1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 1/2 Study of VX-445 in Healthy Subjects and Subjects With Cystic Fibrosis

Vertex Study Number: VX16-445-001

[redacted]

EudraCT Number: 2017-000797-11

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2 PROTOCOL SYNOPSIS

Title A Phase 1/2 Study of VX-445 in Healthy Subjects and Subjects With Cystic Fibrosis

Brief Title A Study of VX-445 in Healthy Subjects and Subjects With Cystic Fibrosis

Clinical Phase and Clinical Study Type Phase 1; safety, tolerability, and pharmacokinetics (PK)
Phase 2; safety and efficacy

Objectives

Parts A and B

Primary Objectives

Part A: To evaluate the safety and tolerability of single ascending doses of VX-445 in healthy subjects

Part B: To evaluate the safety and tolerability of multiple ascending doses of VX-445 administered in healthy subjects

Secondary Objectives

Part A

- To evaluate the PK of VX-445 after administration of single ascending doses of VX-445 in healthy subjects
- To evaluate the effect of food on VX-445 PK in healthy subjects
- To evaluate the absolute bioavailability (BA) of VX-445 when administered orally relative to intravenous (IV) administration in healthy subjects

Part B: To evaluate the PK of VX-445 after multiple ascending doses of VX-445 in healthy subjects

Part C

Primary Objective**:** To evaluate the safety and tolerability of multiple doses of VX-445 in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA) for 14 days in healthy subjects

Secondary Objectives:

- To evaluate the PK of VX-445 after multiple ascending doses of VX-445 in TC with TEZ and IVA for 14 days in healthy subjects
- To evaluate the PK of TEZ and metabolites (M1-TEZ and M2-TEZ), and IVA and metabolites (M1-IVA and M6-IVA) after administration in TC with VX-445 for 14 days in healthy subjects

Parts D and E:

Primary Objectives:

- To evaluate the safety and tolerability of VX-445 in TC with TEZ and IVA in subjects with cystic fibrosis (CF)
- To evaluate the efficacy of VX-445 in TC with TEZ and IVA in subjects with CF

Secondary Objectives

- To evaluate the pharmacodynamic (PD) effect of VX-445 in TC with TEZ and IVA on CFTR function in subjects with CF
- To evaluate the PK of VX-445 when administered in TC with TEZ and IVA in subjects with CF

- To evaluate the PK of TEZ, IVA, and their respective metabolites (M1-TEZ and M1-IVA) when administered in TC with VX-445 in subjects with CF

Part F (Optional):

Primary Objectives:

- To evaluate the safety and tolerability of VX-445 in TC with TEZ and VX-561 (deuterated IVA, also known as CTP-656) in subjects with CF
- To evaluate the efficacy of VX-445 in TC with TEZ and VX-561 in subjects with CF

Secondary Objectives

- To evaluate the PD effect of VX-445 in TC with TEZ and VX-561 on CFTR function in subjects with CF
- To evaluate the PK of VX-445 when administered in TC with TEZ and VX-561 in subjects with CF
- To evaluate the PK of TEZ and metabolite (M1-TEZ), and VX-561 when administered in TC with VX-445 in subjects with CF

Endpoints

Primary Endpoints

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

Parts D, E, and F:

- Safety and tolerability assessments of AEs, clinical laboratory values, standard 12-lead ECGs, vital signs, pulse oximetry, and spirometry
- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline through Day 29

Secondary Endpoints

Parts A and B: PK parameter estimates of VX-445 derived from plasma concentration-time data

Part C:

- PK parameter estimates of VX-445 derived from plasma concentration-time data
- 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

Parts D and E:

- Absolute change in sweat chloride concentrations from baseline through Day 29
- Relative change in $ppFEV_1$ from baseline through Day 29
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline at Day 29
- PK parameters of VX-445, TEZ, M1-TEZ, IVA, and M1-IVA

Part F:

- Absolute change in sweat chloride concentrations from baseline through

Day 29

- Relative change in ppFEV$_1$ from baseline through Day 29
- Absolute change in CFQ-R respiratory domain score from baseline at Day 29
- PK parameters of VX-445, TEZ, M1-TEZ, and VX-561

[redacted]

Number of Subjects

Approximately 224 subjects: approximately 56 in Part A, approximately 48 in Part B, approximately 16 in Part C, approximately 56 in Part D (8 in D1 and 48 in D2), approximately 24 in Part E, and approximately 24 in Part F (if conducted)

Study Population

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

Parts D, E, and F: Female and male subjects aged 18 years or older with CF

Parts D and F**:** *F508del*/minimal function (F/MF) genotypes (an MF mutation is a minimal CFTR function mutation that is not expected to respond to TEZ, IVA, or TEZ/IVA)

Part E**:** *F508del*/*F508del* (F/F) genotype

Investigational Drug

Active substance: VX-445 (Parts A, B, C, D, E, and F)

Activity: CFTR Corrector (increased Cl^- secretion)

Strength and route of administration:

Tablet: 20-mg, 50-mg, and 100-mg tablets for oral administration

IV dose: 0.1 mg/mL for IV administration (Cohort A7 only)

Oral dose:

Parts A, B, and C: Doses starting at 20 mg. No dose will be predicted to result in an exposure that exceeds the nonclinical no-observed-adverse-effect level (NOAEL) exposure in the male rat (i.e., NOAEL exposure at the 50-mg/kg/day dose in male rats in the 28-day GLP toxicity study)

Parts D, E, and F: 50 mg qd (Part D only), 100 mg qd (Part D only), or 200 mg qd

Active substance: TEZ (tezacaftor; VX-661) and IVA (ivacaftor; VX-770) (Parts C, D, and E)

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

Strength and route of administration:

100-mg TEZ/150-mg IVA fixed-dose combination (FDC) (light yellow) film-coated tablet for oral administration

Dose administered: TEZ 100 mg/IVA 150 mg in the morning

Active substance: IVA (Parts C, D, and E)

Activity: CFTR potentiator (increased Cl^- secretion)

Strength and route of administration:

150-mg IVA (light blue) film-coated tablet for oral administration

Dose administered: 150 mg in the evening

Active substance: VX-561 (deuterated IVA, or CTP-656) (Part F)
Activity: CFTR potentiator
Strength and route of administration:
50-mg VX-561 tablet for oral administration
Dose administered: 150 mg qd

Active substance: TEZ (Part F)
Activity: CFTR corrector (increased Cl^- secretion)
Strength and route of administration:
50-mg TEZ (white) tablet for oral administration
Dose administered: 100 mg qd

Study Duration

Excluding the Screening Period, the study duration for each subject is as follows:

Part A, Cohorts A1 through A6: 9 to 12 days

Part A, Cohort A7: up to 21 to 24 days

Part B: 18 to 21 days

Part C: 22 to 25 days

Parts D1 and D2: approximately 9 weeks (5 weeks for the Treatment Period [consisting of Dosing Periods 1 and 2] and 4 weeks for the Safety Follow-up Period)

Part E: approximately 16 weeks (4 weeks for the Run-in Period, 4 weeks for the Treatment Period [Period 1], 4 weeks for the Washout Period, and 4 weeks for the Safety Follow-up Period)

Part F: approximately 8 weeks (4 weeks for the Treatment Period [Period 1] and 4 weeks for the Safety Follow-up Period)

Study Design

This is a first-in-human study of VX-445. The study includes 6 parts. Parts A, B, and C will be conducted in healthy subjects. Parts D, E, and F will be conducted in subjects with CF. Part F is an optional part of the study that may be conducted at the sponsor's discretion.

Parts A, B, and C (Healthy Subjects)

Parts A, B, and C are randomized, double-blind, placebo-controlled, single- and multiple-dose parts in healthy subjects of this first-in-human study of VX-445. Part A also includes an evaluation of the effect of food on VX-445 PK and an evaluation of absolute BA. Part C doses VX-445 in TC with TEZ/IVA.

Approximately 8 subjects in each cohort of Part A (except Cohort A7) and Part B will be randomized 3:1 to receive VX-445 or placebo. Cohort A7 will enroll approximately 8 subjects who will receive open-label VX-445 to evaluate the food effect on the tablet and the absolute BA.

The decision to initiate successive cohorts and dose selection will be based on safety, tolerability, and available PK data from preceding cohort(s). In Parts A and B, 6 dose escalation cohorts are planned, although fewer than 6 or up to 2 additional cohorts each may be enrolled in each part, based on data from previous cohorts. In Part C, 2 cohorts are planned, while fewer or up to 2 additional cohorts each may be enrolled based on data from previous cohorts.

Part A includes Cohorts A1 through A6, which are single-dose escalation cohorts, and Cohort A7, a single cohort evaluating the food effect and absolute BA.

Cohorts A1 through A6: VX-445 or placebo will be administered in the morning of Day 1. Dosing will be staggered in Cohort A1 so that 2 subjects are dosed (1 with VX-445 and 1 with placebo) at least 24 hours before the remaining 6 subjects. Dosing may be staggered in subsequent cohorts if deemed necessary based on review of emerging safety data. The planned doses for Cohorts A1 through A6 are 20 mg, 60 mg, 120 mg, 240 mg, 480 mg, and 800 mg. Doses may be modified upward or downward based on emerging data.

Cohort A7 has an open-label, single sequence design in which subjects will receive a single dose of VX-445 on up to 3 dosing occasions with at least 6-day washouts between dosing occasions. VX-445 doses include 2 single oral doses of tablet (dose to be determined [TBD], pending PK data from previous Part A cohorts, but will not exceed the highest dose that was safe and well tolerated) and a single IV dose (the planned dose is 20 mg, which may be adjusted pending data from previous Part A cohorts, but will not be predicted to exceed the highest exposure that was safe and well tolerated). If the IV formulation or the data supporting the use of the IV formulation are not available, then the third dosing period, in which subjects receive the IV dose, will not be conducted.

Part B may be initiated while Part A is ongoing after review of safety, tolerability, and PK data. The total daily dose in the starting 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 that is safe and well tolerated.

Part C may be initiated while Parts A and B are ongoing after review of safety, tolerability, and PK data. The VX-445 starting dose (Cohort C1) will be at least 1 dose level below the highest Part B dose for which safety and tolerability results are available and supportive. The dosage of TEZ/IVA in the TC will be TEZ 100 mg once per day (qd)/IVA 150 mg every 12 hours (q12h).

Dosing will be staggered in Cohort C1, with 2 subjects dosed (1 with VX-445 in TC with TEZ/IVA and 1 with 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.

Parts D, E, and F (Subjects With CF)

Part D, which is comprised of Parts D1 and D2, is randomized, double-blind, placebo-controlled, and evaluates VX-445 in TC with TEZ/IVA in subjects with CF (F/MF genotypes).

Part E is randomized, double-blind, TEZ/IVA-controlled, and evaluates VX-445 in TC with TEZ/IVA in subjects with CF (F/F genotype).

Part F, an optional part of the study which will be conducted at the sponsor's discretion, is randomized, double-blind, placebo-controlled, and evaluates VX-445 in TC with TEZ and VX-561 in subjects with CF (F/MF genotypes).

Part D may be initiated while Parts A, B, and C are ongoing after review of safety, tolerability, and PK data. After all Part D1 subjects complete the Day 15 Visit, a blinded review of all available safety and PK data will be conducted by the Vertex study team and lead investigator(s). Dosing in Parts D2, E, and F will start after this review, if supported by safety and PK data.

VX-445 will be dosed qd.

Part D1 has 1 VX-445 dose level (mid: 100 mg qd). Part D2 has 3 VX-445 dose levels (low: 50 mg qd; mid: 100 mg qd; high: 200 mg qd). The TC-high dose of VX-445 in Part D2 does not exceed the highest dose that was safe and well tolerated in healthy subjects dosed with TC in Part C. Parts E and F will use the highest dose used in Part D2 (200 mg qd).

Randomization will be stratified by $ppFEV_1$ in Parts D2, E, and F. Randomization will not be stratified in Part D1 because of the small number of subjects in that Part

(N ~ 8).

Schematics of the Part D, E, and F treatment periods are shown below. Each part also includes a 4-week screening period and a 4-week safety follow-up period.

Part D1: Subjects with F/MF genotypes

	Period 1 (4 weeks)		Period 2 (1 week)	
Screening Period (4 weeks)	TC-mid (VX-445/TEZ/IVA)	N = 6	TEZ/IVA	Safety Follow-up Period (4 weeks)
	Triple Placebo	N = 2	Dual Placebo	

Dosing Period 2 is included in Parts D1 and D2 to enable a more thorough evaluation of VX-445 exposure-response relationships by conducting PK and PD assessments during the VX-445 washout.

Part D2: Subjects with F/MF genotypes

	Period 1 (4 weeks)		Period 2 (1 week)	
Screening Period (4 weeks)	TC-high (VX-445/TEZ/IVA)	N = 18	TEZ/IVA	Safety Follow-up Period (4 weeks)
	TC-mid (VX-445/TEZ/IVA)	N = 12		
	TC-low (VX-445/TEZ/IVA)	N = 9		
	Triple Placebo	N = 9	Dual Placebo	

In Parts D1 and D2, placebo is the control because efficacy has not been established for a corrector, potentiator, or any corrector/potentiator combination in subjects with F/MF genotypes.

Part E: Subjects with F/F genotype

	Run-in Period (4 weeks)	Period 1 (4 weeks)		Washout Period (4 weeks)	
Screening Period (4 weeks)	TEZ/IVA	TC-high (VX-445/TEZ/IVA)	N = 18	TEZ/IVA	Safety Follow-up Period (4 weeks)
		Placebo + TEZ/IVA	N = 6		

The Washout Period is designed to evaluate the effect on PD and efficacy endpoints as subjects step down from TC to TEZ/IVA.

TEZ/IVA is the control because results from a previous study (Study VX11-661-101)

demonstrated the potential for benefit for TEZ/IVA treatment in subjects with the F/F genotype.

Part F (optional): Subjects with F/MF genotypes

<table>
<tr><td></td><td colspan="2">Period 1
(4 weeks)</td><td></td></tr>
<tr><td rowspan="2">Screening Period
(4 weeks)</td><td>TC2-high
(VX-445/TEZ/VX-561)</td><td>N = 18</td><td rowspan="2">Safety Follow-up Period
(4 weeks)</td></tr>
<tr><td>Triple Placebo</td><td>N = 6</td></tr>
</table>

Placebo is the control because efficacy has not been established for a corrector, potentiator, or any corrector/potentiator combination in subjects with F/MF genotypes.

Assessments

Safety

AEs, clinical laboratory assessments, clinical evaluation of vital signs, ECGs, physical examinations, spirometry (Parts B, C, D, E, and F), and pulse oximetry (Parts D, E, and F).

Pharmacokinetics

Blood samples will be collected for the evaluation of plasma concentrations of VX-445 (all subjects) and for the evaluation of plasma concentrations of TEZ and metabolites (Parts C, D, E, and F), IVA and metabolites (Parts C, D, and E), and VX-561 (Part F).

Efficacy

Spirometry and CFQ-R (Parts D, E, and F)

Pharmacodynamics

Sweat chloride (Parts [redacted] D, E, and F)

[redacted]

Statistical Analyses

Parts A, B, and C:

No formal sample size calculations have been performed. Eight subjects per dose cohort randomized 3:1 (active to placebo) is a typical sample size for first-in-human studies in healthy subjects and are considered sufficient to achieve the objectives of the study. Descriptive analyses will be performed on safety data and PK data. No statistical hypothesis testing will be done. [redacted]

Parts D, E, and F:

The primary efficacy endpoint is the absolute change from baseline through Day 29 for $ppFEV_1$. All $ppFEV_1$ hypothesis tests will be performed within the mixed-effects model for repeated measures (MMRM) framework at a 5% alpha level, with appropriate adjustment for baseline covariates. The null within-group hypothesis of no difference in the mean absolute change from baseline through Day 29 for $ppFEV_1$, in all treatment groups, by part, will be tested using MMRM. The adjusted means and

2-sided 95% confidence intervals of the average treatment effects through Day 29, for all within-group and between-group comparisons will be estimated within MMRM.

The safety analysis will be descriptive only.

Interim Analyses

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

Parts D, E, and F: IAs for each part (D1, D2, E, and F) may be performed after at least 50% of subjects in the part have completed the Day 15 Visit.

IDMC Reviews

Parts D, E, and F: An independent monitoring committee (IDMC) will conduct safety reviews of study data. The IDMC Chair will review available safety and PK data from Parts A, B, and C of the study prior to commencement of dosing in Part D1 to determine if it is appropriate to proceed with the study.

3 SCHEDULE OF ASSESSMENTS

Parts A, B, and C: Schedules of Assessments are shown in Table 3-1 (Screening, Parts A though C), Table 3-2 (Part A, Cohorts A1 through A6), Table 3-3 (Part A, Cohort A7), Table 3-4 (Part B), and Table 3-5 (Part C).

Parts D, E, and F: Schedules of assessments are provided in Table 3-6 (Screening through Follow-up, Part D), Table 3-7 (Screening through Follow-up, Part E), and Table 3-8 (Screening through Follow-up, Part F). All visits will be scheduled relative to the Day 1 Visit (first dose of VX-445 or VX-445 matched placebo).

Assessments may be performed in any order when more than 1 assessment is required at a particular time point except for informed consent, which must be completed before any assessments are done at the Screening Visit, and the CFQ-R assessment in Parts D, E, and F, which must be completed before any other assessment at the clinic visit when it is required. All assessments will be performed before dosing, unless noted otherwise.

Table 3-1 Study VX16-445-001: 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 PE	X
Standard 12-lead ECG[c]	X
Serum FSH (suspected postmenopausal female subjects only)	X
Serum β-hCG (all female subjects)	X
Serology (HBsAg, HCV, HIV-1 and HIV-2 Abs, and p24 antigen)	X
G6PD activity test[d]	X
Serum chemistry[e]	X
Hematology[e]	X
Coagulation[e]	X
Drug test (urine or blood), including cotinine	X
Alcohol test (urine, blood, or breath)	X
Urinalysis	X
Spirometry (Parts B and C only)	X
[redacted]	
AEs	Continuous from signing of ICF through Safety Follow-up Visit

AE: adverse event; β-hCG: beta-human chorionic gonadotropin; BMI: body mass index; ECG: electrocardiogram; FSH: follicle-stimulating hormone; G6PD: glucose-6-phosphate dehydrogenase; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV-1/HIV-2 Abs: antibodies against human immunodeficiency viruses 1 and 2; ICF: informed consent form; PE: physical examination

[a] All medications taken within 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 subject has been seated for at least 5 minutes.

