1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety and Efficacy of VX-121 Combination Therapy in Subjects Aged 18 Years and Older With Cystic Fibrosis

Vertex Study Number: VX18-121-101

EudraCT Number: 2018-002496-18

Date of Protocol: 09 May 2019 (Version 4.0)
Replaces Version 3.0, dated 04 March 2019

Vertex Pharmaceuticals Incorporated
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2 PROTOCOL SYNOPSIS

Title A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety and Efficacy of VX-121 Combination Therapy in Subjects Aged 18 Years and Older With Cystic Fibrosis

Brief Title A Study to Evaluate the Safety and Efficacy of VX-121 Combination Therapy in Subjects With Cystic Fibrosis

Clinical Phase and Clinical Study Type Phase 2, safety and efficacy

Objectives

Primary Objectives

Parts 1 (Subjects with F/MF genotypes) and 2 (Optional; Subjects with the F/F genotype)

- To evaluate the safety and tolerability of VX-121 in triple combination (TC) with tezacaftor (TEZ)/VX-561 (deuterated ivacaftor [IVA])
- To evaluate the efficacy of VX-121 in TC with TEZ/VX-561

[redacted]

Secondary Objectives

Parts 1 and 2

- To evaluate the pharmacodynamic (PD) effect of VX-121 in TC with TEZ/VX-561
- To evaluate the pharmacokinetics (PK) of VX-121 when administered in TC with TEZ/VX-561
- To evaluate the PK of TEZ, VX-561, and their respective metabolites when administered in TC with VX-121

[redacted]

Endpoints

Primary Endpoints

- Safety and tolerability, based on the assessment of adverse events (AEs), laboratory test results, standard 12-lead ECGs, vital signs, and spirometry
- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline through Day 29

Secondary Endpoints

- Absolute change in sweat chloride concentrations 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-121, TEZ, VX-561, [redacted] and relevant metabolites

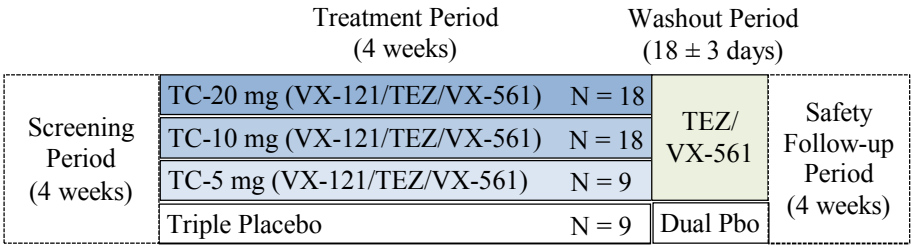
[redacted]

Number of Subjects	Approximately 108 subjects (including optional parts): 54 in Part 1, 27 in Part 2, [redacted]
Study Population	**Parts 1** [redacted] Male subjects and female subjects with cystic fibrosis (CF), heterozygous for *F508del* and a minimal *CFTR* function mutation that is not responsive to TEZ, IVA, or TEZ/IVA (F/MF genotypes), ages 18 and older **Part 2**: Male subjects and female subjects with CF, homozygous for *F508del* (F/F genotype), ages 18 and older
Investigational Drug	**Active substance**: VX-121 **Activity**: CFTR corrector (increased Cl^- secretion) **Strength and route of administration**: 5-mg tablet for oral administration **Active substance**: TEZ (VX-661) **Activity**: CFTR corrector (increased Cl^- secretion) **Strength and route of administration**: 50-mg TEZ tablet for oral administration **Active substance**: VX-561 **Activity**: CFTR potentiator (increased Cl^- secretion) **Strength and route of administration**: 50-mg VX-561 tablet for oral administration **Active substance**: TEZ (VX-661) and IVA (VX-770) **Activity**: CFTR corrector and potentiator (increased Cl^- secretion) **Strength and route of administration**: 100-mg TEZ/150-mg IVA, film-coated fixed-dose combination (FDC) tablet for oral administration **Active substance**: IVA (VX-770) **Activity**: CFTR potentiator (increased Cl^- secretion) **Strength and route of administration**: 150-mg film-coated tablet for oral administration
Study Duration	Excluding the Screening Period, the study duration for each subject is 9 to 11 weeks for Parts 1 [redacted] and 15 to 17 weeks for Part 2.
Study Design	This is a Phase 2, [redacted] randomized, double-blind, placebo- and TEZ/IVA-controlled, proof-of-concept study of VX-121. Study parts may be conducted in parallel or sequentially. Randomization will be stratified by $ppFEV_1$. Schematics of the study design are shown in Figure 2-1, Figure 2-2, [redacted] **Part 1: Subjects with F/MF genotypes** Part 1 evaluates VX-121 in TC with TEZ/VX-561 as shown in Figure 2-1. The Washout Period (18 ± 3 days) is included to enable a more thorough evaluation of VX-121 exposure-response relationships by conducting PK and PD assessments during the VX-121 washout.

Planned Doses

- TC-5 mg is optional. The planned VX-121 doses of 5 mg, 10 mg, and 20 mg qd may be adjusted based on emerging data from subjects with CF in Part D of Study VX17-121-001 (Study 001). However, no more than 3 dose levels of VX-121 will be evaluated, and the highest dose will not exceed 20 mg qd.
- The dosage of TEZ and VX-561 will be TEZ 100 mg daily (qd) and VX-561 150 mg qd.

