports lack of responsiveness to TEZ, IVA, or TEZ/IVA, and evidence of clinical severity on a population basis (as reported in large patient registries).

Inclusion of MF Mutations Based on In Vitro Testing

Mutations that were considered to be MF mutations based on in vitro testing met the following criteria in in vitro experiments:

- baseline chloride transport that was <10% of wild-type CFTR
- an increase in chloride transport of <10% over baseline following the addition of TEZ, IVA, or TEZ/IVA in the assay

These mutations also had evidence of clinical severity on a population basis (per CFTR2 patient registry; accessed on 15 May 2018). Patients with these mutations on one allele and *F508del* on the other allele exhibited evidence of clinical severity as defined as:

- average sweat chloride >86 mmol/L, and
- prevalence of pancreatic insufficiency (PI) >50%

These clinical severity criteria do not apply to the individual subjects to be enrolled in the study, but were used to categorize each mutation on a population level.

Eligible MF Mutations

The list below represents acceptable mutations, which are detectable by an FDA-cleared genotyping assay or other method (e.g., sequencing); 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 VX17-121-001 (Part D)

MF Mutation Category	Mutation				
Nonsense mutations	Q2X	L218X	Q525X	R792X	E1104X
	S4X	Q220X	G542X	E822X	W1145X
	W19X	Y275X	G550X	W882X	R1158X
	G27X	C276X	Q552X	W846X	R1162X
	Q39X	Q290X	R553X	Y849X	S1196X
	W57X	G330X	E585X	R851X	W1204X
	E60X	W401X	G673X	Q890X	L1254X
	R75X	Q414X	Q685X	S912X	S1255X
	L88X	S434X	R709X	Y913X	W1282X
	E92X	S466X	K710X	Q1042X	Q1313X
	Q98X	S489X	Q715X	W1089X	Q1330X
	Y122X	Q493X	L732X	Y1092X	E1371X
	E193X	W496X	R764X	W1098X	Q1382X
	W216X	C524X	R785X	R1102X	Q1411X
Canonical splice mutations	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
	296+1G→T	1248+1G→A	1811+1G→C	3040G→C (G970R)	3600+2insT
	405+1G→A	1249-1G→A	1811+1.6kbA→G		3850-1G→A
	405+3A→C	1341+1G→A	1811+1643G→T	3120G→A	4005+1G→A
	406-1G→A	1525-2A→G	1812-1G→A	3120+1G→A	4374+1G→T
	621+1G→T	1525-1G→A	1898+1G→A	3121-2A→G	
	711+1G→T		1898+1G→C		
Small (≤3 nucleotide) insertion/deletion (ins/del) frameshift mutations	182delT	1078delT	1677delTA	2711delT	3737delA
	306insA	1119delA	1782delA	2732insA	3791delC
	306delTAGA	1138insG	1824delA	2869insG	3821delT
	365-366insT	1154insTC	1833delT	2896insAG	3876delA
	394delTT	1161delC	2043delG	2942insT	3878delG
	442delA	1213delT	2143delT	2957delT	3905insT
	444delA	1259insA	2183AA→G [a]	3007delG	4016insT
	457TAT→G	1288insTA	2184delA	3028delA	4021dupT
	541delC	1343delG	2184insA	3171delC	4022insT
	574delA	1471delA	2307insA	3171insC	4040delA
	663delT	1497delGG	2347delG	3271delGG	4279insA
	849delG	1548delG	2585delT	3349insT	4326delTC
	935delA	1609del CA	2594delGT	3659delC	
Non-small (>3 nucleotide) insertion/deletion (ins/del) frameshift mutations	CFTRdele1	CFTRdele16-17b	1461ins4		
	CFTRdele2	CFTRdele17a,17b	1924del7		
	CFTRdele2,3	CFTRdele17a-18	2055del9→A		
	CFTRdele2-4	CFTRdele19	2105-2117del13insAGAAA		
	CFTRdele3-10,14b-16	CFTRdele19-21	2372del8		
	CFTRdele4-7	CFTRdele21	2721del11		
	CFTRdele4-11	CFTRdele22-24	2991del32		
	CFTR50kbdel	CFTRdele22,23	3667ins4		
	CFTRdup6b-10	124del23bp	4010del4		
	CFTRdele11	602del14	4209TGTT→AA		
	CFTRdele13,14a	852del22			
	CFTRdele14b-17b	991del5			

CFTR Mutations Eligible for VX17-121-001 (Part D)

MF Mutation Category	Mutation			
Missense mutations that • Are not responsive in vitro to TEZ, IVA, or TEZ/IVA **and** • %PI >50% and $SwCl^-$ >86 mmol/L	A46D[b] G85E R347P L467P[b] I507del	V520F A559T[b] R560T R560S A561E	Y569D[b] L1065P R1066C L1077P[b] M1101K	N1303K

CFTR: cystic fibrosis transmembrane conductance regulator; IVA: ivacaftor; SwCl: sweat chloride; TEZ: tezacaftor

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 May 2018.

Notes: %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.

[b] Unpublished data.

15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX17-121-001	Version #: 3.0	Version Date: 27 JUL 2018
Study Title: A Phase 1/2 Study of VX-121 in Healthy Subjects and in Subjects With Cystic Fibrosis		

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

[redacted]

15.2 Investigator Signature Page

Protocol #: VX17-121-001	Version #: 3.0	Version Date: 27 JUL 2018
Study Title: A Phase 1/2 Study of VX-121 in Healthy Subjects and in Subjects With Cystic Fibrosis		

I have read Protocol VX17-121-001, Version 3.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-121, tezacaftor, and ivacaftor and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date