[c] A standard 12-lead ECG will be performed after the subject has been seated or supine for at least 5 minutes (Section 11.7.5.1).

[d] A single blood sample will be collected from all subjects for the G6PD activity test.

[e] Following at least a 4-hour fast, blood samples will be collected for clinical laboratory assessments.

[redacted]

Table 3-2 Study VX16-445-001: Part A, Cohorts A1 Through A6, Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Study Day						Safety Follow-up Visit (7 to 10 days After Last Dose of Study Drug)
	-1	1	2	3	4	5	
Inpatient days	X	X	X	X	X	X[b]	
Outpatient visit							X
Randomization		X					
Weight[c]	X						
Continuous ECGs[d]		X	X				
Standard 12-lead ECG[e]	X	X					X
Vital signs[f]	X	X	X	X	X	X	X
Full PE	X						X
Serum chemistry	X		X				X
Hematology	X		X				X
Blood for PK analysis[g]		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					
AEs	Continuous from signing of ICF through Safety Follow-up Visit						
Medications review[i]	Continuous from signing of ICF through Safety Follow-up Visit						

AE: adverse event; CRU: clinical research unit; ECG: electrocardiogram; ICF: informed consent form; PE: physical examination; PK: pharmacokinetic

[a] On dosing days, assessments will be performed before dosing, unless noted otherwise.
[b] Subjects will be discharged from the CRU on Day 5 after completion of the study visit assessments.
[c] Weight will be measured with shoes off.
[d] Continuous ECGs will be extracted in up to 10 replicates on Day 1 before dosing (at -60, -50, and -40 minutes) and at 1, 2, 3, 4, 6, 8, 12 and 24 hours (Day 2) after dosing. Subjects should be supine or semi-recumbent for at least 15 minutes before these time points.
[e] Standard 12-lead ECGs will be performed after the subject has been seated or supine for at least 5 minutes. 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 seated for at least 5 minutes.
[g] Blood samples for PK assessments will be collected on Day 1 before dosing (0 hours) and at 0.5, 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.
[h] Study drug will be administered in the fed state. Details are provided in Section 9.6.1.1.
[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 VX16-445-001: Part A, Cohort A7, Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Study Day																		Safety Follow-up Visit (7 to 10 Days After Last Dose of Study Drug)
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14[b]	15[b]	16[b]	17[b]	
Inpatient days	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]	X	X	X	X[d]	
Outpatient visit																			X
Weight[e]	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	X	X	X
Full PE	X																		X
Serum chemistry	X		X						X						X				X
Hematology	X		X						X						X				X

[a] On dosing days, assessments will be performed before dosing, unless noted otherwise.
[b] If data to support use of the IV dose is not available, Dosing Period 3 will not be conducted and assessments on Days 14 to 17 will not be performed.
[c] Subjects will be discharged from the CRU on Day 13 after completion of the study visit assessments if Dosing Period 3 is not conducted.
[d] Subjects will be discharged from the CRU on Day 17 after completion of the study visit assessments.
[e] Weight will be measured with shoes off.
[f] Standard 12-lead ECGs will be performed after the subject has been seated or supine for at least 5 minutes. On Days 1, 7 and 13, ECGs will be collected before dosing and approximately 1, 3, 5, and 6 hours (± 15 min) after dosing.
[g] Vital signs will be performed after the subject has been seated for at least 5 minutes.

Table 3-3 Study VX16-445-001: Part A, Cohort A7, Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Study Day																		Safety Follow-up Visit (7 to 10 Days After Last Dose of Study Drug)
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14[b]	15[b]	16[b]	17[b]	
Blood for PK analysis[h]		X	X	X	X	X	X	X	X	X	X	X	X	X[i]	X	X	X	X	
Drug test (urine or blood), including cotinine	X																		
Alcohol test (urine, blood, or breath)	X																		
Urinalysis																			X
Study drug adminstration[j]		X						X						X[k]					
AEs	Continuous from signing of ICF through Safety Follow-up Visit																		
Medications review[l]	Continuous from signing of ICF through Safety Follow-up Visit																		

AE: adverse event; CRU: clinical research unit; ECG: electrocardiogram; ICF: informed consent form; IV: intravenous; PE: physical examination; PK: pharmacokinetic

[h] Blood samples for PK assessments will be collected on Days 1 and 7 before dosing (0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 (Days 2, 8), 36 (Days 2, 8), 48 (Days 3, 9), 72 (Days 4, 10), 96 (Days 5 and 11), and 120 (Days 6 and 12) hours postdose. Blood samples for PK assessments will be collected on Day 13 before dosing (0 hours, before the start of the IV infusion) and at 0.5 (after the end of the IV infusion), 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 (Day 14), 36 (Day 14), 48 (Day 15), 72 (Day 16), and 96 hours (Day 17) after the start of the IV infusion. Acceptable PK sampling windows are provided in Table 11-1.

[i] If Dosing Period 3 is not conducted, a blood sample for PK assessment will be collected on Day 13 (144 hours after dosing on Day 7).

[j] Study drug will be administered as a tablet in the fasted state on Day 1 and in the fed state on Day 7. On Day 13, study drug will be administered in the fed state as a single IV dose infused over 30 minutes (See Section 9.6.1.1 for details). If the IV dose is not administered, subjects will be discharged on Day 13 after completion of the study visit assessments.

[k] If data to support use of the IV dose is not available, Dosing Period 3 will not be conducted and subjects will not receive the IV dose.

[l] 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 VX16-445-001: Part B, Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Study Day															Safety Follow-up Visit (7 to 10 Days After Last Dose of Study Drug)
	-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[b]	
Outpatient visits																X
Randomization		X														
Weight[c]	X										X					
Standard 12-lead ECG[d]	X	X				X										X
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full PE	X															X
Serum chemistry	X		X		X		X				X					X
Hematology	X		X		X		X				X					X
4β-hydroxycholesterol		X									X					
Blood for PK analysis[f]		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
Spirometry[g]	X	X								X						

[a] On dosing days, assessments will be performed before dosing, unless noted otherwise. If Part B study drug is administered every q12h, assessments on dosing days will be performed relative to the morning dose only.

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

[c] Weight will be measured with shoes off.

[d] Standard 12-lead ECGs will be performed after the subject has been seated or supine for at least 5 minutes. On Days 1 and 5, ECGs will be collected before dosing and at approximately 1, 3, 5, and 6 hours (± 15 min) after dosing.

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

[f] Blood samples for PK assessments of VX-445 will be collected on Day 1 before dosing (0 hours), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours after dosing. If dosing is q12h, the 12-hour sample will be collected before the next administered dose. On Days 2, 3, and 4, a blood sample will be collected in the morning before dosing. On Day 10, blood samples for PK assessments will be collected before dosing (0 hours), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 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.

Table 3-4 Study VX16-445-001: Part B, Treatment Period and Safety Follow-up Visit

Event/Assessment[a]	Study Day															Safety Follow-up Visit (7 to 10 Days After Last Dose of Study Drug)
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Study drug administration[h]		X	X	X	X	X	X	X	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															

CRU: clinical research unit; ECG: electrocardiogram; ICF: informed consent form; PK: pharmacokinetic; q12h: every 12 hours

[g] On Day 1, spirometry will be performed approximately 6 hours (± 1 hour) after dosing. On Day 9, spirometry will be performed before dosing and at approximately 6 hours (± 1 hour) after dosing. The assessment on Day -1 will be performed at approximately the same time of day (± 2 hours) as the nominal time of the 6-hour postdose assessments on Days 1 and 9.

[h] Study drug will be administered in the fed state (see Section 9.6.1.2) If dosing is q12h, the last dose of study drug will be administered on the morning of Day 10.

[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 VX16-445-001: Part C, Treatment Period and Safety Follow-up Visit

	Study Day																			Safety Follow-up (7 to 10 Days After Last Dose of Study Drug)
Event/Assessment[a]	**-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[b]	
Outpatient visits																				X
Randomization		X																		
Weight	X														X					
Standard 12-lead ECG[c]	X	X						X												X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full PE	X																			X
Serum chemistry	X		X			X				X					X					X
Hematology	X		X			X				X					X					X
[redacted]																				
Blood for VX-445 PK analysis[e]		X	X	X	X	X		X	X						X	X	X	X	X	
Blood for TEZ/IVA PK analysis[f]		X	X	X	X	X		X	X						X	X	X	X	X	

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

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

[c] Standard 12-lead ECGs will be performed after the subject has been seated or supine for at least 5 minutes. On Days 1 and 7, ECGs will be collected before dosing and approximately 1, 3, 5, and 6 hours (± 15 min) after dosing.

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

[e] Blood samples for PK assessments of VX-445 will be collected on Day 1 and Day 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 if dosing is q12h. On Days 2, 3, 4, 5, and 8, 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.

[f] Blood samples for PK assessments of TEZ and metabolites, and IVA and metabolites will be collected on Day 1 and Day 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 IVA dose. On Days 2, 3, 4, 5, and 8, 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.

Table 3-5 Study VX16-445-001: Part C, Treatment Period and Safety Follow-up Visit

	Study Day																			Safety Follow-up (7 to 10 Days After Last Dose of Study Drug)
Event/Assessment[a]	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	
Drug test (urine or blood), including cotinine	X																			
Alcohol test (urine, blood, or breath)	X																			
Urinalysis	X							X							X					X
Spirometry[g]	X	X								X										
[redacted]																				
Study drug administration[i]: VX-445 or placebo		X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Study drug administration[i]: TEZ/IVA or placebo		X	X	X	X	X	X	X	X	X	X	X	X	X	X					
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																			

CRU: clinical research unit; [redacted]; ECG: electrocardiogram; ICF: informed consent form; IVA: ivacaftor; PE: physical examination; PK: pharmacokinetic; q12h: every 12 hours; TEZ: tezacaftor

[g] On Day 1, spirometry will be performed approximately 6 hours (± 1 hour) after dosing. On Day 9, spirometry will be performed before dosing and at approximately 6 hours (± 1 hour) after dosing. The assessment on Day -1 will be performed at approximately the same time of day (± 2 hours) as the nominal time of the 6-hour postdose assessments on Days 1 and 9

[redacted]

[i] Study drug will be administered in the fed state (see Section 9.6.1.3). The last dose of study drug will be administered on the morning of Day 14.

[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 VX16-445-001: Schedule of Assessments for Parts D1 and D2

Event/Assessment[a]	Screening	Treatment Period					ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
		Period 1				Period 2		
	Days -28 to -1	Day 1[c]	Day 8 for Part D1 only (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)	Period 2 Visit[d]		
Informed consent	X							
Randomization[e]		X						
Demographics	X							
Medical history	X							
CFQ-R[f,g]		X		X	X			
Weight[h]	X	X	X	X	X		X	X
Height[h]	X							
Vital signs[i]	X	X	X	X	X	X	X	X
Pulse oximetry[i]	X	X	X	X	X	X	X	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., if subject prematurely discontinued study drug treatment).

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

[c] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 9.1.2.4.

[d] The Period 2 Visit will occur 6 to 10 days after the actual date of the Day 29 Visit.

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

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

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

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

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

Table 3-6 Study VX16-445-001: Schedule of Assessments for Parts D1 and D2

Event/Assessment[a]	Screening	Treatment Period					ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
		Period 1				Period 2		
	Days -28 to -1	Day 1[c]	Day 8 for Part D1 only (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)	Period 2 Visit[d]		
Physical examination[j]	Complete	Abbrev.		Abbrev.	Abbrev.		Abbrev.	Complete
Standard 12-lead ECG[k]	X	X	X	X	X		X	X
Sweat chloride[g,l]	X	X	X	X	X	X[m]	X	X
Spirometry[n]	X[o]	X	X	X	X	X[m]	X	X
Urinalysis[g]	X	X	X	X	X		X	X
Pregnancy test (all females of childbearing potential)	Serum	Urine			Urine		Serum	Serum
CFTR genotype[p]	X							
FSH[q]	X							
G6PD activity test[r]	X							

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

[k] All standard 12-lead ECGs will be performed after the subject has been seated or supine for at least 5 minutes. On the Day 1 and 15 Visits, ECGs will be collected before dosing and 5 hours (± 1 hour) after dosing. At all other visits, ECGs will be collected before dosing (as applicable). ECGs collected on the Day 1 Visit before dosing will be performed in triplicate.

[l] Sweat chloride will be measured in all subjects as described in Section 11.4.1. If the value cannot be determined from the screening test, a sweat chloride value documented in a laboratory report may be used to establish eligibility. See Section 8.2.1 (Inclusion Criterion #5) for additional detail.

[m] At the Period 2 Visit, sweat chloride and $ppFEV_1$ assessments should be done within 2 hours before TEZ/IVA dosing in the morning.

[n] 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 visit. On the Day 1 and Day 15 Visits, spirometry will also be performed 5 hours (± 1 hour) after study drug administration (pre-bronchodilator).

[o] For Part D2 subjects only: The $ppFEV_1$ assessment that will be used for stratification of randomization can be done any time during the Screening Period. See Section 9.1.2.2.

[p] *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. However, as outlined in Section 9.9, 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.

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

Table 3-6 Study VX16-445-001: Schedule of Assessments for Parts D1 and D2

Event/Assessment[a]	Screening	Treatment Period					ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
		Period 1				Period 2		
	Days -28 to -1	Day 1[c]	Day 8 for Part D1 only (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)	Period 2 Visit[d]		
[redacted]								
Serum chemistry and hematology[g]	X	X	X	X	X		X	X
Coagulation[g]	X	X		X	X		X	X
PK sampling[t]		X		X	X	X	X	
TEZ/IVA or placebo dosing[u]		Day 1 through Period 2 Visit						
VX-445 or placebo dosing[v]		Day 1 through Day 29						
AEs, medications[w], treatments, and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit							

AE: adverse event; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; *CFTR*: CF transmembrane conductance regulator gene; [redacted]; ECG: electrocardiogram; ETT: early termination of treatment; FSH: follicle-stimulating hormone; G6PD: glucose-6-phosphate dehydrogenase; ICF: informed consent form; IVA: ivacaftor; PE: physical examination; PK: pharmacokinetic; $ppFEV_1$: percent predicted forced expiratory volume in 1 second ; TEZ: tezacaftor

r Blood samples will be collected for the G6PD activity test.

[redacted]

Blood samples will be collected for PK analysis of VX-445, TEZ, M1-TEZ, IVA, and M1-IVA. On the Day 1 Visit, samples will be collected before dosing (0 hours) and at 1, 2, 4, and 6 hours after dosing (relative to the morning dose). On the Day 15 Visit, samples will be collected before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing. On the Day 29 Visit, a predose sample will be collected before the morning dose of study drug. At the Period 2 Visit, a single predose sample will be collected before TEZ/IVA dosing in the morning. At the ETT Visit, a single blood sample for PK analysis will be collected.

u On days of scheduled visits, the in-clinic dose of study drugs will be given in the morning, at least 6 hours apart from any other scheduled dose and after all predose assessments are complete. The last dose of TEZ/IVA or placebo in Period 2 will be the morning dose of the Period 2 Visit. See Section 9.6.2 for additional information about study drug administration.

v On days of scheduled visits, the in-clinic dose of study drugs will be given in the morning, at least 6 hours apart from any other scheduled dose and after all predose assessments are complete. The last dose of VX-445 or placebo in Period 1 will be the morning dose on the Day 29 Visit. See Section 9.6.2 for additional information about study drug administration.

w Refer to Section 9.5.2 for details.

Table 3-7 Study VX16-445-001: Schedule of Assessments for Part E

Event/Assessment[a]	Screening	Run-in Period		Treatment Period: Period 1			Washout Period		ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose[c]
	Days -56 to -29	Day -28 (± 1 day)	Day -14[d] (+ 13 days)	Day 1[e]	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	Day 57 (± 3 days)		
Informed consent	X									
Randomization[f]				X						
Demographics	X									
Medical history	X									
CFQ-R[g,h]				X	X	X		X		
Weight[i]	X	X		X	X	X	X	X	X	X
Height[i]	X									
Vital signs[j]	X	X		X	X	X	X	X	X	X
Pulse oximetry[j]	X	X		X	X	X	X	X	X	X
Physical examination[k]	Complete	Abbreviated		Abbreviated	Abbreviated	Abbreviated		Abbreviated	Abbreviated	Complete

[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., if subject prematurely discontinued study drug treatment).

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

[c] Part E subjects who meet criteria specified in Section 9.1.2.6 will not have a Safety Follow-up Visit.

[d] The Day -14 Visit is only required for subjects who are not transitioning directly from at least 14 days of uninterrupted TEZ/IVA treatment. Assessments at this visit may be performed postdose.

[e] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 9.1.2.4.

[f] Randomization may occur on the previous day (Day -1 Visit) after all inclusion and exclusion criteria and criteria for entry into the Treatment Period have been confirmed. See Section 9.1.2.2.2.

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

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

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

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

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

Table 3-7 Study VX16-445-001: Schedule of Assessments for Part E

Event/Assessment[a]	Screening	Run-in Period		Treatment Period: Period 1			Washout Period		ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose[c]
	Days -56 to -29	Day -28 (± 1 day)	Day -14[d] (+ 13 days)	Day 1[e]	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	Day 57 (± 3 days)		
Standard 12-lead ECG[l]	X	X		X	X	X	X	X	X	X
Sweat chloride[h,m]	X		X	X	X	X	X	X	X	
Spirometry[n]	X[o]		X[o]	X	X	X	X	X	X	X
Urinalysis[h]	X	X		X	X	X	X	X	X	X
Pregnancy test (all females of childbearing potential)	Serum	Urine		Urine		Urine		Urine	Serum	Serum
CFTR genotype[p]	X									
FSH[q]	X									
G6PD activity test[r]	X									

[l] All standard 12-lead ECGs will be performed after the subject has been seated or supine for at least 5 minutes. On the Days 1 and 15 Visits, ECGs will be collected before dosing and 5 hours (± 1 hour) after dosing. At all other visits, ECGs will be collected before dosing (as applicable). ECGs collected on the Day 1 Visit before dosing will be performed in triplicate.