Figure 2-1 VX18-121-101 Study Design for Part 1 (F/MF Genotypes)



Part 2 (Optional): Subjects with F/F genotype

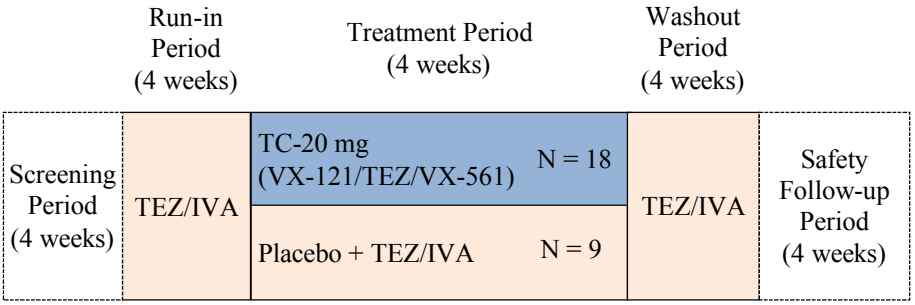
Part 2, an optional part of the study, which will be conducted at the sponsor's discretion, evaluates VX-121 in TC with TEZ/VX-561 as shown in Figure 2-2.

All subjects are required to complete the TEZ/IVA Run-in Period to establish a reliable on-treatment (TEZ/IVA) baseline. The 4-week Washout Period is included to evaluate the effect on PD and efficacy endpoints as subjects step down from TC to TEZ/IVA, after the VX-121 washout.

Planned Doses

- Part 2 will evaluate the same VX-121 dose (20 mg qd) used in Part 1. This dose may be adjusted downward based on emerging data from Part D of Study 001.
- The dosage of TEZ and VX-561 will be TEZ 100 mg qd and VX-561 150 mg qd.
- The dosage of TEZ/IVA will be TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h).

Figure 2-2 VX18-121-101 Study Design for Part 2 (F/F Genotype)



[redacted]

[redacted]

Assessments

Safety: AEs, clinical laboratory assessments, clinical evaluation of vital signs, ECGs, physical examinations, spirometry

Efficacy: Spirometry, CFQ-R respiratory domain

PD: Sweat chloride

PK: VX-121, TEZ, VX-561, [redacted], and relevant metabolites

[redacted]

Statistical Analyses

A sample size of 18 subjects per treatment group provides at least 90% power to detect a mean within-treatment change of 7 percentage points. These calculations assumed a standard deviation of 8 percentage points for the absolute change from baseline in $ppFEV_1$.

To analyze the absolute change from baseline in $ppFEV_1$ through Day 29, a primary endpoint in Parts 1, 2, [redacted] a mixed-effects model for repeated measures (MMRM) with change from baseline for $ppFEV_1$ at Days 15 and 29 as the dependent variable will be performed for each part. 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% CIs of the average treatment effects through Day 29 for all within-group comparisons will be estimated within MMRM. *P* values will also be provided for these comparisons. All $ppFEV_1$ hypothesis tests will be performed within the MMRM framework at a 5% alpha level, with appropriate adjustment for baseline covariates.

P values reported for all endpoints other than the primary endpoint should be considered nominal as no adjustment for multiplicity will be performed.

Descriptive analyses will be provided for the safety data comprising AEs, clinical laboratory assessments, ECGs, vital signs, and spirometry; no statistical hypothesis testing will be performed. The PK results for VX-121, TEZ, VX-561, [redacted] and relevant metabolites will be reported with descriptive statistics.

IDMC Reviews

An independent data monitoring committee (IDMC) will conduct safety reviews of study data as outlined in the IDMC charter.

3 SCHEDULE OF ASSESSMENTS

Schedules of assessments are in Table 3-1, Table 3-2, [redacted]

Table 3-1 Study VX18-121-101: Part 1, Screening, Treatment Period, Washout Period, and Safety Follow-up Visit

Event/Assessment[a]	Screening Visit[b]	Treatment Period					Washout Visit	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose of Study Drug[d]
	Day -28 to Day -1	Day 1	Day 2[e]	Day 8 (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 47 (± 3 days)		
Outpatient visits	X	X	X	X	X	X	X	X	X
Informed consent	X								
Randomization[f]		X							
Demographics	X								
Medical history	X								
CFQ-R[g,h]		X			X	X			
Weight[i]	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	Abbrev.		Abbrev.	Abbrev.	Abbrev.		Complete	Complete
Standard 12-lead ECG[l]	X	X		X	X	X		X	X
Sweat chloride[h,m]	X	X			X	X	X[n]	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., premature discontinuation of study drug treatment).

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

[c] If the subject prematurely discontinues study drug, an ETT Visit should be scheduled as soon as possible after the decision to terminate study drug treatment (Section 9.1.6). A final PK sample will be drawn from subjects who discontinue study drug for any reason (except withdrawal of consent). Safety assessments may also be performed at the discretion of the investigator..

[d] Study drug refers to VX-121, TEZ, VX-561, and matching placebos.

[e] Approximately 20 subjects enrolled in the study will have spirometry performed at 24 hours (± 2 hours) after the first dose. Only subjects participating in this spirometry assessment are required to complete the Day 2 Visit; this assessment should be performed predose on Day 2. Vertex will work with study sites to manage the allocation of subjects participating in the 24-hour postdose spirometry assessment. See Section 11.5.1 for more details.

[f] Randomization may occur on the previous day (Day -1) after eligibility has been confirmed.

[g] The CFQ-R must be completed before any other assessments scheduled at relevant visits.

[h] The predose assessment on Day 1 may be performed on the previous day (Day -1) 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 at rest for at least 5 minutes (Sections 11.6.3 and 11.6.4).

[k] Complete and abbreviated PEs are described in Section 11.6.3.

[l] Standard 12-lead ECGs will be performed in the supine position after the subject has been at rest for at least 5 minutes (Section 11.6.5). The ECG will be done before any other procedures that may affect heart rate, such as blood draws. ECGs collected on Day 1 before dosing will be performed in triplicate.

[m] See Section 8.1 for information about the sweat chloride assessment for study eligibility.

[n] Sweat chloride and ppFEV$_1$ assessments should be done within 2 hours before study drug dosing in the morning (Sections 11.3 and 11.5.1).

Table 3-1 Study VX18-121-101: Part 1, Screening, Treatment Period, Washout Period, and Safety Follow-up Visit

Event/Assessment[a]	Screening Visit[b]	Treatment Period					Washout Visit	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose of Study Drug[d]
	Day -28 to Day -1	Day 1	Day 2[e]	Day 8 (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 47 (± 3 days)		
Spirometry[o]	X	X	X	X	X	X	X[n]	X	X
Urinalysis[h]	X	X		X	X	X		X	X
[redacted]									
β-hCG[q]	serum	urine				urine		serum	serum
CFTR genotype[r]	X								
FSH[s]	X								
[redacted]									
Serum chemistry and hematology[h]	X	X		X	X	X		X	X
Coagulation[h]	X	X		X	X	X		X	X
[redacted]									
PK sampling[u]		X	X	X	X	X	X	X	

[o] Spirometry may be performed pre- or post-bronchodilator at the Screening Visit. Spirometry will be performed pre-bronchodilator, before the morning dose of study drugs, and should be performed at approximately the same time at every other study visit.

[redacted]

[q] The serum β-hCG test is to be performed for all female subjects at screening. Subsequent urine or serum β-hCG tests are to be performed as indicated for women of childbearing potential. A definition of non-childbearing potential is provided in Section 11.6.7.1.

[r] *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used to establish eligibility (Section 8.1).

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

[redacted]

[u] Blood samples will be collected for PK analysis of VX-121, TEZ and metabolites, and VX-561 and metabolites. On Day 1, samples will be collected before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing (relative to the morning dose). Samples will also be collected at 24 hours after dosing on Day 1 (i.e., predose on Day 2) for subjects participating in the Day 2 Visit (see Footnote e). On Days 8, 15, and 29, a predose sample will be collected before the morning dose of study drug (0 hours). On Day 47, a single predose sample will be collected before study drug dosing in the morning. Acceptable PK sampling windows are provided in Table 11-1. At the ETT Visit, a single blood sample for PK analysis will be collected.

Table 3-1 Study VX18-121-101: Part 1, Screening, Treatment Period, Washout Period, and Safety Follow-up Visit

Event/Assessment[a]	Screening Visit[b]	Treatment Period					Washout Visit	ETT Visit[c]	Safety Follow-up 28 (± 7) Days After Last Dose of Study Drug[d]
	Day -28 to Day -1	Day 1	Day 2[e]	Day 8 (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 47 (± 3 days)		
TEZ/VX-561 or placebo dosing[v]		Day 1 through Washout Visit							
VX-121 or placebo dosing[w]		Day 1 through Day 29							
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit								
Medications review[x]	Continuous from signing of ICF through Safety Follow-up Visit								
Treatment and procedures review	Continuous from signing of ICF through Safety Follow-up Visit								

[v] The last dose of study drug will be the morning dose at the Washout Visit.
[w] The last dose of study drug will be the morning dose on the Day 29 Visit.
[x] All medications taken from 28 days before the Screening Period through the end of the study will be recorded.

Table 3-2 Study VX18-121-101: Part 2 (Optional), Screening, Run-in Period, Treatment Period, Washout Period, and Safety Follow-up Visit

Event/Assessment[a]	Screening Visit[b]	Run-in Period		Treatment Period[c]				Washout Period		ETT Visit[d]	Safety Follow-up 28 (± 7) Days After Last Dose of Study Drug[e,f]
	Day -56 to Day -29	Day -28 (± 1 day)	Day -14[g] (+ 13 days)	Day 1	Day 8 (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	Day 57 (± 3 days)		
Outpatient visits	X	X	X	X	X	X	X	X	X	X	X
Informed consent	X										
Randomization[h]				X							
Demographics	X										
Medical history	X										
CFQ-R[i,j]				X		X	X		X		
Weight[k]	X	X		X	X	X	X	X	X	X	X
Height[k]	X										
Vital signs[l]	X	X		X	X	X	X	X	X	X	X
Pulse oximetry[l]	X	X		X	X	X	X	X	X	X	X
Physical examination[m]	Complete	Abbrev.		Abbrev.	Abbrev.	Abbrev.	Abbrev.		Abbrev.	Complete	Complete
Standard 12-lead ECG[n]	X	X		X	X	X	X	X	X	X	X
Sweat chloride[j,o]	X		X	X		X	X	X[p]	X[p]	X	
Spirometry[q]	X		X[r]	X	X	X	X	X[p]	X[p]	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., premature discontinuation of study drug treatment).

[b] All screening results must be reviewed before the Run-in Period.

[c] To qualify to continue into the Treatment Period, conditions for entry must be satisfied (Section 9.1.3).

[d] If the subject prematurely discontinues study drug, an ETT Visit should be scheduled as soon as possible after the decision to terminate study drug treatment (Section 9.1.6). A final PK sample will be drawn from subjects who discontinue study drug for any reason (except withdrawal of consent). Safety assessments may also be performed at the discretion of the investigator.

[e] Part 2 subjects who meet criteria specified in Section 9.1.5 will not have a Safety Follow-up Visit.

[f] Study drug refers to VX-121, TEZ, VX-561, TEZ/IVA, IVA, and matching placebos.

[g] Assessments at this visit may be performed postdose.

[h] Randomization may occur on the previous day (Day -1) after all conditions for entering the Treatment Period have been confirmed (Section 9.1.3).