[m] Sweat chloride will be measured in all subjects as described in Section 11.4.1. If the value cannot be determined from the screening test (e.g. due to laboratory error), a sweat chloride value documented in a previous laboratory report may be used to establish eligibility. See Section 8.2.1 (Inclusion Criterion #5) for additional detail.

[n] 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 (except at the Day -14 Visit when spirometry may be performed postdose), and should be performed at approximately the same time at every visit. On the Day 1 and Day 15 Visits, spirometry will also be performed 5 hours (± 1 hour) after study drug administration (pre-bronchodilator).

[o] The $ppFEV_1$ assessment for stratification of randomization will be done at the Screening Visit for subjects transitioning directly from at least 14 days of uninterrupted TEZ/IVA treatment. For all other subjects, this assessment will be done at the Day -14 Visit. See Section 9.1.2.2

[p] *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before the Day -28 Visit, a previous *CFTR* genotype laboratory report may be used to establish eligibility. However, as outlined in Section 9.9, 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.

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

[r] Blood samples will be collected for the G6PD activity test.

Table 3-7 Study VX16-445-001: Schedule of Assessments for Part E

Event/Assessment[a]	Screening	Run-in Period		Treatment Period: Period 1			Washout Period		ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose[c]
	Days -56 to -29	Day -28 (± 1 day)	Day -14[d] (+ 13 days)	Day 1[e]	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	Day 57 (± 3 days)		
[redacted]										
Serum chemistry and hematology[h]	X	X		X	X	X	X	X	X	X
Coagulation[h]	X	X		X	X	X			X	X
PK sampling[t]				X	X	X	X		X	
TEZ/IVA dosing[u]		Day -28 through Day 57								
VX-445 or placebo dosing[v]				Day 1 through Day 29						
AEs, medications[w], treatments and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit									

AE: adverse event; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; *CFTR*: CF transmembrane conductance regulator gene; [redacted]; ECG: electrocardiogram; ETT: early termination of treatment; FSH: follicle-stimulating hormone; G6PD: glucose-6-phosphate dehydrogenase; ICF: informed consent form; IVA: ivacaftor; PE: physical examination; PK: pharmacokinetic; $ppFEV_1$: percent predicted forced expiratory volume in 1 second ; TEZ: tezacaftor

[redacted]

t Blood samples will be collected for PK analysis of VX-445, TEZ, M1-TEZ, IVA, and M1-IVA. On the Day 1 Visit, samples will be collected before dosing (0 hours) and at 1, 2, 4, and 6 hours after dosing (relative to morning dose). On the Day 15 Visit, samples will be collected before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing. On the Day 29 Visit, a predose sample will be collected before the morning dose of study drug. At the Day 43 Visit, a single blood sample for PK analysis will be collected before the morning dose of TEZ/IVA. At the ETT Visit, a single blood sample for PK analysis will be collected.

u The last dose of TEZ/IVA will be the morning dose on the Day 57 Visit. See Section 9.6.2 for additional information about study drug administration.

v The last dose of VX-445 or placebo will be the morning dose on the Day 29 Visit. See Section 9.6.2 for additional information about study drug administration.

w Refer to Section 9.5.2 for details.

Table 3-8 Study VX16-445-001: Schedule of Assessments for Part F (if Conducted)

Event/Assessment[a]	Screening	Treatment Period: Period 1				ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
	Days -28 to -1	Day 1[c]	Day 8[d] (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)		
Informed consent	X						
Randomization[e]		X					
Demographics	X						
Medical history	X						
CFQ-R[f,g]		X		X	X		
Weight[h]	X	X		X	X	X	X
Height[h]	X						
Vital signs[i]	X	X		X	X	X	X
Pulse oximetry[i]	X	X		X	X	X	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., if subject prematurely discontinued study drug treatment).

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

[c] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 9.1.2.4.

[d] The laboratory assessment may be collected at the clinic, at a local laboratory, or during a visit by a qualified individual (e.g., home nurse). If the laboratory assessment is not collected at the clinic, a telephone call to the clinic is required for the collection of AEs. When the laboratory assessment is done in the clinic, the AE collection will also occur in the clinic.

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

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

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

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

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

Table 3-8 Study VX16-445-001: Schedule of Assessments for Part F (if Conducted)

Event/Assessment[a]	Screening	Treatment Period: Period 1				ETT Visit[b]	Safety Follow-up
	Days -28 to -1	Day 1[c]	Day 8[d] (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)		28 (± 7) Days After Last Dose
Physical examination[j]	Complete	Abbrev.		Abbrev.	Abbrev.	Abbrev.	Complete
Standard 12-lead ECG[k]	X	X		X	X	X	X
Sweat chloride[g,l,]	X	X		X	X	X	X
Spirometry[m]	X[n]	X		X	X	X	X
Urinalysis[g]	X	X		X	X	X	X
Pregnancy test (all females of childbearing potential)	Serum	Urine			Urine	Serum	Serum
CFTR genotype[o]	X						
FSH[p]	X						
G6PD activity test[q]	X						
[redacted]							
Serum chemistry and hematology[g]	X	X	X	X	X	X	X

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

[k] All standard 12-lead ECGs will be performed after the subject has been seated or supine for at least 5 minutes. On the Day 1 and 15 Visits, ECGs will be collected before dosing and 5 hours (± 1 hour) after dosing. At all other visits, ECGs will be collected before dosing (as applicable). ECGs collected on the Day 1 Visit before dosing will be performed in triplicate.

[l] Sweat chloride will be measured in all subjects as described in Section 11.4.1. If the value cannot be determined from the screening test, a sweat chloride value documented in a previous laboratory report may be used to establish eligibility. See Section 8.2.1 (Inclusion Criterion #5) for additional detail.

[m] 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 visit. On the Day 1 and 15 Visits, spirometry will also be performed pre-bronchodilator, 5 hours (± 1 hour) after study drug administration.

[n] The ppFEV$_1$ assessment that will be used for stratification of randomization can be done any time during the Screening Period. See Section 9.1.2.2.

[o] *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. However, as outlined in Section 9.9, 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.

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

[q] Blood samples will be collected for the G6PD activity test.

[redacted]

Table 3-8 Study VX16-445-001: Schedule of Assessments for Part F (if Conducted)

Event/Assessment[a]	Screening	Treatment Period: Period 1				ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
	Days -28 to -1	Day 1[c]	Day 8[d] (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)		
Coagulation[g]	X	X		X	X	X	X
PK sampling[s]		X		X	X	X	
VX-445/TEZ/VX-561 or placebo dosing[t]		Day 1 through Day 29					
AEs, medications[u], treatments, and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit						

AE: adverse event; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; *CFTR*: CF transmembrane conductance regulator gene; [redacted] ECG: electrocardiogram; ETT: early termination of treatment; FSH: follicle-stimulating hormone; G6PD: glucose-6-phosphate dehydrogenase; ICF: informed consent form; IVA: ivacaftor; PE: physical examination; PK: pharmacokinetic; $ppFEV_1$: percent predicted forced expiratory volume in 1 second ; TEZ: tezacaftor

[s] Blood samples will be collected for PK analysis of VX-445, TEZ, M1-TEZ, and VX-561. On the Day 1 Visit, samples will be collected before dosing (0 hours) and at 1, 2, 4, and 6 hours after dosing (relative to the morning dose). On the Day 15 Visit, samples will be collected before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing. On the Day 29 Visit, a predose sample will be collected before the morning dose of study drug. At the ETT visit, a single blood sample for PK analysis will be collected.

[t] On days of scheduled visits, the in-clinic dose of study drugs will be given in the morning, at least 6 hours apart from any other scheduled dose and after all predose assessments are complete. The last dose of VX-445/TEZ/VX-561 or placebo will be the morning dose on the Day 29 Visit. See Section 9.6.2 for additional information about study drug administration.

[u] Refer to Section 9.5.2 for details.

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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_{0-24h}	AUC from the time of dosing to 24 hours
$AUC_{0-\infty}$	AUC from the time of dosing extrapolated to infinity
β-hCG	beta-human chorionic gonadotropin
BA	bioavailability
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator gene
CFTR	CF transmembrane conductance regulator protein
C_{max}	maximum observed concentration
C_{trough}	predose concentration
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_{max}	maximum effect
E-R	exposure-response
ETT	early termination of treatment
EU	European Union
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
F/F	*F508del*/*F508del* genotype
F/MF	*F508del*/minimal function genotypes
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
FSH	follicle-stimulating hormone

Abbreviation	Definition
FVC	forced vital capacity
G6PD	glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
GLI	Global Lung Function Initiative
GLP	Good Laboratory Practice
GPS	Global Patient Safety (Vertex)
HBE	human bronchial epithelial
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HED	human equivalent dose
HIPAA	Health Insurance Portability and Accountability Act
HIV-1/HIV-2 Abs	antibodies against human immunodeficiency viruses 1 and 2
HR	heart rate
IA	interim analysis
ICF	informed consent form
ICH	International Conference on Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IPD	important protocol deviation
IRB	institutional review board
IV	intravenous
IVA	ivacaftor
IWRS	interactive web response system
LLN	lower limit of normal
LUM	lumacaftor
max	maximum
MCP	multiple comparisons procedure
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal function
min	minimum
MMRM	mixed-effects model for repeated measures
n	number of subjects
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
OATP1B1	organic anion transporting polypeptide 1B1
P	probability
PD	pharmacodynamic, pharmacodynamics
PE	physical examination
PK	pharmacokinetic, pharmacokinetics
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
PR	PR interval
q12h	every 12 hours

Abbreviation	Definition
QC	quality control
qd	once daily
QRS	portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QTc	QT interval corrected
QTcB	QT interval corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
RR	interval from the onset of 1 QRS complex to the next
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SET	study execution team
SI	International System
SUSAR	suspected, unexpected, serious adverse reaction
TBD	to be determined
TC	triple combination
TC2	triple combination 2 (VX-445/TEZ/VX-561)
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
ULN	upper limit of normal
US	United States
UV	ultraviolet
Vertex	Vertex Pharmaceuticals Incorporated
WHO-DDE	World Health Organization-Drug Dictionary Enhanced

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 approximately 70,000 individuals worldwide[1] (approximately 30,000 in the US[1,2] and 32,000 in the EU).[3] Based on its prevalence, CF qualifies as an orphan disease.[4,5]

CF is caused by reduced quantity and/or function of the CFTR (CF transmembrane conductance regulator) 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 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.[2,6,7] Progressive loss of lung function is the leading cause of mortality.[8] More effective treatments are needed for CF.

More than 2000 mutations of the *CFTR* gene have been identified.[9] Most of these mutations are not associated with CF disease or are very rare. Currently, the CFTR2 database contains information on only 322 of these identified mutations, with sufficient evidence to define 281 mutations as disease-causing.[10] The most common disease-causing CFTR mutation, *F508del-CFTR*, accounts for 70% of the identified alleles in patients with CF; nearly half of all people with CF are homozygous for *F508del*.

Based on the understanding of the molecular defects caused by *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 cellular processing and trafficking to increase the quantity of functional 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 amount of residual CFTR channel activity in the membrane and the pathophysiology of that activity (reflecting the CFTR genotype of the patient and possibly other factors), both approaches may be required to ameliorate lung disease in patients with CF.

The therapeutic activity of CFTR correctors and potentiators has been established with products that were developed by Vertex Pharmaceuticals Incorporated (Vertex) and approved for the treatment of CF: ivacaftor (IVA) monotherapy (Kalydeco®) and lumacaftor (LUM) in combination with IVA (Orkambi®). Kalydeco and Orkambi are approved to treat CF in patients with specific *CFTR* genotypes. Tezacaftor (TEZ; VX-661), like LUM, is a first-generation CFTR corrector that improves the processing and trafficking of the F508del-CFTR protein, resulting in an increase in the quantity of F508del-CFTR protein at the cell surface. IVA increases the open-channel probability of the F508del-CFTR protein that has been delivered to the cell surface by TEZ, thereby enhancing total chloride transport. The combined effect of TEZ and IVA is increased quantity and function of F508del-CFTR at the cell surface.

VX-445 is a next-generation CFTR corrector. In vitro, VX-445 improves the processing and trafficking of F508del-CFTR, thereby increasing the quantity of functional F508del-CFTR protein at the cell surface. [11] The effect of VX-445 was additive to the effect of TEZ. The CFTR protein delivered to the cell surface by VX-445 alone or in combination with TEZ

(VX-445/TEZ) was potentiated by IVA.[11] In human bronchial epithelial (HBE) cells studied in vitro, the triple combination (TC) of VX-445, TEZ, and IVA (VX-445/TEZ/IVA) increased CFTR chloride transport more than any of the dual combinations (VX-445/TEZ, VX-445/IVA, and TEZ/IVA) or individual (VX-445, TEZ, and IVA) regimens.[11]

VX-561 (also known as CTP-656 or C-10355) is a deuterated isotope of IVA with a specific pattern of 9 substituted deuteriums. In vitro data indicate similar potency of VX-561 in HBE cells relative to IVA. Safety pharmacology and nonclinical toxicology studies of VX-561 demonstrate a similar safety profile relative to IVA. Phase 1 clinical studies in healthy subjects have shown that VX-561 had a reduced rate of clearance, increased exposure, greater plasma levels at 24 hours, and a longer half-life compared to IVA, thereby supporting once daily dosing.[12]

5.2 Rationale for the Present Study

Results from nonclinical pharmacology, pharmacokinetic (PK), and toxicology studies of VX-445 alone and in combination with TEZ/IVA, and the unmet medical need for new treatments for CF, support the clinical development of VX-445 for the treatment of CF.

This is the first clinical study of VX-445 and is designed to evaluate the safety, tolerability, and PK of VX-445 as monotherapy and in TC with TEZ/IVA in healthy subjects (Parts A, B, and C), as well as the safety and efficacy of VX-445 in TC with TEZ/IVA in subjects with CF who have F/MF (*F508del*/minimal function) or F/F genotypes (Parts D and E, respectively). Additionally, the safety and efficacy of VX-445 in TC with TEZ/VX-561 will be evaluated in subjects with F/MF genotypes in Part F, if the sponsor chooses to conduct this optional part of the study.

6 STUDY OBJECTIVES

6.1 Primary Objectives

Part A: To evaluate the safety and tolerability of single ascending doses of VX-445 in healthy subjects

Part B: To evaluate the safety and tolerability of multiple ascending doses of VX-445 administered in healthy subjects

Part C: To evaluate the safety and tolerability of multiple doses of VX-445 in TC with TEZ and IVA for 14 days in healthy subjects

Parts D and E

- To evaluate the safety and tolerability of VX-445 in TC with TEZ and IVA in subjects with CF
- To evaluate the efficacy of VX-445 in TC with TEZ and IVA in subjects with CF

Part F

- To evaluate the safety and tolerability of VX-445 in TC with TEZ and VX-561 (deuterated IVA) in subjects with CF
- To evaluate the efficacy of VX-445 in TC with TEZ and VX-561 in subjects with CF

6.2 Secondary Objectives

Part A

- To evaluate the PK of VX-445 after administration of single ascending doses of VX-445 in healthy subjects
- To evaluate the effect of food on VX-445 PK in healthy subjects
- To evaluate the absolute bioavailability (BA) of VX-445 when administered orally relative to intravenous (IV) administration in healthy subjects

Part B: To evaluate the PK of VX-445 after multiple ascending doses of VX-445 administered to healthy subjects

Part C

- To evaluate the PK of VX-445 after multiple ascending doses of VX-445 in TC with TEZ and IVA for 14 days in healthy subjects
- To evaluate the PK of TEZ and metabolites (M1-TEZ and M2-TEZ), and IVA and metabolites (M1-IVA and M6-IVA) after administration in TC with VX-445 for 14 days in healthy subjects

Parts D and E

- To evaluate the PD effect of VX-445 in TC with TEZ and IVA on CFTR function in subjects with CF
- To evaluate the PK of VX-445 when administered in TC with TEZ and IVA in subjects with CF
- To evaluate the PK of TEZ, IVA, and their respective metabolites (M1-TEZ and M1-IVA) when administered in TC with VX-445 in subjects with CF

Part F

- To evaluate the PD effect of VX-445 in TC with TEZ and VX-561 on CFTR function in subjects with CF
- To evaluate the PK of VX-445 when administered in TC with TEZ and VX-561 in subjects with CF
- To evaluate the PK of TEZ and metabolite (M1-TEZ) and VX-561 when administered in TC with VX-445 in subjects with CF

7 STUDY ENDPOINTS

7.1 Primary Endpoints

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

Parts D, E, and F:

- Safety and tolerability assessments of AEs, clinical laboratory values, standard 12-lead ECGs, vital signs, pulse oximetry, and spirometry
- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline through Day 29

7.2 Secondary Endpoints

Parts A and B: PK parameter estimates of VX-445 derived from plasma concentration-time data

Part C:

- PK parameter estimates of VX-445 derived from plasma concentration-time data
- 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

Parts D and E:

- Absolute change in sweat chloride concentrations from baseline through Day 29
- Relative change in $ppFEV_1$ from baseline through Day 29
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline at Day 29
- PK parameters of VX-445, TEZ, M1-TEZ, IVA, and M1-IVA

Part F:

- Absolute change in sweat chloride concentrations from baseline through Day 29
- Relative change in $ppFEV_1$ from baseline through Day 29
- Absolute change in CFQ-R respiratory domain score from baseline at Day 29
- PK parameters of VX-445, TEZ, M1-TEZ, and VX-561

[redacted]

8 STUDY POPULATION

Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects are randomized (Parts A, B, C, D, and F) or receive TEZ/IVA in the Run-in Period (Part E).

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: Parts A, B, and C

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. Female subjects must be of non-childbearing potential. To be considered of non-childbearing potential, female subjects must meet at least 1 of the following criteria:
   a. Postmenopausal: spontaneous amenorrhea for at least 12 consecutive months with a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal females
   b. Documented bilateral oophorectomy or hysterectomy

   Note: All other female subjects (including subjects with tubal ligations and subjects who do not have a documented bilateral oophorectomy or hysterectomy) will be considered to be of childbearing potential and are not eligible for this study.
4. 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.
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: Parts A, B, and C

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, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years).
2. History of febrile illness within 14 days before the first study drug dose
3. Any condition possibly affecting drug absorption (e.g., gastrectomy, cholecystectomy, or other gastrointestinal tract surgery, except appendectomy)
4. Standard 12-lead ECG demonstrating QTc >450 msec at screening. If QTc exceeds 450 msec, the ECG will be repeated 2 more times, and the average of the 3 QTc values will

be used to determine the subject's eligibility. As stated in Section 11.7.5.1, study sites should use QTcF unless they receive approval in advance from the medical monitor to use QTcB.