[i] The CFQ-R must be completed before any other assessments scheduled at relevant visits.

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

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

[l] Vital signs and pulse oximetry will be collected after the subject has been at rest for at least 5 minutes (Sections 11.6.3 and 11.6.4).

[m] Complete and abbreviated PEs are described in Section 11.6.3.

[n] Standard 12-lead ECGs will be performed in the supine position after the subject has been at rest for at least 5 minutes (Section 11.6.5). The ECG will be done before any other procedures that may affect heart rate, such as blood draws. ECGs collected on Day 1 before dosing will be performed in triplicate.

[o] See Section 8.1 for information about the sweat chloride assessment for study eligibility.

[p] Sweat chloride and ppFEV$_1$ assessments should be done within 2 hours before study drug dosing in the morning (Sections 11.3 and 11.5.1).

[q] Spirometry may be performed pre- or post-bronchodilator at the Screening Visit. Spirometry will be performed pre-bronchodilator, before the morning dose of study drugs (except at the Day -14 Visit when spirometry may be performed postdose), and should be performed at approximately the same time at every other study visit. See Section 11.5.1 for more details.

Table 3-2 Study VX18-121-101: Part 2 (Optional), Screening, Run-in Period, Treatment Period, Washout Period, and Safety Follow-up Visit

Event/Assessment[a]	Screening Visit[b]	Run-in Period		Treatment Period[c]				Washout Period		ETT Visit[d]	Safety Follow-up 28 (± 7) Days After Last Dose of Study Drug[e,f]
	Day -56 to Day -29	Day -28 (± 1 day)	Day -14[g] (+ 13 days)	Day 1	Day 8 (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	Day 57 (± 3 days)		
Urinalysis[j]	X	X		X	X	X	X	X	X	X	X
[redacted]											
β-hCG[t]	serum	urine		urine			urine		urine	serum	serum
CFTR genotype[u]	X										
FSH[v]	X										
[redacted]											
Serum chemistry and hematology[j]	X	X		X	X	X	X	X	X	X	X
Coagulation[j]	X	X		X	X	X	X			X	X
[redacted]											

[r] The ppFEV$_1$ assessment for stratification of randomization will be done at the Day -14 Visit. See Section 9.1.2 and Section 9.2.

[redacted]

[t] The serum β-hCG test is to be performed for all female subjects at Screening. Subsequent urine or serum β-hCG tests are to be performed as indicated for women of childbearing potential. A definition of non-childbearing potential is provided in Section 11.6.7.1.

[u] *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before the Run-in Period, a previous *CFTR* genotype laboratory report may be used to establish eligibility (Section 8.1).

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

[redacted]

Table 3-2 Study VX18-121-101: Part 2 (Optional), Screening, Run-in Period, Treatment Period, Washout Period, and Safety Follow-up Visit

Event/Assessment[a]	Screening Visit[b]	Run-in Period		Treatment Period[c]				Washout Period		ETT Visit[d]	Safety Follow-up 28 (± 7) Days After Last Dose of Study Drug[e,f]
	Day -56 to Day -29	Day -28 (± 1 day)	Day -14[g] (+ 13 days)	Day 1	Day 8 (± 1 day)	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	Day 57 (± 3 days)		
PK sampling[x]				X	X	X	X	X	X	X	
TEZ/IVA dosing[y]		Day -28 to evening on Day -1						Evening of Day 29 through Day 57			
VX-121/TEZ/VX-561 or TEZ/IVA dosing[z]				Day 1 through Day 29							
Adverse events	Continuous from signing of ICF through Safety Follow-up Visit										
Medications review[aa]	Continuous from signing of ICF through Safety Follow-up Visit										
Treatment and procedures review	Continuous from signing of ICF through Safety Follow-up Visit										

[x] Blood samples will be collected for PK analysis of VX-121, TEZ and metabolites, and VX-561 and metabolites. On Day 1, samples will be collected before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing (relative to the morning dose). On Days 8, 15, and 29, a predose sample will be collected before the morning dose of study drug (0 hours). On Days 43 and 57, a single blood sample for PK analysis will be collected before the morning dose of TEZ/IVA. Acceptable PK sampling windows are provided in Table 11-1. At the ETT Visit, a single blood sample for PK analysis will be collected.

[y] The final dose during the Run-in Period will be administered on Day -1, the evening before the Day 1 Visit. The final dose during the Washout Period will be the morning dose on the Day 57 Visit.

[z] The last dose of VX-121/TEZ/VX-561 or TEZ/IVA will be the morning dose on the Day 29 Visit.

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

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the concentration versus time curve
AUC_{0-24h}	AUC from the time of dosing to 24 hours
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
CD	compact disc
CF	cystic fibrosis
CFQ-R	CF Questionnaire-Revised
CFTR	*CF transmembrane conductance regulator gene*
CFTR	CF transmembrane conductance regulator protein
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRO	clinical research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	predose concentration
CYP	cytochrome P450
[redacted]	[redacted]
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
ETT	Early Termination of Treatment
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
F508del	CFTR protein lacking the phenylalanine normally found at position 508 of the wild-type protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
[redacted]	[redacted]
FEV_1	forced expiratory volume in 1 second
F/F	*F508del/F508del*
F/MF	*F508del/*minimal function
FSH	follicle-stimulating hormone
[redacted]	[redacted]
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLI	Global Lung Function Initiative

Abbreviation	Definition
GPP	Good Publication Practices
GPS	Global Patient Safety
HBE	human bronchial epithelial (cells)
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IDMC	independent data monitoring committee
IEC	independent ethics committee
IPD	important protocol deviation
IRB	institutional review board
[redacted]	[redacted]
IVA	ivacaftor
IWRS	interactive web response system
LS	least squares
LUM	lumacaftor
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal function
min	minimum value
MMRM	mixed-effects model for repeated measures
N	number of subjects
OATP	organic anion transporting polypeptide
P	probability
pbo	placebo
PD	pharmacodynamic, pharmacodynamics
PE	physical examination
PI	pancreatic insufficient
PK	pharmacokinetic, pharmacokinetics
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
PR	PR interval
PT	Preferred Term
q12h	every 12 hours
qd	daily
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
[redacted]	[redacted]
RR	interval from the onset of 1 QRS complex to the next
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SET	study execution team
SI	SI units (International System of Units)
SOC	System Organ Class

Abbreviation	Definition
SUSAR	suspected, unexpected, serious adverse reaction
SwCl	sweat chloride
TC	triple combination
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
ULN	upper limit of normal
UV	ultraviolet
WHO-DD	World Health Organization-Drug Dictionary

5 INTRODUCTION

5.1 Background

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

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

There are more than 2000 variants described in the *CFTR* gene. The most commonly seen variants that are clearly associated with CF have been identified (336 to date), but many rare cases remain uncharacterized.[7]

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

The therapeutic activity of CFTR correctors and potentiators has been established with products developed by Vertex Pharmaceuticals Incorporated and approved for the treatment of CF in patients with specific *CFTR* genotypes: ivacaftor (IVA) monotherapy (Kalydeco®), lumacaftor (LUM) in combination with IVA (Orkambi®), and tezacaftor (TEZ) in combination with IVA (Symdeko™/ Symkevi®). TEZ and LUM are first-generation CFTR correctors that improve the processing and trafficking of mutated CFTR protein, resulting in an increase in the quantity of protein at the cell surface. IVA increases the open-channel probability of the mutated CFTR protein that has been delivered to the cell surface, thereby enhancing total chloride transport. VX-561 (formerly known as CTP-656) is a deuterated isotope of IVA with a specific pattern of 9 substituted deuteriums. In vitro data indicate similar potency of VX-561 in human bronchial epithelial (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 (refer to VX-561 Investigator's Brochure).

VX-121 is a next-generation CFTR corrector. In vitro, VX-121 also improves the processing and trafficking of mutated CFTR, thereby increasing the quantity of functional protein at the cell surface. The effect of VX-121 was additive to the effect of TEZ. The CFTR protein delivered to the cell surface by VX-121 alone or in combination with TEZ (VX-121/TEZ) was potentiated by IVA. In HBE cells derived from people homozygous for *F508del* and people heterozygous for *F508del* and a minimal function (MF) *CFTR* mutation (F/MF-HBE cells) and studied in vitro,

the triple combination (TC) of VX-121, TEZ, and IVA (VX-121/TEZ/IVA) increased CFTR chloride transport more than the dual combination of VX-121 and either TEZ or IVA under most conditions studied (refer to VX-121 Investigator's Brochure).

5.2 Study Rationale

This is the second clinical study of VX-121 and Part 1 is designed to evaluate the safety and efficacy of VX-121 in TC with TEZ/VX-561 in subjects with CF who are heterozygous for *F508del* and a MF *CFTR* mutation (F/MF genotypes). Conducting the study in subjects with these genotypes investigates the effect of treating 1 responsive allele (*F508del*). Additionally, the safety and efficacy of VX-121 in TC with TEZ/VX-561 will be evaluated in subjects with CF who are homozygous for *F508del* (F/F genotype) in Part 2, [redacted] if the sponsor chooses to conduct these optional parts of the study based on overall development goals for the program and results from other studies.

6 STUDY OBJECTIVES

6.1 Primary Objectives

Parts 1 (Subjects with F/MF genotypes) and 2 (Optional; Subjects with the F/F genotype)

- To evaluate the safety and tolerability of VX-121 in TC with TEZ/VX-561 (deuterated IVA)
- To evaluate the efficacy of VX-121 in TC with TEZ/VX-561

[redacted]

6.2 Secondary Objectives

Parts 1 and 2

- To evaluate the pharmacodynamic (PD) effect of VX-121 in TC with TEZ/VX-561
- To evaluate the pharmacokinetics (PK) of VX-121 when administered in TC with TEZ/VX-561
- To evaluate the PK of TEZ, VX-561, and their respective metabolites when administered in TC with VX-121

[redacted]

7 STUDY ENDPOINTS

7.1 Primary Endpoints

- Safety and tolerability, based on the assessment of adverse events (AEs), laboratory test results, standard 12-lead ECGs, vital signs, and spirometry
- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline through Day 29

7.2 Secondary Endpoints

- Absolute change in sweat chloride concentrations 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-121, TEZ, VX-561, and relevant metabolites

8 STUDY POPULATION

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

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

8.1 Inclusion Criteria

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

   Subjects must have a sweat chloride value ≥60 mmol/L at screening or documented in the form of a laboratory report in the subject's medical record.
7. Confirmed diagnosis of CF as determined by the investigator.
8. Subjects must have an eligible *CFTR* genotype as noted below. If the screening *CFTR* genotype result is not received before the Run-in Period (Part 2) or randomization (Parts 1 a previous *CFTR* genotype laboratory report may be used to establish

eligibility. Subjects who have been enrolled and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9).

- Parts 1 [redacted]: Heterozygous for *F508del* with a second *CFTR* allele carrying a mutation that does not produce a protein, or produces a protein that is not responsive to TEZ, IVA, or TEZ/IVA therapy (Appendix A)
- Part 2: Homozygous for *F508del*

9. Subjects must have a forced expiratory volume in 1 second (FEV_1) ≥40% and ≤90% of predicted normal for age, sex, and height (equations of the Global Lung Function Initiative [GLI])[8] at the Screening Visit. Spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria[9] for acceptability and repeatability.
10. Stable CF disease as judged by the investigator.
11. Willing to remain on a stable CF treatment regimen (other than protocol-specified changes in CFTR modulator regimen) through the Safety Follow-up Visit (Section 9.5).