5. For female subjects: Pregnant or nursing subjects

   For male subjects: Male subjects with a female partner who is pregnant, nursing, or planning to become pregnant during the study or within 90 days after the last study drug dose
6. Blood donation (of approximately 1 pint [500 mL] or more) within 56 days before the first study drug dose or any significant loss of blood, as determined by the investigator, within 56 days before first study drug dose
7. Use of the following substances, activities, or devices during the time periods indicated in Table 9-4
   - Medications: hormonal methods of contraception, hormone-replacement therapies, other prescription medications, or nonprescription medications
   - Foods and supplements: herbal supplements, vitamins, or other dietary supplements (e.g., grapefruit juice, etc., as applicable)
   - Caffeine
   - Alcohol
   - Tobacco- or nicotine-containing products
   - Strenuous exercise
   - Other investigational drugs or devices
8. A screen positive for alcohol or drugs listed in Section 11.7.2
9. A screen positive for p24 antigen, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or antibodies against human immunodeficiency virus 1 or 2 (HIV-1 and HIV-2 Abs)
10. Glucose-6-phosphate dehydrogenase (G6PD) deficiency, defined as G6PD activity less than the lower limit of normal (LLN) or 70% of the mean of the LLN and the upper limit of normal (ULN), whichever is greater
11. History of hemolysis
12. Total bilirubin level >2 × ULN at screening
13. Forced expiratory volume in 1 second (FEV_1) (L) or forced vital capacity (FVC) (L) <80 percent predicted (Parts B and C only)
14. Subject, or close relative of the subject, is the investigator or a sub-investigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site.

8.2 Parts D, E, and F

8.2.1 Inclusion Criteria: Parts D, E, and F

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 will be aged 18 years or older on the date of informed consent.
4. Body weight ≥35 kg.
5. Subjects must be able to produce a valid (quantity-sufficient) sweat sample at screening, in addition to having a sweat chloride value ≥60 mmol/L documented at screening or in a previous laboratory report. If the initial screening collection results in insufficient sweat volume, then the sweat chloride collection may be repeated once, after approval by the medical monitor. For the laboratory report requirement, it is acceptable to use a sweat chloride value that was obtained before previous treatment with IVA, LUM/IVA, or an investigational CFTR modulator, if applicable.
6. Subjects must have an eligible *CFTR* genotype as noted below. If the screening *CFTR* genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used to establish eligibility. Note: Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9).
   - Parts D and F: Heterozygous for *F508del* with a second *CFTR* allele carrying a MF mutation that is not expected to respond to TEZ, IVA, and TEZ/IVA (Appendix A)
   - Part E: Homozygous for *F508del*
7. Subjects must have an FEV_1 ≥40% and ≤90% of predicted normal for age, sex, and height (equations of the Global Lung Function Initiative [GLI])[13] at the Screening Visit. Spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria[14] for acceptability and repeatability.
8. Stable CF disease as judged by the investigator.
9. Willing to remain on a stable CF treatment regimen through the planned end of treatment or, if applicable, the Safety Follow-up Visit.

8.2.2 Exclusion Criteria: Parts D, E, and F

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, including but not limited to, history of any of the following: familial long QT syndrome, chronic hypokalemia, heart failure, left ventricular hypertrophy, chronic bradycardia, myocardial infarction, cardiomyopathy, history of arrhythmia (ventricular or atrial fibrillation), obesity, acute neurologic events (subarachnoid hemorrhage, intracranial hemorrhage, cerebrovascular accident, or intracranial trauma), or autonomic neuropathy.

4. History of hemolysis.
5. G6PD deficiency, defined as G6PD activity less than the LLN or 70% of the mean of the LLN and the ULN, whichever is greater.
6. Any of the following abnormal laboratory values at screening:
   - Hemoglobin <10 g/dL
   - Total bilirubin ≥2 × ULN
   - Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT), or alkaline phosphatase (ALP) ≥3 × ULN
   - Abnormal renal function defined as glomerular filtration rate ≤50 mL/min/1.73 m^2 (calculated by the Modification of Diet in Renal Disease Study Equation)[15, 16]
7. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for sino-pulmonary disease within 28 days before the first dose of study drug.
8. Lung infection with organisms associated with a more rapid decline in pulmonary status (e.g., *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*). For subjects who have had a history of a positive culture in the past, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
   - The subject has had 2 respiratory tract cultures negative for these organisms within the past 12 months, with no subsequent positive cultures.
   - These 2 respiratory tract cultures were separated by at least 3 months, and 1 of them was obtained within the past 6 months.
9. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug.
10. A standard digital ECG demonstrating QTc >450 msec at screening. If QTc exceeds 450 msec for the screening ECG, the ECG should be repeated 2 more times during the Screening Period, and the subject will be excluded if the average of the 3 QTc values is >450 msec. As stated in Section 11.7.5.1, study sites should use QTcF unless they receive approval in advance from the medical monitor to use QTcB.
11. History of solid organ or hematological transplantation.
12. History of alcohol or drug abuse in the past year, including but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator.
13. Ongoing or prior participation in a study of an investigational treatment other than a CFTR modulator within 28 days or 5 terminal half-lives (whichever is longer) before screening. The duration of the elapsed time may be longer if required by local regulations.
14. Use of prohibited medications as defined in Table 9-5, within the specified window before the first dose of study drug.
15. For female subjects: Pregnant or nursing females. Females of childbearing potential must have a negative pregnancy test at screening, Day -28 (Part E only), and Day 1.

For male subjects: Male subjects with a female partner who is pregnant, nursing, or planning to become pregnant during the study or within 90 days after the last study drug dose.

16. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study. An adult (aged 18 years or older) who is a relative of a study staff member may be randomized in the study provided that
    - the adult lives independently of and does not reside with the study staff member, and
    - the adult participates in the study at a site other than the site at which the family member is employed.

9 STUDY IMPLEMENTATION

9.1 Study Design

This is a first-in-human study of VX-445. Approximately 224 subjects will be enrolled: 120 healthy subjects (Parts A, B, and C) and 104 subjects with CF (Parts D, E, and F). Part F is an optional part of the study, which will be conducted at the sponsor's discretion.

No subject will be allowed to randomize to more than 1 dose cohort.

9.1.1 Parts A, B, and C

Parts A, B, and C are randomized, double-blind, placebo-controlled, single- and multiple-dose parts in healthy subjects of this first-in-human study of VX-445. Part A also includes an evaluation of the effect of food on VX-445 PK and an evaluation of absolute BA. Part C doses VX-445 in TC with TEZ/IVA.

There is no pre-specified ratio of males to females, but reasonable effort will be made to enroll females of non-childbearing potential in all dosing cohorts.

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.

Number of Cohorts

In Parts A and B, 6 dose escalation cohorts are planned, although fewer than 6 or up to 2 additional cohorts may be enrolled in each part, based on data from previous cohorts. The additional cohorts will follow the corresponding schedule of assessments. In Part C, 2 cohorts are planned, while fewer or up to 2 additional cohorts each may be enrolled based on data from previous cohorts. The decision to initiate successive cohorts and dose selection will be based on safety, tolerability, and available PK data from preceding cohort(s). Refer to Section 9.7.1 for dose escalation criteria and Section 9.8.1 for stopping criteria.

Staggering of Dosing

In Cohort A1 (first single dose cohort) and in Cohort C1 (first TC cohort), dosing will be staggered so that 2 subjects are dosed (Cohort A1: 1 with VX-445 and 1 with placebo; Cohort C1: 1 with TC and 1 with triple placebo) at least 24 hours before the remaining 6 subjects in each cohort. Doses may be staggered in other cohorts if deemed necessary based on review of emerging safety data.

Timing of Part B and C Initiation

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

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

Starting Dose in Parts B and C

Information about the starting doses of Cohorts B1 and C1 can be found in Table 9-1 and Section 9.3.2.1.

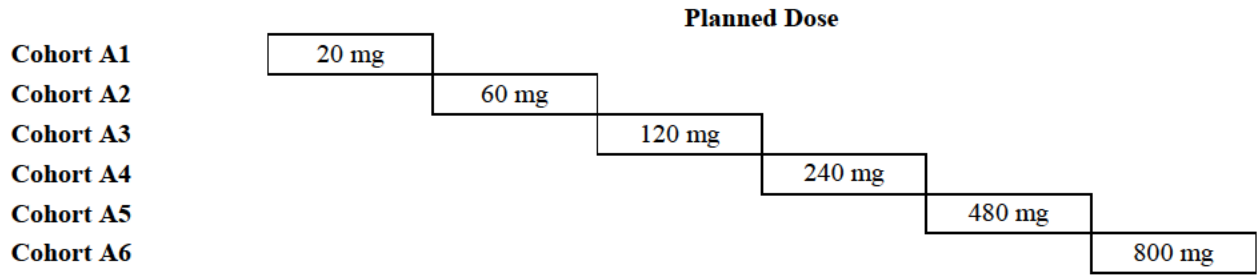
Table 9-1 Study Design for Parts A, B, and C

Part A: Single-dose escalation of VX-445

Cohorts A1 to A6: 8 subjects per cohort, randomized 3:1 (VX-445:placebo). Planned doses are shown; doses may be modified upward or downward based on emerging data.

Cohort A7: 8 subjects. VX-445 tablet dose is TBD, pending PK data from previous Part A cohorts, but will not exceed the highest dose that was safe and well tolerated. The planned IV dose is 20 mg.

No dose increment will be predicted to yield greater than a 3-fold increase (Cohorts A1 through A3) or a 2-fold increase (all other Part A cohorts except Cohort A7) in exposure from the preceding dose level.



Cohort A7 (open label VX-445, single sequence)[a]

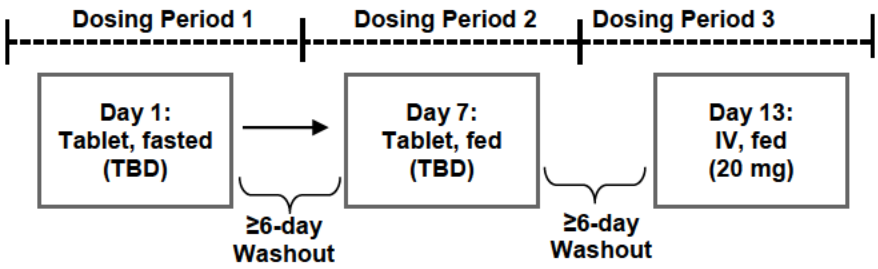
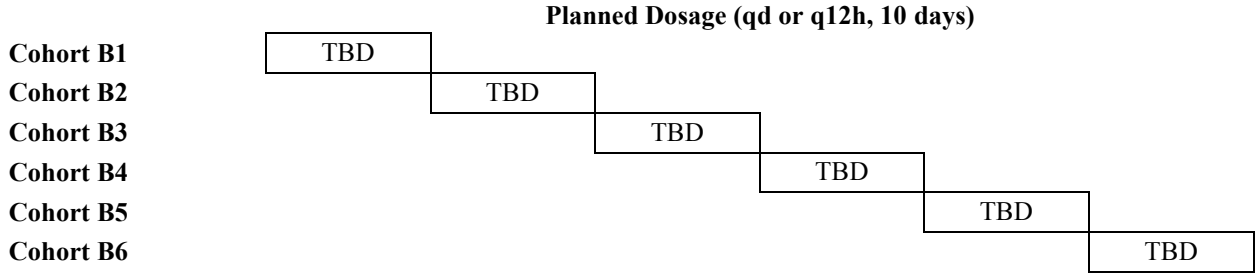
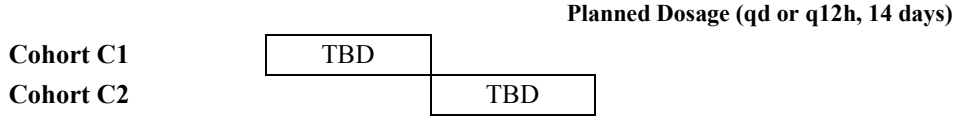


Table 9-1 Study Design for Parts A, B, and C

Part B: Multiple-dose escalation of VX-445
8 subjects per cohort, randomized 3:1 (VX-445:placebo)
The total daily dose in 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 that is safe and well tolerated.



Part C: Multiple-dose escalation of VX-445 in TC with TEZ/IVA[b]
8 subjects per cohort, randomized 3:1 (VX-445/TEZ/IVA:triple placebo)
The starting dose for Part C (Cohort C1) will be at least 1 dose level below the highest Part B dose for which safety and tolerability results are available and supportive.



CRU: clinical research unit; IV: intravenous; IVA: ivacaftor; PK: pharmacokinetic; q12h: every 12 hours; qd: once daily; TBD: to be determined; TC: triple combination (VX-445/TEZ/IVA); TEZ: tezacaftor
Note: Dose escalation criteria are described in Section 9.7.1, and dose escalation will be stopped when the predefined stopping criteria is met (see Section 9.8.1).
[a] The Washout Period is a minimum of 6 days and may be increased as needed based on emerging data from earlier cohorts (Cohorts A1 through A6). Subjects in Cohort A7 will receive a single dose of VX-445 on up to 3 dosing occasions. VX-445 doses include 2 single oral doses of tablet (dose TBD, pending PK data from previous Part A cohorts, but will not exceed the highest dose that was safe and well tolerated) and a single IV dose (the planned dose is 20 mg, but may be adjusted pending data from previous Part A cohorts; however, the final selected dose will not be predicted to exceed the highest exposure that was safe and well tolerated). If the IV formulation or the data supporting the use of the IV formulation are not available, then the third dosing period, in which subjects receive the IV dose, will not be conducted. If the IV dose is not administered, subjects will be discharged from the CRU on Day 13 after completing all study visit assessments and will return for a Safety Follow-up Visit (Table 3-3).
[b] 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 (Parts A, B, and C)

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 9.4.1).

A subject who qualified but did not enroll for an earlier cohort may enroll 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. No subject will be allowed to participate in more than 1 dose cohort or in more than 1 study part.

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)
- 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 damaged sample, laboratory error, or equipment malfunction. In all cases, the principal investigator must authorize retesting.

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

9.1.1.2 Treatment Period (Parts A, B, and C)

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), Table 3-3 (Cohort A7), Table 3-4 (Part B), and Table 3-5 (Part C).

The treatment periods will be conducted as described in Section 9.1. 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 (Parts A, B, and C)

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), Table 3-3 (Cohort A7), Table 3-4 (Part B), and Table 3-5 (Part C).

9.1.1.4 Early Discontinuation (Parts A, B, and C)

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), Table 3-3 (Cohort A7), Table 3-4 (Part B), and Table 3-5 (Part C).

9.1.2 Parts D, E, and F

Part D, which is comprised of Parts D1 and D2, is randomized, double-blind, placebo-controlled and evaluates VX-445 in TC with TEZ/IVA in subjects with CF (F/MF genotypes). Part E is randomized, double-blind, TEZ/IVA-controlled and evaluates VX-445 in TC with TEZ/IVA in subjects with CF (F/F genotype). Part F is randomized, double-blind, placebo-controlled, and evaluates VX-445 in TC with TEZ/VX-561 in subjects with CF (F/MF genotypes). Part F is an optional part of the study, which will be conducted at the sponsor's discretion. All parts are multicenter and designed to evaluate the safety and efficacy of VX-445 in TC.

Approximately 104 subjects with CF will be enrolled. Part D may be initiated while Parts A, B, and C are ongoing after review of safety, tolerability, and PK data. Enrollment of Parts D1 and D2 will be sequential, while enrollment of Parts E and F will be in parallel with Part D2.

After all Part D1 subjects complete the Day 15 Visit, a blinded review of all available safety and PK data will be conducted by the Vertex study team and lead investigator(s). Dosing in Parts D2, E, and F will start after this review, if supported by safety and PK data.

Part E subjects who are participating in Study VX11-661-110 (Study 661-110), an open-label study of TEZ/IVA combination therapy, will not need to washout TEZ/IVA treatment; these subjects will transition directly from their prior treatment to the TEZ/IVA Run-in Period providing that they meet all eligibility criteria. These subjects can have screening assessments for this study done while they are continuing to participate in Study 661-110.

Key study elements are summarized in Table 9-2. The treatment arms and randomization ratios for each part are summarized in Table 9-3. A schematic of the study design is shown in Figure 9-1. Study visits and assessments are shown in Table 3-6 (Parts D1 and D2), Table 3-7 (Part E), and Table 3-8 (Part F).

Table 9-2 Parts D, E, and F: Key Study Elements

Element	Part D1	Part D2	Part E	Part F
Study population				
Genotype(s)	F/MF	F/MF	F/F	F/MF
Age	≥18 years	≥18 years	≥18 years	≥18 years
$ppFEV_1$ criteria	≥40 to ≤90	≥40 to ≤90	≥40 to ≤90	≥40 to ≤90
Number of subjects	Approximately 8	Approximately 48	Approximately 24	Approximately 24
Study design	Parallel group	Parallel group	Parallel group	Parallel group
Control	Placebo	Placebo	TEZ/IVA	Placebo

IVA: ivacaftor; MF: minimal function; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Table 9-3 Treatment Arms and Planned Doses by Part in the Treatment Period (Period 1)

Part Randomization ratio	Treatment Arm	VX-445 Dosage	TEZ Dosage	IVA Dosage	VX-561 Dosage
Part D1[a]	TC-mid	100 mg qd	100 mg qd	150 mg q12h	N/A
3:1	Triple placebo	Placebo	Placebo	Placebo	N/A
Part D2[a]	TC-high	200 mg qd	100 mg qd	150 mg q12h	N/A
6:4:3:3	TC-mid	100 mg qd	100 mg qd	150 mg q12h	N/A
	TC-low	50 mg qd	100 mg qd	150 mg q12h	N/A
	Triple placebo	Placebo	Placebo	Placebo	N/A
Part E[b]	TC-high	200 mg qd	100 mg qd	150 mg q12h	N/A
3:1	TEZ/IVA	Placebo	100 mg qd	150 mg q12h	N/A
Part F	TC2-high	200 mg qd	100 mg qd	N/A	150 mg qd[c]
3:1	Triple placebo	Placebo	Placebo	N/A	Placebo

TC2: triple combination 2 (VX-445/TEZ/VX-561); IVA: ivacaftor; N/A: not applicable; q12h: every 12 hour; qd: once daily; TC: triple combination (VX-445/TEZ/IVA); TEZ: tezacaftor

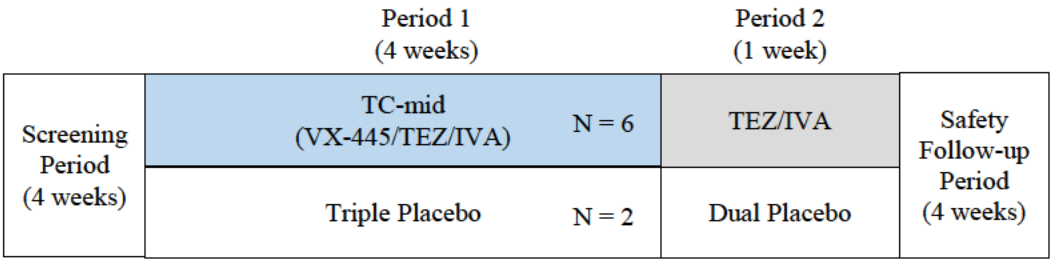
[a] In Parts D1 and D2, all subjects will also receive TEZ 100 mg qd/IVA 150 mg q12h or dual placebo during Period 2.