8.2 Exclusion Criteria

1. History of any comorbidity that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject.
2. History of clinically significant cirrhosis with or without portal hypertension.
3. Risk factors for Torsade de Pointes and other ventricular arrhythmias, including but not limited to, history of any of the following: familial long QT syndrome, chronic hypokalemia, heart failure, left ventricular hypertrophy, chronic bradycardia, myocardial infarction, cardiomyopathy, history of arrhythmia (ventricular or atrial fibrillation), obesity, acute neurologic events (subarachnoid hemorrhage, intracranial hemorrhage, cerebrovascular accident, or intracranial trauma), or autonomic neuropathy.
4. Any of the following abnormal laboratory values at screening:
   - Hemoglobin <10 g/dL
   - Total bilirubin ≥2 × upper limit of normal (ULN)
   - Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP) ≥3 × ULN
   - Abnormal renal function defined as glomerular filtration rate ≤50 mL/min/1.73 m^2 (calculated by the Modification of Diet in Renal Disease Study Equation)[10,11] for subjects ≥18 years of age
5. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for sinopulmonary disease within 28 days before the first dose of TEZ/IVA in the Run-in Period (Part 2) or the first dose of study drug in the Treatment Period (Parts 1 [redacted]).

6. Lung infection with organisms associated with a more rapid decline in pulmonary status (e.g., *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*). For subjects who have had a history of a positive culture, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
    - The subject has not had a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent.
    - The subject has had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent 1 within the 6 months before the date of informed consent.
7. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of TEZ/IVA in the Run-in Period (Part 2) or the first dose of study drug in the Treatment Period (Parts 1 [redacted]).
8. Standard 12-lead ECG demonstrating QTcF >450 msec at screening. If QTcF exceeds 450 msec, the ECG will be repeated 2 more times, and the average of the 3 QTcF values will be used to determine the subject's eligibility.
9. History of solid organ or hematological transplantation.
10. History of alcohol or drug abuse in the past year, including, but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator.
11. Ongoing or prior participation in a study of an investigational treatment with the exception of the following:
    - Ongoing or prior participation in an investigational study of a Vertex CFTR modulator. A washout period of 28 days must elapse before Day 1.
    - For prospective subjects with ongoing or prior participation in all other interventional studies, a washout period of 28 days or 5 terminal half-lives (whichever is longer) must elapse before screening. The duration of the elapsed time may be longer if required by local regulations.
    - Ongoing participation in a noninterventional study (including observational studies and studies requiring assessments without administration of study drug or assignment to other interventions) is permitted.
12. Use of prohibited medications as defined in Table 9-1, within the specified window before the first dose of TEZ/IVA in the Run-in Period (Part 2) or the first dose of study drug in the Treatment Period (Parts 1 [redacted]).

13. Subject, or close relative of the subject, is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site. However, an adult (aged 18 years or older) who is a relative of a study staff member may be enrolled in the study provided that
    - the adult lives independently of and does not reside with the study staff member, and
    - the adult participates in the study at a site other than the site at which the family member is employed.
14. Pregnant or nursing female subjects.

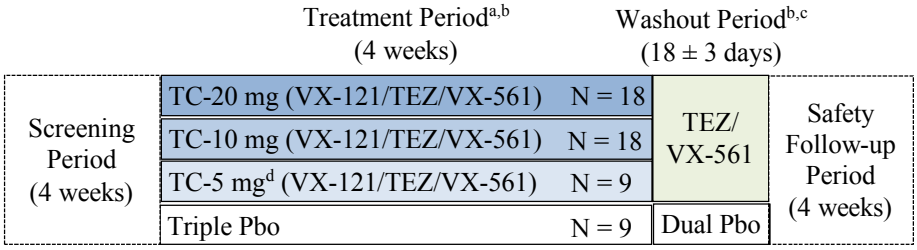
9 STUDY IMPLEMENTATION

9.1 Study Design

This is a Phase 2, [redacted] proof-of-concept study of VX-121. Study parts may be conducted in parallel or sequentially.

A schematic of the study design for Part 1 is shown in Figure 9-1, which has a randomized, double-blind, placebo-controlled, parallel-group design and evaluates VX-121 in TC with TEZ/VX-561.

Figure 9-1 VX18-121-101 Study Design for Part 1 (F/MF Genotypes)



FDC: fixed-dose combination; F/MF: *F508del/*minimal function; N: number of subjects; pbo: placebo;

PD: pharmacodynamic; PK: pharmacokinetic; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; qd: daily; TC: triple combination; TEZ: tezacaftor

Note: Randomization will be stratified by $ppFEV_1$.

[a] The planned VX-121 doses of 5 mg, 10 mg, and 20 mg qd may be adjusted based on emerging data from subjects with CF in Part D of Study VX17-121-001 (Study 001). However, no more than 3 dose levels of VX-121 will be evaluated, and the highest dose will not exceed 20 mg qd.

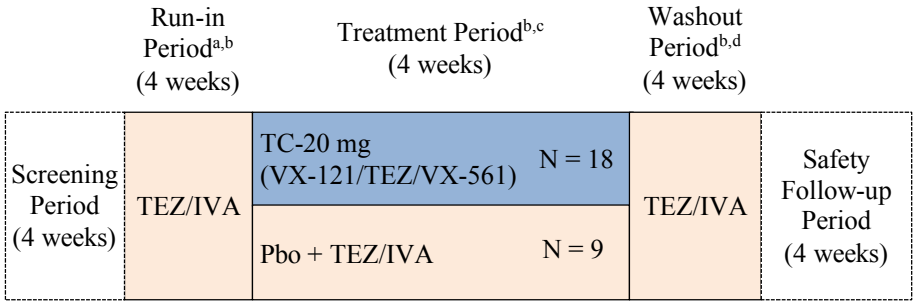
[b] The dosage of TEZ and VX-561 will be TEZ 100 mg qd and VX-561 150 mg qd.