[b] In Part E, all subjects will also receive TEZ 100 mg qd/IVA 150 mg q12h during the Run-in Period and the Washout Period, which is the dosage evaluated in Phase 3 studies of TEZ/IVA.

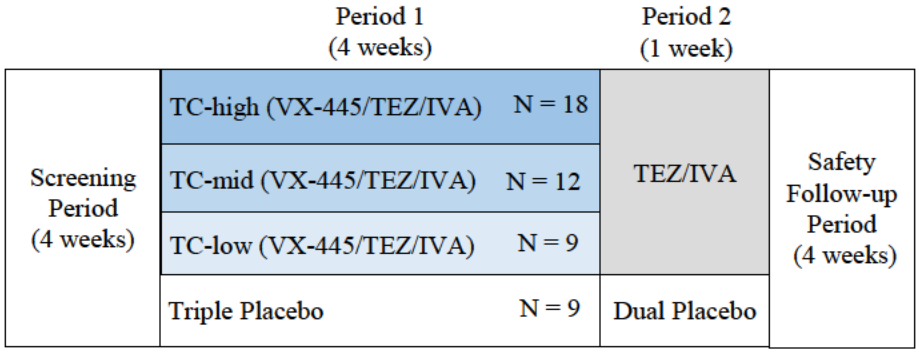
[c] See Section 9.3.2.2 for information relating to the selection of the VX-561 dose.

Figure 9-1 Parts D, E, and F: Schematic of Study Design

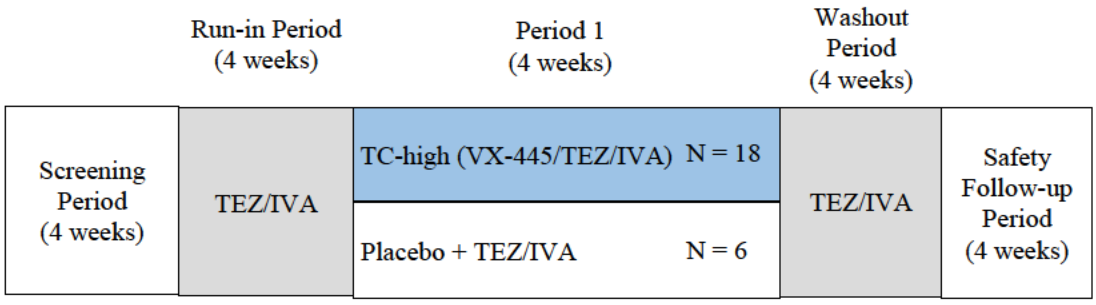
Part D1: F/MF
N ~ 8
Randomization: 3:1



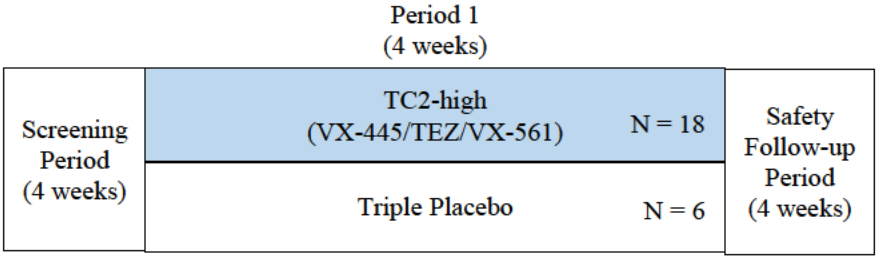
Part D2: F/MF
N ~ 48
Randomization: 6:4:3:3
Stratification: ppFEV$_1$: ≥70 versus <70



Part E: F/F
N ~ 24
Randomization: 3:1
Stratification: ppFEV$_1$: ≥70 versus <70



Part F (if Conducted): F/MF
N ~ 24
Randomization: 3:1
Stratification: $ppFEV_1$: ≥70 versus <70



TC2: triple combination 2 (VX-445/TEZ/VX-561); IVA: ivacaftor; MF: minimal function; N: number of subjects; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TC: triple combination (VX-445/TEZ/IVA); TEZ: tezacaftor
Note: to maintain the blind, matching placebo tablets will be administered, as applicable, so that all subjects receive the same number of tablets within a given dosing period.

9.1.2.1 Screening (Parts D, E, and F)

Screening will occur within 28 days before the first dose of study drug. Screening assessments will be used to confirm that subjects meet the eligibility criteria for the study. See Table 3-6, Table 3-7, and Table 3-8.

9.1.2.1.1 Repetition of Screening Assessment(s) (Parts D, E, and F)

If screening spirometry measurements fail to meet acceptability and repeatability criteria as specified by American Thoracic Society/European Respiratory Society guidelines[14], repeat spirometry evaluation may be performed.

Otherwise, repeating individual screening assessment(s) that did not meet eligibility criteria is not permitted, with the following exceptions that require the approval of the medical monitor:

- If there is clear evidence of a damaged sample, laboratory error, or equipment malfunction, collection of a repeat sample for the appropriate laboratory test or assessment may be permitted.
- Exclusionary liver function test results, which may be retested once within 14 days of the original screening date.
- Assessments required for eligibility may be repeated if permitted, as described in Section 8.2.
- If the screening G6PD value is exclusionary, it may be repeated by the site following the conduct described in Section 11.7.2.

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 (Parts D, E, and F)

Subjects may only be rescreened with the approval of the medical monitor. If a subject is rescreened, all screening assessments will be repeated except for *CFTR* genotyping, FSH level (if serum FSH level was ≥40 mIU/mL during prior screening), G6PD activity test, and the sweat chloride concentration. 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 (Parts D, E, and F)

A subject may have the Screening Period window extended without medical monitor approval 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

A subject may have the Screening Period window extended for an additional 2 weeks (total of 4 weeks) with medical monitor approval.

9.1.2.2 Stratification and Randomization (Parts D, E, and F)

All subjects will have a spirometry assessment done at the Screening Visit. Subjects in Part E may have an additional spirometry assessment done for stratification purposes before randomization based on prior CFTR modulator treatment.

9.1.2.2.1 Stratification (Parts D, E, and F)

Part D1

No $ppFEV_1$ stratification will be performed.

Part D2

$ppFEV_1$ stratification (<70 versus ≥70) will be performed using the screening (Days -28 to -1) $ppFEV_1$ value.

Part E

$ppFEV_1$ stratification (<70 versus ≥70) will be performed using a value obtained at the following visit:

- Screening Visit (Days -56 to -29) for subjects transitioning directly from at least 14 days of uninterrupted TEZ/IVA treatment
- Day -14 Visit (+ 13 days) for all other subjects

Part F

$ppFEV_1$ stratification (<70 versus ≥70) will be performed using the screening (Days -28 to -1) $ppFEV_1$ value.

9.1.2.2.2 Randomization (Parts D, E, and F)

Randomization will occur before the first dose of study drug and may be done on either Day -1 or Day 1, after all inclusion and exclusion criteria have been satisfied and the criteria for entry into the Treatment Period have been confirmed (see Section 9.1.2.4).

9.1.2.3 Run-in Period (Part E)

The Run-in Period of Part E is 4 weeks and is designed to establish a reliable on-treatment (TEZ/IVA) baseline for the Treatment Period (Period 1). Subjects will receive TEZ 100 mg qd/IVA 150 mg q12h during the Run-in Period. The first dose of TEZ/IVA will be administered at the Day -28 Visit. The last dose of TEZ/IVA within the Run-in Period will be administered on Day -1 (1 day before the Day 1 Visit).

Study eligibility for Part E subjects will be confirmed before the first dose of TEZ/IVA in the Run-in Period (on the Day -28 Visit). Subjects who prematurely discontinue TEZ/IVA during the Run-in Period will not be randomized or participate in the Treatment Period (Period 1), unless they rescreen and complete a 4-week Run-in Period (Section 9.1.2.1.2).

Study visits during the Run-in Period will occur as shown in Table 3-7.

9.1.2.4 Treatment Period (Parts D, E, and F)

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

The VX-445 treatment duration is 4 weeks. The Treatment Period duration is approximately 5 weeks for Parts D1 and D2 (Period 1 + Period 2), 4 weeks for Part E (Period 1), and 4 weeks for Part F (Period 1). All study periods will be conducted as described in Section 9.1. Study drug administration details are provided in Section 9.6.2.

9.1.2.5 Washout Period (Part E)

The Washout Period of Part E will last approximately 4 weeks and is designed to evaluate the effect on PD and efficacy endpoints as subjects step down from TC to TEZ/IVA. Subjects will receive TEZ 100 mg qd/ IVA 150 mg q12h during the Washout Period.

9.1.2.6 Follow-up (Parts D, E, and F)

There will be a Safety Follow-up Visit occurring approximately 28 days after the last dose of study drug for subjects who complete study drug dosing and for subjects who prematurely discontinue study drug dosing.

A subject who was enrolled in Study 661-110 and then enrolled in Part E of this study can re-enroll in Study 661-110 after completing the Washout Period of this study. If the subject completes the Day 57 Visit of this study and then re-enters Study 661-110, the subject will not have a Safety Follow-up Visit in this study.

9.1.2.7 Early Termination of Treatment (Parts D, E, and F)

If a subject prematurely discontinues treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the decision to terminate study drug treatment. All subjects who prematurely discontinue treatment (other than those who re-enroll in

Study 661-110, as described in Section 9.1.2.6) will also be required to complete the Safety Follow-up Visit, approximately 28 days after their last dose of study drug.

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

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

9.1.2.8 Independent Data Monitoring Committee (Parts D, E, and F)

This study will be monitored by an independent data monitoring committee (IDMC), which will conduct reviews of safety data from all parts of the study. The IDMC Charter, which will be finalized before the first subject is screened, will include procedural details of the IDMC structure and function, triggers for meetings, and plans for data to be reviewed. The IDMC Chair will review available safety and PK data from Parts A, B, and C of the study prior to commencement of dosing in Part D1 to determine if it is appropriate to proceed with the study.

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).

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. Randomized subjects will be assigned a unique subject number.

For Parts A, B, and C, a list identifying subjects by their subject number will be maintained in the study file at the CRU.

For Parts D, E, and F, 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

9.3.1.1 Parts A, B, and C

Parts A (except Cohort A7) and B have a parallel-group, dose-escalation design, with each subject participating in only 1 cohort to avoid PK and/or PD carryover effects.

VX-445 is being developed in TC with TEZ/IVA for the treatment of CF, and subjects with CF will be dosed with the TC in Parts D and E of this study (see Section 9.3.1.2). Part C of this study is included to evaluate the safety, tolerability, and PK of the TC in healthy subjects before subjects with CF are dosed with the TC.

Parts A (except Cohort A7), B, and C will be randomized, double-blind, and placebo-controlled in order to avoid bias in the collection and evaluation of safety and tolerability data during study conduct. Placebo was chosen as the control treatment to assess whether any observed effects are treatment-related or simply related to the study conditions.

Staggered Dosing in Cohorts A1 and C1

In Cohorts A1 and C1, after the first 2 subjects are dosed (1 active, 1 placebo), there will be at least a 24-hour observation period before the remaining subjects in Cohorts A1 and C1 are dosed. Staggered dosing will be used in Cohort A1 because this is the first time VX-445 will be administered to humans. In addition, staggered dosing is proposed for Part C as it is the first time VX-445 will be administered in TC with TEZ/IVA in humans. Staggered dosing for Part B is not considered necessary because the total daily dose 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 that is safe and well tolerated. Therefore, the relative risk to subjects dosed in Cohort B1 is considered to be less than that of subjects in Cohorts A1 and C1.

Cohort A7

Cohort A7 will not be initiated until all data required to support administration of the VX-445 tablet and IV formulations are available. Subjects in Cohort A7 will receive up to 3 single doses of VX-445: 2 single oral doses of tablet (dose to be determined [TBD] pending PK data from previous Part A cohorts, but not to exceed the highest dose that was safe and well tolerated) and a single IV dose (the planned dose is 20 mg, but may be adjusted pending data from previous Part A cohorts; however, the final selected dose will not be predicted to exceed the highest exposure that was safe and well tolerated). Each dosing occasion will be separated by at least 6 days. Based on nonclinical data, the interval between dosing occasions is considered adequate to minimize any potential for carryover. However, the washout interval of 6 days may be increased if needed based on emerging PK data from earlier Part A cohorts.

9.3.1.2 Parts D, E, and F

This is the first time that VX-445 will be administered to subjects with CF. The TC regimen of VX-445/TEZ/IVA will be evaluated in Parts D and E because in vitro, the TC has shown high levels of efficacy and has shown to provide a greater increase in chloride transport than any of the dual combinations or individual compounds.[11] The safety of VX-445 monotherapy will be evaluated in Parts A and B in healthy subjects, and the safety of VX-445 in TC with TEZ/IVA will be evaluated in Part C in healthy subjects. A Phase 3 program for TEZ/IVA is ongoing. Parts D and E are designed to evaluate the safety and efficacy of VX-445 in TC with TEZ/IVA and to establish proof-of-concept in 2 populations of subjects defined by *CFTR* genotype (F/MF and F/F). Additionally, Part F will evaluate the safety and efficacy of VX-445 in TC with TEZ and VX-561 (a deuterated form of IVA) in subjects with F/MF genotypes, if conducted at the sponsor's discretion.

Efficacy has not been demonstrated for a corrector, potentiator, or any corrector/potentiator combination in subjects with F/MF genotypes. A Phase 3 study of TEZ/IVA in subjects with F/MF genotypes (Study VX14-661-107) was terminated following a planned interim futility analysis which showed that the combination of TEZ/IVA did not result in a pre-specified improvement in lung function. Because there is no effective treatment for this population, placebo is the control in Parts D1, D2, and F.

A potential for benefit was demonstrated for TEZ/IVA in subjects with the F/F genotype in Study VX11-661-101[17], and a Phase 3 study of TEZ/IVA in subjects with the F/F genotype (Study VX14-661-106) demonstrated a clinically meaningful benefit across multiple endpoints.[18] Therefore, TEZ/IVA is the active control in Part E.

Parts D1 and D2 include a second dosing period (Period 2) during which subjects will be administered TEZ/IVA (or dual placebo, for the placebo arm). Period 2 is included to enable a more thorough evaluation of exposure-response relationships for the TC during VX-445 washout.

The Washout Period of Part E is described in Section 9.1.2.5.

Randomization for subjects in Parts D2, E, and F will be stratified as outlined in Section 9.1.2.2.1.

9.3.2 Study Drug Dose and Duration

9.3.2.1 Parts A, B, and C

VX-445 Starting Dose

[redacted] Using the lowest of the HED values (4.8 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 28 mg/day. The selected starting dose of 20 mg for Cohort A1 [redacted]

Part A VX-445 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 9.7.1.1. Stopping criteria are presented in Section 9.8.1. Dose escalation may be adjusted upward or downward based on safety, tolerability, and PK data from preceding dose group(s).

The decision to initiate successive cohorts and dose selection will be based on safety, tolerability, and available PK data from preceding cohort(s).

Cohort A7 VX-445 Dose Selection

The oral dose of VX-445 will be administered in Cohort A7 as a tablet fasted versus fed, which will be selected based on emerging PK data from Part A. The oral dose will not exceed a dose shown to be safe and well tolerated in a previous Part A cohort. The planned IV dose of 20 mg was selected so as not to exceed the exposure cap or exposure levels expected following oral doses in Part A. [redacted] The IV dose may be adjusted pending data from previous Part A cohorts, but will not be predicted to exceed the highest exposure that was safe and well tolerated. If data to support use of the IV dose is not available, the IV dose will not be administered.

Part B VX-445 Starting Dose and Dose Escalation

The starting dose in Part B will be selected based on safety, tolerability, and PK data in Part A. The total daily dose in 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 that is safe and well tolerated.

Initiation of successive cohorts and dose selection will be based on safety and PK data as described in Section 9.7.1.2.

Part C VX-445 Starting Dose and Dose Escalation

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 available and supportive. Dosing will be staggered in Cohort C1, with 2 subjects dosed (1 with VX-445 in TC with TEZ/IVA and 1 with 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.

Parts B and C Treatment Duration

The duration of dosing in Part B (10 days) and Part C (14 days) is a standard duration for multiple-dosing in first-in-human studies and is of sufficient length for an early assessment of safety and tolerability and for assessment of steady-state PK.

TEZ and IVA Doses (Part C)

The doses of TEZ and IVA are the same as those being 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-445 that evaluated similar levels of TEZ and IVA exposure after correction for protein-binding.

Administration of VX-445 with Food

Doses of VX-445 will be administered under fed conditions in all cohorts except Cohort A7, which includes a dosing period where VX-445 is also administered under fasting conditions to evaluate the food effect. Only a mild food effect is predicted for VX-445 oral absorption. However, given the ultimate intent to administer VX-445 in combination with TEZ/IVA, which are administered with fat-containing food, this early assessment of safety and PK will be conducted under fed conditions.

9.3.2.2 Parts D, E, and F

VX-445 Dosage

VX-445 will be given qd.

Part D may be initiated while Parts A, B, and C are ongoing after review of safety, tolerability, and PK data. Single doses of VX-445 up to 360 mg were safe and well tolerated in Part A, and multiple doses of VX-445 up to 340 mg qd for 10 days were safe and well tolerated in Part B. In Part C, multiple doses of VX-445 up to 280 mg qd in TC with TEZ 100 mg qd and IVA 150 mg q12h were safe and well tolerated after 14 days of dosing.

Part D1 will evaluate 1 dose level (mid-dose: 100 mg qd) of VX-445 in TC with TEZ/IVA to assess safety, tolerability, and PK in a smaller subset of subjects before enrolling a larger number

of subjects and evaluating a higher VX-445 dose. The mid-dose of VX-445 100 mg qd was selected to ensure a sufficient safety margin relative to nonclinical data and the clinical experience in Parts A, B, and C in healthy subjects, and is at least 1 dose level below the highest Part C dose for which safety and tolerability results are available and supportive.

Part D2 will evaluate 3 dose levels of VX-445 (low: 50 mg qd; mid: 100 mg qd; and high: 200 mg qd) in TC with TEZ/IVA. The TC-high dose of VX-445 does not exceed the highest dose shown to be safe and well tolerated in Parts A, B, and C.

The dose levels evaluated in Part D2 will be expected to provide clinical benefit (based on in vitro data) and will be selected to provide a range of exposure for exposure-response analyses of safety and efficacy.

The highest TC dose of 200 mg qd VX-445 used in Part D2 will also be used in Parts E and F. Dose- and exposure-response information obtained for the TC in Part D (subjects with F/MF genotypes) is expected to be applicable to other populations with an *F508del* mutation, including F/F, based on similar potency of the TC in HBE cells that have 1 copy or 2 copies of *F508del*.[11]

TEZ Dosage

In all study parts, the TEZ dosage will be 100 mg qd, which is the same dose being evaluated in Phase 3 studies of TEZ/IVA.

IVA Dosage

In Parts D and E, the IVA dosage will be 150 mg q12h. This dosage is being used in Phase 3 studies of TEZ/IVA and is also the approved IVA monotherapy dosage for patients aged 12 years and older.

VX-561 Dosage

A VX-561 dose of 150 mg qd was selected for evaluation in Part F based on preliminary PK results from a relative bioavailability study (Study VX16-770-018) evaluating the 50-mg tablet formulation of VX-561. 150-mg qd is predicted to result in similar PK parameters as IVA when administered alone at a dose of 150 mg q12h, including $AUC_{0\text{-}24h}$ and C_{trough}. The VX-561 dose selection accounts for differences in the PK profile relative to IVA. VX-561 has been dosed up to 225 mg qd for 7 days in a Phase 1 study.

Treatment Duration

The 4-week treatment duration for the TC is based on previous experience with CF correctors and potentiators in clinical studies of subjects with CF. In previous studies of TEZ and IVA, PD effects were observed within 4 weeks of treatment. In Study VX06-770-101, treatment with IVA for 4 weeks resulted in statistically significant within-group changes from baseline in $ppFEV_1$ as well as a trend toward clinically meaningful improvements in the respiratory domain of the CFQ-R; differences in biomarkers of CFTR activity (sweat chloride) between IVA and placebo groups were also demonstrated. Furthermore, in Study VX11-661-101 dose-dependent improvements in lung function were observed for TEZ/IVA after 4 weeks of treatment, with the 2 highest dose groups showing statistically significant improvement in lung function versus placebo.[17] In both studies, improvements in sweat chloride and $ppFEV_1$ were observed during the first week of dosing, with most of the effect observed within 14 days. Given the increased in vitro response of the TC relative to TEZ/IVA, it is expected that the 4-week treatment duration

of VX-445 will be sufficient to observe differences between treatment arms with respect to efficacy and PD endpoints.

Administration of VX-445, TEZ, IVA, and VX-561 With Food

Oral doses of VX-445, TEZ, IVA, and VX-561 will be administered under fed conditions. This is consistent with how VX-445, TEZ, IVA, and VX-561 were administered in nonclinical studies, including the GLP toxicity studies. Only a mild food effect is predicted for VX-445 oral absorption.

9.3.3 Study Population (Parts D, E, and F)

The study will include subjects with F/MF and F/F genotypes. The inclusion of subjects with F/MF and F/F genotypes is based on in vitro data that indicate the potential for significant improvements in chloride transport for CF patients with 1 or 2 copies of *F508del* in response to treatment with TC.[11] Subjects homozygous and heterozygous for *F508del* will be evaluated in different parts of the study because of the potential for differences in the magnitude of treatment response across the 2 genotype categories, and also because of the differences in current standard of care (See Section 9.3.1.2).

9.3.4 Study Assessments

9.3.4.1 Parts A, B, and C

The majority of safety and PK assessments are standard parameters for Phase 1 clinical studies.

Rationales for other safety, PK, and PD assessments are listed below:

4β-hydroxycholesterol (Part B)

4β-hydroxycholesterol is an endogenous marker for cytochrome P450 (CYP) 3A activity.[20] Evaluation of 4β-hydroxycholesterol is increasingly being used to assess potential clinical CYP3A induction. In Part B, comparison of 4β-hydroxycholesterol on Day 10 (predose) relative to baseline (Day 1 predose) will be used to evaluate potential induction of CYP3A by VX-445. Based on in vitro data, VX-445 is not expected to be an inducer of CYP3A.[11]

Spirometry (Parts B and C)

Transient declines in lung function have been observed at initiation of treatment with another CFTR corrector that is not included in the current study (LUM).[21] Although nonclinical toxicity results do not indicate a risk of lung function decline for VX-445, lung function, as assessed by spirometry, will be included in Parts B and C as a precautionary safety measure.

[redacted]

[redacted]

Continuous ECG Monitoring (Part A, with the exception of Cohort A7)

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.[22] Therefore, continuous ECG monitoring will be performed in subjects in Part A (with the exception of Cohort A7) for possible later extraction and high-precision QTc analysis of 10 ECG replicate measurements. 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-445. If analyzed, a separate analysis plan will be created for the evaluation of the data. 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.

G6PD Activity Test

The G6PD activity test will be performed for all subjects at screening. [redacted]

9.3.4.2 Parts D, E, and F

All safety and PK assessments are common assessments for clinical studies, with the exception of the G6PD activity test to be performed at screening in this study (see G6PD activity test paragraph above in Section 9.3.4.1).

The PD and efficacy assessments are widely accepted and are relevant to the study of patients in CF. All assessments are consistent with those measured in the registration studies of IVA (Kalydeco) or LUM/IVA combination therapy (Orkambi).

9.4 Study Restrictions

9.4.1 Parts A, B, and C

In Part A (with the exception of Cohort A7), subjects will be confined for the first 4 hours after dosing on Day 1 during continuous ECG monitoring, except to use the bathroom. After this time, if the equipment setup allows, subjects may be ambulatory during the continuous ECG monitoring, 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).

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

Other study restrictions are summarized in Table 9-4.

Table 9-4 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
Other investigational drugs or devices	30 days or 5 half-lives before first study drug dose, or time determined by local requirements (whichever is longest)	Completion of Safety Follow-up Visit assessments
Hormonal methods of contraception (oral 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 (≤2 g/day) is allowed for pain.	Completion of Safety Follow-up Visit assessments
Herbal supplements, vitamins, or other dietary supplements	14 days before first study drug dose	Completion of Safety Follow-up Visit assessments
Grapefruit; grapefruit, 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
Alcohol	Not more than 14 drinks/week for female subjects or 21 drinks/week for male subjects, where 1 drink equals 5 oz (150 mL) of wine, 12 oz (360 mL) of beer, or 1.5 oz (45 mL) of hard liquor, 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
Strenuous exercise (e.g., heavy lifting, weight training, and aerobics)	96 hours before first clinical laboratory testing	Completion of Safety Follow-up assessments

CRU: clinical research unit; PK: pharmacokinetic.

[a] See Section 9.5.1 for guidance on concomitant medications.

9.4.2 Parts D, E, and F

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

9.4.2.1 Prohibited Medications

Table 9-5 lists prohibited medications. TEZ, IVA, and VX-561 are metabolized extensively via cytochrome P450 (CYP) 3A4. VX-445 has a low potential to be an inhibitor or inducer of CYP enzymes based on in vitro data but is metabolized by CYP3A4/5. Therefore, use of moderate and strong inducers and inhibitors of CYP3A, which have the potential to alter the exposure of VX-445, TEZ, IVA, and VX-561 will be prohibited. VX-445 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") are prohibited during treatment. Commercially available CFTR modulators are also prohibited.

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

Table 9-5 Parts D, E, and F: Prohibited Medications

	Timing of Restriction	
Medication	**Start of Restriction**	**End of Restriction**
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through the Safety Follow-up Visit
Moderate and strong CYP3A inhibitors (except ciprofloxacin)	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through the Safety Follow-up Visit
Sensitive OATP1B1 substrates	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through the Safety Follow-up Visit
CFTR modulators (investigational or approved, except for study drug)	Parts D and F: None allowed within 28 days before Screening	Parts D and F: None allowed through the Safety Follow-up Visit
	Part E: None allowed beginning on Day -28 Visit	Part E: None allowed through Day 57

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

9.5 Prior and Concomitant Medications

9.5.1 Parts A, B, and C

- Subjects will abstain from medication as described in Table 9-4.
- 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 Parts D, E, and F

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 Visit through the Safety Follow-up Visit, if applicable, will be recorded in each subject's source documents. For subjects who are screened but not subsequently randomized, details of prior medication will only be documented in the subjects' source documents.

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

9.6 Study Drug 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-445 and matching placebo will be administered as a tablet, and VX-445 will be administered as an IV solution for infusion if Dosing Period 3 of Cohort A7 is conducted. TEZ and IVA and their matching placebos will be administered as tablets (Part C).

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.

- When study drug is administered as a tablet, subjects will swallow the tablet(s) whole with 240 mL of water. Subjects may take additional water, as needed, to swallow tablets.
- Subjects will be supine if VX-445 is administered intravenously
- To standardize the conditions on PK sampling days, all subjects will be required to refrain from lying down (except when required for PK sampling, continuous ECG measurements, and IV dosing), eating, and drinking beverages other than water during the first 4 hours after dosing.

9.6.1.1 Part A

Part A, Cohorts A1 Through A6: Single-ascending Dose Escalation

Cohorts A1 though A6 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 4 to 6 hours after dosing. Dinner will be provided 8 to 11 hours after dosing.

An evening snack will be permitted.

Part A, Cohort A7: Food Effect and Absolute Bioavailability

Day 1 (Fasted State)

Subjects will receive VX-445 tablets on Day 1.

On Day 1 (fasted state), subjects must abstain from all food and drink (except water) at least 8 hours before and 4 hours after study drug dosing. Water is permitted until 1 hour before the dose of study drug and beginning 1 hour after dosing.

Lunch will be provided 4 to 6 hours after dosing. Dinner will be provided 8 to 11 hours after dosing.

An evening snack will be permitted.

Days 7 and 13 (Fed State)

Subjects will receive VX-445 tablets on Day 7. If Dosing Period 3 is conducted (Section 9.1), subjects will receive a single IV dose of VX-445 infused over 30 minutes on Day 13.

On Days 7 and 13 (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.

Lunch will be provided 4 to 6 hours after dosing. Dinner will be provided 8 to 11 hours after dosing.

An evening snack will be permitted.

9.6.1.2 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. Additionally, if dosing is every 12 hours, a standard dinner, containing approximately 40 g of fat, will be served 45 minutes before evening dosing. Subjects must complete the entire meal in 30 minutes or less (for breakfast) or 45 minutes or less (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 dose, but water and other clear liquids may be consumed without restriction beginning 1 hour after the morning dose.

9.6.1.3 Part C

All doses of VX-445, TEZ, and IVA will be administered under fed conditions, consistent with the dosing recommendations for TEZ/IVA.

On all days of study drug administration, a standard breakfast, containing approximately 20 g of fat, will be served 30 minutes before morning dosing. Additionally, if dosing is every 12 hours, a standard dinner, containing approximately 40 g of fat, will be served 45 minutes before evening dosing. Subjects must complete the entire meal in 30 minutes or less (for breakfast) or 45 minutes or less (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 doses.

9.6.2 Parts D, E, and F

Study drug will be administered orally. In each part, subjects in all groups will receive the same number of tablets at each dosing occasion to maintain the blind. Additional information is provided in the Pharmacy Manual.

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

1. It is recommended that the dose be taken within 30 minutes of the start of the meal or snack.
2. Study drug will be administered qd (± 2 hours) or q12h (± 2 hours). For each subject, doses of study drugs will be taken at approximately the same time each day. For example, if dosing is q12h, 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 all predose assessments are complete. A meal or snack will be provided by the site for the morning dose of study drug. For subjects in Part E requiring a Day -14 Visit, study drug does not need to be administered at the site for that visit only.
5. Subjects will be instructed to return all used and unused materials associated with the 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 (q12h dosing) or within 12 hours (qd dosing), the subject should take his/her dose with food. If more than 6 hours (q12h dosing) or 12 hours (qd dosing) have elapsed after his/her usual dosing time, the subject should skip that dose and resume his/her normal schedule for the following dose. Examples are provided below:

If study drug is administered q12h:

- 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.

If study drug is administered qd:

- if the 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 dose of study drug should have been taken at approximately 08:00, and more than 12 hours have elapsed beyond the scheduled dosing time (i.e., the time is past 20:00), the subject would resume dosing the following day at approximately 08:00.

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, tolerability, and available PK data from preceding cohort(s), as indicated in Sections 9.7.1.1, 9.7.1.2, and 9.7.1.3. 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.

9.7.1.1 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 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 except Cohort A7) in exposure from the preceding dose level. Dose escalation will be stopped when the predefined stopping criteria are met (see Section 9.8).

The decision to initiate successive cohorts and dose selection will be based on safety, tolerability, and available PK data from all subjects in each preceding cohort.

9.7.1.2 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, tolerability, and PK results are available and that is safe and well tolerated.

The decision to initiate successive cohorts and dose selection will be based on safety, tolerability, and available PK data through Day 10 from previous cohorts. Doses may be adjusted upward or downward based on safety, tolerability, and PK data from preceding dose group(s). The highest daily dose of VX-445 in Part B will not exceed the highest Part A dose for which safety and tolerability results are supportive. Stopping criteria are presented in Section 9.8.1.

9.7.1.3 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 available and supportive. The highest dose of VX-445 in Part C will not exceed the highest Part B dose for which safety and tolerability results are available and supportive.

9.7.2 Parts D, E, and F

If any unacceptable toxicity arises, individual subjects will discontinue dosing (Section 9.1.2.7). No dose modifications for toxicity are allowed.

9.8 Stopping Criteria

9.8.1 Parts A, B, and C

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 290 µg·h/mL or the C_{max} is predicted to exceed 19.5 µg/mL (NOAEL exposure at the 50 mg/kg/day dose in male rats in the 28-day GLP toxicity study).

An individual subject will discontinue study drug dosing if the subject has a serious adverse event (SAE) or an AE that jeopardizes the subject's safety. The investigator must immediately notify the Vertex medical monitor if either an SAE or a severe (or greater) AE occurs that is considered related or possibly related to study drug. All SAEs, regardless of the presumed relationship to study drug, must also be reported to Vertex GPS within 24 hours (Section 13.1.2.3).

If an 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 (i.e., 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. The study may be restarted if the sponsor and the investigator decide that this is appropriate.

9.8.2 Parts D, E, and F

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

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

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

- ALT or AST >8 × ULN
- ALT or AST >5 × ULN for more than 2 weeks
- ALT or AST >3 × ULN, in association with total bilirubin >2 × ULN and/or clinical jaundice
- Indirect bilirubin >2 × ULN (defined as ULN for total bilirubin minus ULN for direct bilirubin)

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

Study drug administration **must be discontinued**, if either of the following criteria is met:

- 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, or alcohol ingestion) is identified, regardless of whether transaminase levels have improved
- Subsequent indirect bilirubin values confirm the initial value as >2 × ULN (defined as ULN for total bilirubin minus ULN for direct bilirubin), in association with decreased haptoglobin

If an alternative, reversible cause of transaminase elevation and/or increased bilirubin or clinical jaundice has been identified, study drug administration may be resumed once transaminases or bilirubin return to baseline or are ≤2 × ULN, whichever is higher. Approval of the medical monitor is required before resumption of study drug. Upon resumption of study drug, transaminases and bilirubin should be assessed weekly for 4 weeks. If a protocol-defined transaminase or bilirubin elevation interruption threshold recurs during the Treatment Period

(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.

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.

9.9 Removal of Subjects

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

Whenever possible, subjects who have been withdrawn from study drug treatment will continue on study; however, Vertex retains the right to remove a subject from the study.

In Parts D, E, and F, 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 products (Parts D, E, and F), request that the subject return for a Safety Follow-up Visit, if applicable (see Section 9.1.1.3 for Parts A, B, and C and Section 9.1.2.7 for Parts D, E, and F), and follow up with the subject regarding any unresolved AEs.

If the subject withdraws consent for the study, no further evaluations will be performed and no additional data will be collected. Vertex may retain and continue to use the study data and samples collected. The study data and the samples may be used for the development of the study compound, other drugs, or diagnostics, in publications and presentations, or 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. Any information that already has been obtained from the samples will continue to be used.

Stopping criteria are presented in Section 9.8.

9.10 Replacement of Subjects

Subjects who withdraw or are withdrawn before the first dose of study drug (Day 1 for Parts A, B, C, D, and F; Day -28 for Part E) may be replaced.

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

10 STUDY DRUG INFORMATION AND MANAGEMENT

Study drug refers to VX-445, TEZ/IVA, TEZ, IVA, VX-561, 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.

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

The Formulation Preparation Instructions will provide details of the preparation of the VX-445 IV infusion solution, if used in the study.

Parts D, E, and F

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-445 tablets and matching placebos and IV solution (if used), as well as TEZ/IVA FDC tablets, TEZ tablets, IVA tablets, VX-561 tablets, and all matching placebos. Study drug tablets will be supplied in blister cards by Vertex for Parts D, E, and F. Study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing for study drug will be included in the Pharmacy Manual.