[c] The Washout Period (18 ± 3 days) is included to enable a more thorough evaluation of VX-121 exposure-response relationships by conducting PK and PD assessments during the VX-121 washout.

[d] TC-5 mg is optional.

A schematic of the study design for Part 2 is shown in Figure 9-2, which has a randomized, double-blind, TEZ/IVA-controlled, parallel-group design and evaluates VX-121 in TC with TEZ/VX-561. Part 2 is an optional part of the study, which will be conducted at the sponsor's discretion.

Figure 9-2 VX18-121-101 Study Design for Part 2 (F/F Genotype)



FDC: fixed-dose combination; F/F: *F508del/F508del*; IVA: ivacaftor; N: number of subjects; pbo: placebo; PD: pharmacodynamic; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours; qd: daily; TC: triple combination; TEZ: tezacaftor

Note: Randomization will be stratified by $ppFEV_1$.

[a] All subjects are required to complete the TEZ/IVA Run-in Period to establish a reliable on-treatment (TEZ/IVA) baseline.

[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.

[c] Part 2 will evaluate the same VX-121 dose (20 mg qd) used in Part 1. This dose may be adjusted downward based on emerging data from Part D of Study 001. The dosage of TEZ and VX-561 will be TEZ 100 mg qd and VX-561 150 mg qd.

[d] The 4-week Washout Period is included to evaluate the effect on PD and efficacy endpoints as subjects step down from TC to TEZ/IVA, after the VX-121 washout.

9.1.1 Screening

Screening Visit assessments are shown in Table 3-1, Table 3-2,

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

9.1.1.1 Repetition of Screening Assessment(s)

Screening assessments may be repeated once to establish study eligibility. 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.

9.1.1.2 Rescreening

Subjects may be rescreened only once. If a subject is rescreened, all screening assessments will be repeated except for *CFTR* genotyping, follicle-stimulating hormone (FSH) level (if serum FSH level was ≥40 mIU/mL during prior screening), and sweat chloride level. If a subject is rescreened, the new screening window will begin once the first rescreening assessment has been initiated.

9.1.1.3 Extension of Screening Period Window

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

- Repetition of the Screening Period assessments (Section 9.1.1.1)

- Unexpected operational or logistic delays, or to meet the eligibility criteria
- Repetition of spirometry assessment if results are of poor quality

9.1.2 TEZ/IVA Run-in Period (Part 2)

The TEZ/IVA Run-in Period of Part 2 is 4 weeks. Subjects will be evaluated as outpatients.

Study visits during the Run-in Period will occur as shown in Table 3-2. Study drug administration details are provided in Section 9.6.

On the Day -14 Visit, spirometry and sweat chloride will be assessed. The Day -14 Visit spirometry assessment will be used for stratification of randomization (Section 9.2).

Study eligibility 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, unless they rescreen and complete another 4-week Run-in Period (Section 9.1.1.2).

9.1.3 Treatment Period

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

Study visits during the Treatment Period will occur as shown in Table 3-1, Table 3-2, [redacted] All visits will occur within the windows specified. Study drug administration details are provided in Section 9.6.

Subjects in Part 2 must meet both of the following conditions to qualify to continue into the Treatment Period:

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

If these conditions are not met, subjects in Part 2 may not be randomized and enter into the Treatment Period.

Randomization will occur before the first dose of study drug during the Treatment Period and will occur on the Day 1 Visit (or Day -1) after eligibility has been confirmed (Parts 1 [redacted]) or conditions for entry into the Treatment Period have been confirmed (Part 2). Randomization and stratification details are provided in Section 9.2.

9.1.4 Washout Period

The Washout Periods will last approximately 18 days (Parts 1 [redacted]) and 4 weeks (Part 2).

Study visits during the Washout Period will occur as shown in Table 3-1, Table 3-2, [redacted] Study drug administration details are provided in Section 9.6.

9.1.5 Follow-up

Subjects will have a Safety Follow-up Visit approximately 28 days after the last study drug dose. Safety Follow-up Visit assessments are listed in Table 3-1, Table 3-2, [redacted]

The Safety Follow-up is not required for subjects in Part 2 who continue onto a commercially-available, physician-prescribed CFTR modulator within 28 days of completing the Day 57 Visit.

9.1.6 Early Termination of Treatment

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

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

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

If the subject withdraws consent for the study, no further assessments 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.

9.1.7 Lost to Follow-up

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

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

9.1.8 Independent Data Monitoring Committee

This study will be monitored by an independent data monitoring committee (IDMC) to ensure the safety of the subjects. 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.

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).

Subjects will be assigned a unique subject number. Only subjects who have completed screening assessments and are eligible for participation in the study (and completed the Run-in Period and qualify to enter the Treatment Period [Part 2]) will be randomized to receive active study drug or placebo or active control during the Treatment Period.

Randomization will be stratified by $ppFEV_1$ determined during screening (Day -28 to Day -1 assessment; <70 versus ≥70) in Parts 1 [redacted] and the TEZ/IVA Run-in Period (Day -14 assessment; <70 versus ≥70) in Part 2. If the Day -14 $ppFEV_1$ value is not valid or not available, the most recent available $ppFEV_1$ value before the date of randomization will be used for stratification.