10.3 Study Drug Supply, Storage, and Handling

VX-445 and matching placebo will be supplied as tablets of similar size and appearance containing 20 mg, 50 mg, or 100 mg VX-445 and 0 mg VX-445, respectively.

VX-445 will be supplied as a sterile solution for IV administration, if used in the study.

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.

TEZ (50 mg) and matching placebo will be supplied as white tablets of similar size and appearance containing 50 mg TEZ and 0 mg TEZ, respectively, if Part F is conducted.

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.

VX-561 (50 mg) and matching placebo will be supplied as tablets of similar size and appearance containing 50 mg VX-561 and 0 mg VX-561, respectively, if Part F is conducted.

Study drug and blister cards must be stored under conditions noted in Table 10-1 and in the Pharmacy Manual. The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate

records, all study drugs will be accounted for via the drug accountability forms as instructed by Vertex.

Table 10-1 Study Drug

Drug Name	Strength/Formulation/Route	Storage Condition	Part
VX-445	20-mg, 50-mg, and 100-mg tablets, oral	≤ 25°C (77°F) with excursions to 30°C (86°F)	All
VX-445-matching placebo	0-mg tablet, oral	≤ 25°C (77°F) with excursions to 30°C (86°F)	All
TEZ/IVA fixed-dose	100-mg/150-mg tablet; oral	≤25°C (77°F) with excursions to 30°C (86°F)	C, D, and E
TEZ/IVA-matching placebo	0-mg/0-mg tablet; oral	≤25°C (77°F) with excursions to 30°C (86°F)	C, D, and E
TEZ	50-mg tablet, oral	≤25°C (77°F) with excursions to 30°C (86°F)	F
TEZ-matching placebo	0-mg tablet, oral	≤25°C (77°F) with excursions to 30°C (86°F)	F
IVA	150-mg tablet, oral	≤25°C (77°F) with excursions to 30°C (86°F)	C, D, and E
IVA-matching placebo	0-mg tablet, oral	≤25°C (77°F) with excursions to 30°C (86°F)	C, D, and E
VX-561	50-mg tablet, oral	Refer to Pharmacy Manual	F
VX-561-matching placebo	0-mg tablet, oral	Refer to Pharmacy Manual	F

IVA: ivacaftor; TEZ: tezacaftor

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 (Parts D, E, and F only). Subjects in Parts D, E, and F will be instructed to return all used and unused materials associated with the study drug to the site. These materials will be retained at the site according to instructions provided by Vertex or its designee until inventoried by the study monitor. The study monitor will review study drug records and inventory throughout the study.

10.5 Disposal, Return, or Retention of Unused Drug

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

10.6 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 of the tablet in the CRU to ensure 100% study treatment compliance.

10.6.2 Parts D, E, and F

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 A7, 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;
- Bioanalytical CRO analyzing PK samples and Vertex Bioanalytical personnel who is not a member of the SET but reviews raw data from 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 A (with the exception of Cohort A7);
- 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 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-445) will be reported by the bioanalytical CRO using masked identification numbers for PK analysis.

10.7.1.2 Parts D, E, and F

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

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of the subject and her fetus in the event of a pregnancy
- Vertex 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
- IDMC vendor performing the interim analyses (IAs) and preparing the unblinded analysis for the ongoing reviews of efficacy and safety data, and a limited Vertex team not involved in the conduct of the study
- Bioanalytical CRO analyzing PK samples and the Vertex Bioanalytical personnel who is not a member of the SET but reviews raw data from Bioanalytical CRO. The Vertex Bioanalytical SET member will continue to be blinded.
- Vertex Modeling and Simulation personnel or vendor conducting the population PK and PK/PD analyses
- Vertex medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time

The Vertex study team and lead investigator(s) will also conduct blinded reviews of all available safety and PK data after all subjects within a cohort complete the Day 29 Visit to make decisions about dose selection for potential subsequent cohorts.

Blinding of Sweat Chloride and Spirometry Results:

- The Vertex study team will not have access to the spirometry or sweat chloride results after the first dose of study drug until after the data are unblinded for full review per Section 12.3.6.1.2.

- Sites, subjects, and their parents/caregivers/companions should not be informed of a subject's study-related sweat chloride results until after the subject's last study visit, even if the subject prematurely discontinues treatment.
- Subjects and their parents/caregivers/companions should not be informed of a subject's study-related spirometry results until after the subject's last study visit, even if the subject prematurely discontinues treatment.

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 Individual Subject Treatment Assignments by Investigator for Medical Emergencies or Urgent Clinical Situations

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

Unblinding of Individual Subject Treatment Assignments by Vertex GPS or Designee for SAEs or Safety Concerns

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.

Parts D, E, and F Only: Unblinded Reviews of Data by Vertex for Administrative Purposes (Planning, Decision-making, and Regulatory Submission)

A limited Vertex team not involved in the conduct of the study will be unblinded to results of the IAs and will have access to safety, efficacy, and PD data for the purpose of conducting ongoing reviews of safety and efficacy data for planning and enabling clinical development. Members of the limited unblinded Vertex team will not be part of the Vertex study team and will not be involved in or influence the conduct of the study.

Unblinding: Interim Analysis Results

Parts A, B, and C: When an IA is performed after all subjects in Part C have completed the Safety Follow-up Visit, results from Parts A, B, and C will be unblinded for full review by the Vertex study team.

Parts D, E, and F: When an IA is performed after all subjects in a part have completed the Safety Follow-up Visit, results from that part will be unblinded for full review by the Vertex study team.

11 ASSESSMENTS

11.1 Timing of Assessments

For Parts A, B, and C, the timing of assessments is shown in Table 3-1 (Screening), Table 3-2 (Cohorts A1 through A6), Table 3-3 (Cohort A7), Table 3-4 (Part B), and Table 3-5 (Part C).

For Parts D, E, and F, the timing of assessments is shown in Table 3-6 (Part D), Table 3-7 (Part E), and Table 3-8 (Part F).

Assessments may be performed in any order when more than 1 assessment is required at a particular time point except for informed consent, which must be completed before any assessments are done at the Screening Visit, and the CFQ-R assessment in Parts D, E, and F, which must be completed before any other assessment at the clinic visit when it is required.

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 to determine plasma concentrations of VX-445, TEZ and metabolites, IVA and metabolites, and VX-561, according to the Schedules of Assessments (Section 3). Metabolites of VX-561, including D-M1-IVA and D-M6-IVA, may also be evaluated. These samples may also be used for evaluations of potential metabolites of VX-445, for further evaluation of the bioanalytical method, [redacted]

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

Based on emergent data, the number of sampling points for VX-445 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 ≤120 hours after study drug dosing	± 30 minutes
Parts D, E, and F	Predose	-60 minutes
	From 1 up to ≤8 hours after study drug dosing	± 15 minutes

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

In Parts A, B, and C, the date and time of administration of the dose before the PK dose and date and time of the last meal before the PK dose will be recorded accurately in the source document. For each visit in Parts D, E, and F with a PK blood draw, a record of study drug administration will be collected as described in Section 9.6.2. For all parts, the collection date and exact time that each PK blood sample is drawn will also be recorded.

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

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.

In addition to the analysis using validated methods, PK samples may be used to assess potential metabolites of VX-445 by exploratory or validated methods.

11.4 Pharmacodynamics

11.4.1 Sweat Chloride (Parts [redacted] D, E, and F)

Collection of sweat samples will be performed in Parts [redacted] D, E, and F using an approved collection device.

[redacted] In Parts D, E, and F, there are no fasting requirements.

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 collection should occur at approximately the same time at every visit.

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, with the exception of the screening values in Parts D, E, and F.

Specific instructions for collection, handling, processing, and shipping of sweat chloride samples to the central laboratory will be provided separately. See Section 10.7.1.2 for information about blinding of sweat chloride results in Parts D, E, and F.

[redacted]

11.6 Efficacy (Parts D, E, and F)

11.6.1 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines/European Respiratory Society Guidelines[14] and the following additional guidelines:

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-bronchodilators. At all other visits, all spirometry assessments should be performed

"pre-bronchodilator." During the Treatment Period, spirometry assessments must be performed before the in-clinic dose of study drug, at approximately the same time at each visit. For subjects in Part E requiring a Day -14 Visit, spirometry may be performed postdose. An additional spirometry assessment will be performed 5 hours (± 1 hour) after study drug administration on the Day 1 and Day 15 Visits.

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

- If a subject's Day 1 spirometry assessment is pre-bronchodilator, but, on a subsequent visit, the subject forgets to withhold bronchodilator use, a post-bronchodilator spirometry assessment will be obtained for that visit only, and the visit will not be rescheduled.
- If, on Day 1, the subject forgets to withhold his/her dose of bronchodilator, spirometry should be performed post-bronchodilator, and all subsequent spirometric measurements 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.

See Section 10.7.1.2 for information about blinding of spirometry results.

The measured spirometric values listed below will be converted to percent predicted values using the GLI standards.[13]

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

11.6.2 Cystic Fibrosis Questionnaire-Revised

Subjects will be asked to complete the CFQ-R in their native language, if validated translations are available.[23,24] The CFQ-R will be completed before any other study assessments are performed at the study visit. The questionnaires provide information about demographics; general quality of life, school, work, or daily activities; and symptom difficulties (pertaining to CF). Copies of the CFQ-R will be provided in the Study Reference Manual. Validated translations of the CFQ-R, if available, will be provided for participating centers in non-English-speaking countries.[25, 26]

11.7 Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, ECGs, PEs, spirometry (Parts B, C, D, E, and F), and pulse oximetry (Parts D, E, and F).

11.7.1 Adverse Events

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

11.7.2 Clinical Laboratory Assessments

Parts A, B, and C: Blood and urine samples will be analyzed at a local laboratory. At the Screening Visit, blood specimens will be collected for safety laboratory tests following at least a 4-hour fast. Fasting is not required at other time points.

Parts D, E, and F: Blood and urine samples will be analyzed at a central laboratory, with the exceptions noted below. Fasting is not required.

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[a]	Urinalysis[b]
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen[c]	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 (TCO_2)	Basophils	Urine bilirubin
Phosphate	Neutrophils	Urine glucose
Total bilirubin	Lymphocytes	
Direct bilirubin	Monocytes	
Alkaline phosphatase	**Coagulation**	
Aspartate transaminase	Activated partial thromboplastin time	
Alanine transaminase	Prothrombin time	
Amylase	Prothrombin time International Normalized Ratio	
Lipase		
Gamma-glutamyl transferase		
Protein		
Albumin		
Creatine kinase		
Cholesterol		
Triglycerides		
Low-density lipoprotein-direct		
High-density lipoprotein		
Lactate dehydrogenase		
Haptoglobin[d]		

Note: Screening Visit blood draws for Parts A, B, and C will be done after a minimum 4-hour fast. All subsequent blood draws do not require fasting. Fasting is not required for Parts D, E, and F.

[a] Blood smears will be saved for future evaluation, if needed.

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

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

[d] Haptoglobin will be analyzed only if there is evidence of possible hemolysis as determined by the site.

Pregnancy (β-human chorionic gonadotropin) tests

Parts A, B, and C: serum samples will be analyzed at the local laboratory for all female subjects.

Parts D, E, and F: serum samples will be analyzed at the central laboratory for all females of childbearing potential. Urine pregnancy tests will be performed at the site. The urine pregnancy test must be negative before the first dose of study drug (Day 1 for Parts D1, D2, and F; Day -28 for Part E). Additional pregnancy tests may be required according to local regulations and/or requirements.

Follicle-stimulating Hormone, Screening Period only (All Parts): Blood sample for FSH will be measured for any suspected postmenopausal female with at least 12 months of continuous

spontaneous amenorrhea. Serum FSH levels must be within the postmenopausal reference range of the performing laboratory to be considered postmenopausal.

G6PD Activity Test, Screening Period only (All Parts): Blood samples will be collected for the G6PD activity test, which will be performed in an established laboratory that runs the assay routinely. For Parts D, E, and F, the use of a local laboratory that routinely runs quantitative G6PD activity assays is acceptable as an alternative to the central laboratory.

Serology (Parts A, B, and C): HBsAg, HCV antibody, HIV-1 and HIV-2 Abs, and p24 antigen will be tested for.

Drug and Alcohol Testing (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, Screening Period only (Parts D, E, and F): *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used to establish eligibility. Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9).

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

In Parts D, E, and F, for purposes of study conduct, the central laboratory must be used for all laboratory tests with the exceptions noted above. 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 (Section 3). At other visits, symptom-directed PEs and symptom-directed vital sign assessments can be performed at the discretion of the investigator or healthcare provider.

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

Parts D, E, and F only: 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 (oral), pulse rate, and respiration rate. These will be assessed following at least a 5-minute rest in the seated position.

11.7.4 Pulse Oximetry (Parts D, E, and F)

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

11.7.5 Electrocardiograms

11.7.5.1 Safety ECGs

Standard 12-lead ECGs will be performed using a machine with printout according to the Schedule of Assessments (Section 3). Additional standard 12-lead ECGs will be performed at any other time if clinically indicated.

The subject will be instructed to rest in the seated or supine position for at least 5 minutes before having an ECG performed.

The ECG traces will be manually read at the study site, as shown in Section 3. 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. Further details pertaining to ECGs will be provided to sites in a separate document (ECG Manual).

11.7.5.2 Continuous ECGs for Cardiodynamic Assessment (Part A, With the Exception of Cohort A7)

In Part A, continuous ECGs will be obtained per Table 3-2 using a continuous 12-lead digital recorder. 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 3-2 and will be read centrally. 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 the 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-445. If it is determined that the continuous ECG data will be analyzed, a separate analysis plan will be created for the evaluation of the ECG data, including the Cardiodynamic ECG Assessment and Concentration-QTc Analysis.

11.7.6 Spirometry (Parts B, C, D, E, and F)

Spirometry will be performed according to the American Thoracic Society Guidelines/European Respiratory Society Guidelines.[14]

11.7.7 Contraception and Pregnancy

The effects of VX-445, TEZ, IVA, and VX-561 on conception, pregnancy, and lactation in humans are not known. VX-445, TEZ, IVA, and VX-561 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, 12, 17, 27] Reproductive studies of VX-445, TEZ, and IVA have not shown teratogenicity in rats and rabbits.[11, 17, 27]

11.7.7.1 Contraception

Contraception requirement for the couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. True abstinence must be practiced from the Screening Visit through 90 days after the last dose of study drug.
- If the male is infertile (e.g., bilateral orchiectomy). If a male subject is assumed to have complete bilateral absence of the vas deferens, infertility must be documented before the first dose of study drug (e.g., examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound).
- If the female is of non-childbearing potential. To be considered of non-childbearing potential, the female must meet at least 1 of the following criteria:
  - Postmenopausal: Amenorrheic for at least 12 consecutive months and a serum FSH level within the laboratory's reference range for postmenopausal females.
  - Documented hysterectomy or bilateral oophorectomy/salpingo-oophorectomy.

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

- **For subjects for whom the contraception requirement is not waived,** study participation requires a commitment from the subject that at least 1 acceptable method of contraception is used as a couple. Methods of contraception must be in successful use from signing of consent, approximately 28 days before the first dose of study drug (unless otherwise noted), and until 90 days following the last dose of study drug. Additional contraception requirements may need to be followed according to local regulations and/or requirements. Acceptable methods of contraception are listed in Table 11-3.

Table 11-3 Acceptable Methods of Contraception

	All Study Subjects and Their Non-study Partners
Vasectomy 6 months or more previously, with a documented negative postvasectomy semen analysis for sperm	Yes
Bilateral tubal occlusion (e.g., ligation) performed at least 6 months previously.	Yes
Male or female condom with or without spermicide[a]	Yes
Female barrier contraception (such as diaphragm, cervical cap, or sponge) with spermicide	Yes
Continuous use of an intrauterine device for at least 90 days before the first dose of study drug.	Yes
Oral, implanted, injected, or vaginal hormonal contraceptives, if successfully used for at least 60 days before the first dose of study drug.	Yes

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

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.
- Female subjects should not nurse a child 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 must not plan to become pregnant during the study or within 90 days after the last study drug dose.

11.7.7.2 Pregnancy

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

If a female subject or the female partner of a male subject becomes pregnant during study participation, other than a female partner as the result of artificial insemination using sperm banked by the male subject before the first dose of study drug, 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

12.1.1 Parts A, B, and C

No formal sample size calculations have been performed. The number of subjects participating in each cohort is common in early clinical pharmacology studies and is considered sufficient to achieve the objectives of the study.

12.1.2 Parts D, E, and F

12.1.2.1 Primary Objectives

The primary objectives of Parts D, E, and F are the evaluation of safety and tolerability, and efficacy of VX-445 in TC with TEZ/IVA (Parts D and E) and in TC with TEZ/VX-561 (Part F) in subjects with CF. The sample size calculations described below are deemed adequate to evaluate the primary objectives, based on clinical and statistical considerations.

Safety and Tolerability

The primary safety endpoint is the incidence of AEs. Approximately 104 subjects with CF will be enrolled in the study with approximately 81 subjects receiving VX-445 in TC with either TEZ/IVA or TEZ/VX-561. The sample size for each treatment group will provide sufficient data for a descriptive analysis of AEs.

Efficacy

The primary efficacy endpoint is the absolute change from baseline in ppFEV$_1$ through Day 29 in Parts D, E, and F. A sample size of 18 subjects per treatment group provides at least 90% power to detect a mean change of 7 percentage points.

12.1.2.2 Secondary Objectives

A secondary objective of Parts D, E, and F is the evaluation of the PD effect of VX-445 in TC with TEZ/IVA (Parts D and E) and in TC with TEZ/VX-561 (Part F) in subjects with CF.

The absolute change from baseline through Day 29 in sweat chloride is a secondary endpoint used to evaluate the PD objective of the study. In Part D, a test for a decreasing dose-response trend between placebo and the TC dose groups will be performed using a multiple comparisons procedure (MCP). The procedure consists of testing the null hypothesis of the lack of a decreasing dose-response trend versus a decreasing trend using the 1-sided maximum *t*-statistic that controls the type I error at alpha = 5%. The procedure requires a family of candidate

dose-response models to be pre-specified that covers the range of plausible and diverse dose-response profiles.

The candidate models that best describe the expected decreasing dose-response profile of the TC groups compared to placebo include a linear model, a maximum effect (E_{max}) model, and a sigmoid E_{max} model. The contrasts (i.e., linear combinations of the treatment group means through Day 29) selected to perform the MCP and that capture the shape of these candidate models are described in Table 12-1.

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

Candidate Model	Placebo	TC-low	TC-mid	TC-high
Linear	3.0	1.0	-1.0	-3.0
E_{max}	3.0	-1.0	-1.0	-1.0
Sigmoid E_{max}	1.0	1.0	-1.0	-1.0

E_{max}: maximum effect; TC: triple combination (VX-445/TEZ/IVA)

A total sample size of 56 subjects in Part D will provide at least 90% power to detect a dose-response trend with MCP.

12.2 Analysis Sets

12.2.1 Parts A, B, and C

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.

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.

The **Pharmacokinetic 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.

[redacted]

12.2.2 Parts D, E, and F

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

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

The **FAS** will include all randomized subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug. The FAS will be used to summarize subject demographics and baseline characteristics, and for all PD and efficacy analyses, unless otherwise specified. Subjects will be analyzed according to the treatment group they were randomized to.

The **Safety Set** will include all subjects who received at least 1 dose of study drug. The Safety Set will be used for all safety analyses, unless otherwise specified. Subjects will be analyzed according to the treatment they received. If a subject received at least 1 dose of a higher dose TC treatment, the subject will be analyzed in the higher dose TC treatment group. For the purpose of analysis, the priority order of increasing study drug treatment will be defined as placebo, TC-low, TC-mid, and TC-high.

12.3 Statistical Analysis

12.3.1 General Considerations

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

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

The **baseline** value, unless otherwise specified, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the Treatment Period (i.e., Day 1 of Treatment Period for Parts A, B, and C or Day 1 of Period 1 for Parts D, E, and F). For ECG, baseline will be defined as the most recent pretreatment measurement (or the average of triplicate measurements, if the most recent pretreatment measurement is obtained in triplicate) before the first dose of study drug in the Treatment Period (i.e., Day 1, as described above).

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

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

Parts D, E, and F Only

The Treatment-emergent (TE) Period will include the time from the first dose in Period 1 to the Safety Follow-up Visit or 28 days after the last dose of the study drug for subjects who do not complete the Safety Follow-up Visit. An additional TE period related to the Run-in Period in Part E will be defined in the SAP, as appropriate. Only data collected through the end of the study will be included for analysis.

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

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

All data will be summarized for Parts D, E, and F separately, unless specified otherwise.

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

Parts A, B, and C

The number and percentage of subjects in each disposition category (e.g., randomized, included in Safety Set, included in PK Set, PD Set, completed Treatment Period, completed the Safety Follow-up Visit, and discontinued study with a breakdown of the reasons for discontinuation) will be summarized for the All Subjects Set.

Parts D, E, and F

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

12.3.2.2 Demographics and Baseline Characteristics

Parts A, B, and C

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

Parts D, E, and F

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

The following demographics and baseline characteristics will be summarized overall and by treatment group for the FAS and will include (but are not limited to): sex, race, age, baseline weight, baseline height, baseline BMI, baseline ppFEV$_{1,}$ and baseline sweat chloride.

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

12.3.2.3 Prior and Concomitant Medications

Parts A, B, and C

Medications will be coded using the World Health Organization-Drug Dictionary Enhanced (WHO-DDE) and categorized as the following for the purpose of analysis:

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.

Parts D, E, and F

Medications used in this study will be coded using the WHO-DDE and categorized as the following for the purpose of analysis:

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

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

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

An additional classification of concomitant medications related to the Run-in Period in Part E will be defined in the SAP, as appropriate.

12.3.2.4 Study Drug Exposure and Compliance

Parts A, B, and C

Exposure to study drug in Parts B and C (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 B and C only.

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

Parts D, E, and F

Exposure to study drug 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.

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

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

12.3.2.5 Important Protocol Deviations (Parts D, E, and F Only)

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

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

12.3.3 Efficacy Analysis (Parts D, E, and F Only)

12.3.3.1 Analysis of Primary Variables

The primary efficacy variable is the absolute change from baseline for $ppFEV_1$ through Day 29 in Parts D, E, and F. The analysis will be performed using a mixed-effects model for repeated measures (MMRM) with change from baseline as the dependent variable. The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects, subject as random effect, and the continuous baseline $ppFEV_1$ as a covariate. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the F test for fixed effects will be estimated using the Kenward-Roger approximation. An unstructured covariance structure will be used to model the within-subject errors. If the model estimation does not converge, a compound symmetry covariance structure will be used. Conditional on observed data and covariates, missing data due to treatment or study discontinuation will be assumed to be missing at random.

Adjusted means and 95% confidence intervals of the average treatment effects through Day 29, as applicable, with 2-sided *P* values, will be estimated within MMRM using LSMeans via PROC MIXED in SAS, for all within-group and between-group comparisons in both parts.

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

Additional supportive analyses utilizing the Washout Period in Part E to compare treatment groups will be described in the SAP. Subgroup analyses will also be described in the SAP.

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

12.3.3.2 Analysis of Secondary Efficacy Variables

The secondary efficacy variables are relative change in $ppFEV_1$ from baseline through Day 29 and absolute change in the CFQ-R respiratory domain score from baseline at Day 29. Analysis of secondary efficacy variables will be similar to that performed for the primary efficacy variable. Additional details of these analyses will be provided in the SAP.

12.3.4 Pharmacodynamic Analysis

Dose-response Analysis

The absolute change in sweat chloride from baseline through Day 29 is a secondary endpoint used to evaluate the PD objective of the study. The test to detect a decreasing dose-response trend (in Part D) of VX-445 at 3 doses in TC with TEZ/IVA relative to placebo based on sweat chloride, will be performed using the MCP procedure with the pre-specified comparisons (contrasts) of the treatment group means within an MMRM framework. The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects, with the continuous baseline sweat chloride as a covariate. The test will be performed using the 1-sided maximum

t-statistic of the individual *t*-statistics for the multiple pre-specified contrasts at alpha = 5%, based on the treatment group means through Day 29 in Part D.

Estimation of Treatment Effects

In a separate MMRM model, adjusted means and 95% confidence intervals of the average treatment effects through Day 29, with 2-sided *P* values, for all within-group and between-group comparisons for each part, separately, will be estimated within MMRM, with appropriate adjustment for covariates.

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

12.3.5 Safety Analysis

Parts A, B, and C

The overall safety profile of VX-445 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 (Parts B and C)

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.

Parts D, E, and F

All safety analyses will be based on data from the TE Period for all subjects in the Safety Set.

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

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

All safety data will be summarized by treatment group and overall, for each Part.

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

12.3.5.1 Adverse Events

12.3.5.1.1 Parts A, B, and C

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 and Preferred Term. 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.

Treatment-emergent AEs are defined as AEs that were reported or worsened on or after the start of study drug dosing through the Safety Follow-up Visit.

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, 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.

12.3.5.1.2 Parts D, E, and F

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

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

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

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

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

Summaries will be presented by MedDRA System Organ Class and Preferred Term using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once, only the maximum severity level will be presented in the severity summaries, and the strongest relationship level in the relationship summaries. In addition, a listing containing individual subject level AE data for all deaths and other serious and significant AEs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

12.3.5.2 Clinical Laboratory Assessments

12.3.5.2.1 Parts A, B, and C

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. A listing of abnormal individual subject hematology and clinical chemistry values from scheduled and unscheduled time points will be provided. 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.

12.3.5.2.2 Parts D, E, and F

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

The number and percentage of subjects meeting a threshold analysis criterion during the TE Period will be summarized overall and by treatment group for each part. The threshold analysis criterion shift from baseline will also be summarized for selected laboratory parameters. The threshold analysis criteria and the parameter selection criteria will be provided in the SAP.

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

12.3.5.3 Electrocardiogram

12.3.5.3.1 Parts A, B, and C

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 (HR). 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.

Cardiodynamic ECG Assessment (Part A Only, With the Exception of Cohort A7)

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.

12.3.5.3.2 Parts D, E, and F

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

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

Additional ECG analyses will be described in the SAP.

12.3.5.4 Vital Signs

12.3.5.4.1 Parts A, B, and C

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

12.3.5.4.2 Parts D, E, and F

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

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

Additional vital signs analyses will be described in the SAP.

12.3.5.5 Pulse Oximetry (Parts D, E, and F)

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

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

12.3.5.6 Physical Examination

PE results will be presented in individual subject data listings only.

12.3.5.7 Spirometry (Parts B, C, D, E, and F)

The spirometry assessment will be administered in Parts B, C, D, E, and F. The following parameters of FEV_1 (L), FVC (L), FEV_1/FVC (ratio), $FEF_{25\%-75\%}$ (L/s), and the corresponding percent predicted values based on the GLI equations will be summarized using descriptive statistics.

12.3.6 Interim and IDMC Analyses

12.3.6.1 Interim Analysis

12.3.6.1.1 Parts A, B, and C

An IA of the continuous ECG data may be performed after all subjects in Part A (with the exception of Cohort A7) have completed the Safety Follow-up Visit. See Section 12.3.5.3.1.

These interim results will be reviewed by a small unblinded Vertex team.

An IA for Parts A, B, and C may be performed after all subjects in Part C have completed the Safety Follow-up Visit. The results of this analysis will be unblinded for full review by the Vertex study team.

12.3.6.1.2 Parts D, E, and F

IAs for each part (D1, D2, E, and F) may be performed after at least 50% of subjects in the part have completed the Day 15 Visit. The results of these analyses will be reviewed by a limited Vertex team. When an IA is performed after all subjects in a part have completed the Safety Follow-up Visit, results from that part will be unblinded for full review by the Vertex study team.

12.3.6.2 IDMC Analysis (Parts D, E, and F)

Details of the safety reviews will be described in the IDMC Charter. The IDMC Chair will review available safety and PK data from Parts A, B, and C of the study prior to commencement of dosing in Part D1 to determine if it is appropriate to proceed with the study.

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

12.4.1.1 Parts A, B, and C

The PK parameters of VX-445 (all parts), TEZ and metabolites (Part C only), and IVA and metabolites (Part C only) 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.

12.4.1.2 Parts D, E, and F

The PK analysis of VX-445, TEZ and metabolite M1-TEZ, IVA and metabolite M1-IVA, and VX-561 and metabolites, if assessed, will be performed using nonlinear mixed effects modeling. Standard noncompartmental analysis may also be performed as data allow. Descriptive statistics will be used to summarize PK parameter values for all analytes.

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

[redacted]

12.4.3 Pharmacokinetic/Pharmacodynamic Analyses

[redacted]

12.4.3.2 Parts D, E, and F

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

A sequential approach will be used to perform the population PK/PD analysis. The Bayesian estimates of individual PK parameters from the final population PK model will be used to simulate PK profiles for each subject. The simulated VX-445, TEZ, IVA, VX-561, or metabolite plasma concentrations will be used in the potential pharmacological response models to describe changes in each endpoint from baseline. Fixed- and random-effect parameter estimates and the associated asymptotic SEs will be estimated. Descriptive statistics will be used to summarize Bayesian estimates of individual PK/PD parameters obtained from the population PK/PD model.

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

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 Parts D, E, and F 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 9.1.2.7)

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 October 2016). 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 Parts D, E, and F

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 August 2015). 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 13-1.

13.1.1.5 Adverse Event Causality

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

Table 13-2 Classifications for AE Causality

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

13.1.1.6 Study Drug Action Taken

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

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

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

13.1.1.7 Adverse Event Outcome

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

Table 13-4 Classifications for Outcome of an AE

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

13.1.1.8 Treatment Given

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

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

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

- Fatal (death, regardless of cause, that occurs during participation in the study or occurs after participation in the study and is suspected of being a delayed toxicity due to administration of the study drug)
- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred
- Inpatient hospitalization or prolongation of hospitalization

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

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

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

13.1.2.2 Documentation of Serious Adverse Events

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

SAEs will be recorded on the Vertex Organized Safety Information Collection Form (hereafter referred to as the “SAE Form”) using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the investigator for relationship to the investigational study drug(s) and possible etiologies. On the 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]

Fax: [redacted]

Contact Telephone: [redacted]

13.1.2.4 Expedited Reporting and Investigator Safety Letters

Vertex, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities, 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 independent ethics committees (IECs).

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

13.2 Administrative Requirements

13.2.1 Ethical Considerations

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

13.2.2 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject before study participation. The method of obtaining and documenting the informed consent and 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

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

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

13.2.6 Record Retention

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

13.2.7 Study Termination

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

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

- Subject or investigator noncompliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures

- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by the FDA or other regulatory authority

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

13.3 Data Quality Assurance

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

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant.

13.3.1 Parts A, B, and C

Data collected during the study, including results from screening, will be recorded in the enrolled subject's CRF. Each CRF book, once completed, will be signed and dated by the investigator.

13.3.2 Parts D, E, and F

Study data for each enrolled subject will be entered into a CRF by study site personnel using a secure, validated, web-based electronic data capture (EDC) application. Vertex will have read-only access to site-entered clinical data in the EDC application.

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

13.4 Monitoring

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

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

13.5 Data Capture (Parts A, B, and C)

A CRF book will be provided for each subject. All appropriate subject data gathered during the study will be recorded on these forms. The forms will be filled out with either a black or blue ballpoint pen. All corrections will be made by drawing a single line through the error and writing the correct information next to the change. All corrections will be initialed and dated. Correction fluid will not be used to correct an error. CRFs will be completed for each randomized 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 reporting 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.

13.6 Electronic Data Capture (Parts D, E, and F)

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

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

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

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

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

13.7 Publications and Clinical Study Report

13.7.2 Clinical Study Report

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

14 REFERENCES

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APPENDIX A *CFTR* Mutations That Are Predicted to Result in a CFTR Protein With Minimal Function (Parts D and F)

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

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

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

The list below represents acceptable mutations, which are detectable by an FDA-cleared genotyping assay; 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 VX16-445-001, Parts D and F

Criteria	Mutation				
Truncation mutations • %PI >50% and/or $SwCl^-$ >86 mmol/L • no full-length protein	S4X	C276X	G542X	R792X	E1104X
	G27X	Q290X	G550X	E822X	R1158X
	Q39X	G330X	Q552X	W846X	R1162X
	W57X	W401X	R553X	Y849X	S1196X
	E60X	Q414X	E585X	R851X	W1204X
	R75X	S434X	G673X	Q890X	L1254X
	E92X	S466X	Q685X	S912X	S1255X
	Q98X	S489X	R709X	Y913X	W1282X
	Y122X	Q493X	K710X	W1089X	Q1313X
	E193X	W496X	L732X	Y1092X	E1371X
	L218X	C524X	R764X	W1098X	Q1382X
	Q220X	Q525X	R785X	R1102X	Q1411X
Splice mutations • %PI >50% and/or $SwCl^-$ >86 mmol/L • no or little mature mRNA	185+1G→T	711+5G→A	1717-8G→A	2622+1G→A	3121-1G→A
	296+1G→A	712-1G→T	1717-1G→A	2790-1G→C	3500-2A→G
	405+1G→A	1248+1G→A	1811+1G→C	3040G→C (G970R)	3600+2insT
	405+3A→C	1249-1G→A	1811+1.6kbA→G		3850-1G→A
	406-1G→A	1341+1G→A	1812-1G→A	3120G→A	4005+1G→A
	621+1G→T	1525-2A→G	1898+1G→A	3120+1G→A	4374+1G→T
	711+1G→T	1525-1G→A	1898+1G→C	3121-2A→G	
Small (≤3 nucleotide) insertion/deletion (ins/del) frameshift mutations • %PI >50% and/or $SwCl^-$ >86 mmol/L • garbled and/or truncated protein	182delT	1119delA	1782delA	2732insA	3876delA
	306insA	1138insG	1824delA	2869insG	3878delG
	365-366insT	1154insTC	2043delG	2896insAG	3905insT
	394delTT	1161delC	2143delT	2942insT	4016insT
	442delA	1213delT	2183AA→G [a]	2957delT	4021dupT
	444delA	1259insA	2184delA	3007delG	4040delA
	457TAT→G	1288insTA	2184insA	3028delA	4279insA
	541delC	1471delA	2307insA	3171delC	4326delTC
	574delA	1497delGG	2347delG	3659delC	
	663delT	1548delG	2585delT	3737delA	
	935delA	1609del CA	2594delGT	3791delC	
	1078delT	1677delTA	2711delT	3821delT	
Non-small (>3 nucleotide) insertion/deletion (ins/del) frameshift mutations • %PI >50% and/or $SwCl^-$ >86 mmol/L • garbled and/or truncated protein	CFTRdele2,3	1461ins4	2991del32		
	CFTRdele22,23	1924del7	3667ins4		
	124del23bp	2055del9→A	4010del4		
	852del22	2105-2117del13insAGAAA	4209TGTT→AA		
	991del5	2721del11			

CFTR Mutations Eligible for VX16-445-001, Parts D and F

Criteria	Mutation			
Class II, III, IV mutations not responsive to IVA alone or in combination with TEZ or LUM • %PI>50% and/or $SwCl^-$ >86 mmol/L AND • Not responsive in vitro to IVA alone or in combination with TEZ or LUM	A46D[b]	V520F	Y569D[b]	N1303K
	G85E	A559T[b]	L1065P	
	R347P	R560T	R1066C	
	L467P[b]	R560S	L1077P[b]	
	I507del	A561E	M1101K	

CFTR: cystic fibrosis transmembrane conductance regulator; IVA: ivacaftor; LUM: lumacaftor; PI: pancreatic insufficiency; $SwCl^-$: 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 February 2016.

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

[a] Also known as 2183delAA→G.

[b] Unpublished data.

15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX16-445-001	Version #: 7.0	Version Date: 8 August 2017
Study Title: A Phase 1/2 Study of VX-445 in Healthy Subjects and Subjects With Cystic Fibrosis		

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

[redacted]

15.2 Investigator Signature Page

Protocol #: VX16-445-001	Version #: 7.0	Version Date: 8 August 2017
Study Title: A Phase 1/2 Study of VX-445 in Healthy Subjects and Subjects With Cystic Fibrosis		

I have read Protocol VX16-445-001, Version 7.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-445, tezacaftor, ivacaftor, and VX-561 (CTP-656) and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date