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

9.3 Rationale for Study Elements

9.3.1 Study Design

Parts 1 [redacted]

Parts 1 [redacted] will evaluate the safety, tolerability, PK, PD, and efficacy of VX-121 administered in TC with TEZ/VX-561 (Part 1) [redacted] in subjects with CF with F/MF genotypes.

Efficacy has not been established for a corrector, potentiator, or any corrector/potentiator combination in subjects with F/MF genotypes. Because there is no effective treatment for this population, a placebo arm will be included as the control treatment to assess whether any observed effects are treatment-related or simply related to the study conditions.

The Washout Period (18 ± 3 days; Section 9.1.4) is included to enable a more thorough evaluation of VX-121 exposure-response relationships by conducting PK and PD assessments during the VX-121 washout.

Part 2

Part 2 will evaluate the safety, tolerability, PK, PD, and efficacy of VX-121 in TC with TEZ/VX-561 in subjects with CF with the F/F genotype, if the sponsor chooses to conduct this optional part of the study.

The efficacy and safety of TEZ/IVA in F/F subjects have been demonstrated in Study VX14-661-106 (Study 661-106).[12] Therefore, placebo/TEZ/IVA has been chosen as the control treatment to assess whether any observed effects are treatment-related or simply related to the study conditions.

A 4-week TEZ/IVA Run-in Period (Section 9.1.2) is included to establish a reliable on-treatment (TEZ/IVA) baseline for the Treatment Period.

The 4-week Washout Period (Section 9.1.4) is included to evaluate the effect on PD and efficacy endpoints as subjects step down from TC to TEZ/IVA, after the VX-121 washout.

Parts 1, 2, [redacted]

The extent of response to CFTR modulator treatment may depend on the subject's $ppFEV_1$ value (an index of disease severity) before the start of TC study drug dosing. Some subjects in Part 2 (subjects with the F/F genotype) may be receiving treatment with LUM/IVA or TEZ/IVA at screening, while some subjects may not be receiving treatment with CFTR modulators. It is unlikely that subjects enrolling in Parts 1[redacted] (subjects with F/MF genotypes) are receiving LUM/IVA or TEZ/IVA at screening, as the benefit of these drugs has not been established in patients with F/MF genotypes. Therefore, randomization will be stratified by the $ppFEV_1$ value determined during screening for Parts 1 [redacted] and during the TEZ/IVA Run-in Period, after at least 13 days of TEZ/IVA (Day -14 assessment), in Part 2.

9.3.2 Study Drug Dose and Duration

VX-121 Dose Selection

Part 1 will evaluate up to 3 dose levels of VX-121 (5 mg, 10 mg, and 20 mg qd) in TC with TEZ/VX-561. TC-5 mg is optional. The planned doses of 5 mg, 10 mg, and 20 mg in Part 1 may be adjusted based on emerging data from subjects with CF in Part D of Study 001. However, no more than 3 dose levels of VX-121 will be assessed, and the highest dose will not exceed 20 mg qd. In healthy subjects in Study 001, VX-121 was shown to be safe and well tolerated at multiple doses up to 60 mg qd when administered as monotherapy for 10 days and up to 20 mg qd in TC for 14 days. In Part D of Study 001, a dose of 5 mg qd in TC for 28 days is under evaluation in subjects with CF (F/MF genotypes).

The dose levels in Part 1 are expected to provide clinical benefit (based on in vitro data) and will provide a wide range of VX-121 exposure for exposure-response analyses of safety and efficacy.

Dose- and exposure-response information obtained for the TC in Part 1 (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*.

Parts 2 [redacted] will evaluate VX-121 at a dose of 20 mg qd. This dose may be adjusted downward based on emerging data from subjects with CF in Part D of Study 001.

TEZ and IVA Doses

The doses of TEZ and IVA are the same as those evaluated in Phase 3 studies of TEZ/IVA combination therapy (TEZ: 100 mg daily [qd]; IVA: 150 mg every 12 hours [q12h]), as well those evaluated in TC with VX-121 in healthy subjects in Part C of Study 001. These doses of TEZ and IVA are appropriate for evaluation in the TC based on in vitro experiments with VX-121 that evaluated similar levels of TEZ and IVA exposure after correction for protein-binding.

VX-561 Dosage

A VX-561 dose of 150 mg qd was selected for evaluation based on PK, safety, and efficacy results from prior studies of VX-561 administered as monotherapy or in TC with other next-generation correctors. A 150-mg qd dose of VX-561 results 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 dosed q12h.

VX-561 has been dosed up to 225 mg qd for 7 days in a Phase 1 study and up to 200 mg qd for 4 weeks in a Phase 2 study of subjects with CF.

Treatment Duration

Parts 1, 2 [redacted] will have a 4-week treatment duration because previous studies of CFTR modulators (IVA, LUM/IVA, and TEZ/IVA) have demonstrated that efficacy related to lung function ($ppFEV_1$) can be reliably established using an endpoint at Week 4. In these studies, rapid improvements in $ppFEV_1$ are observed by Day 15, with a separation between the active treatment and placebo groups that is sustained through 24 weeks of treatment. These studies were conducted in patients with different genotypes, baseline $ppFEV_1$, and age groups, using CFTR modulators that had different magnitudes of response.

Administration of VX-121, TEZ, and VX-561 or IVA With Food

Oral doses of VX-121, TEZ, and VX-561 or IVA will be administered under fed conditions. This is consistent with how VX-121, TEZ, and IVA were administered in healthy subjects in Study 001. A positive food effect has been established for IVA and VX-561, and is predicted for VX-121.

9.3.3 Rationale for Study Assessments

The PK assessments and the majority of safety assessments are standard measurements for clinical studies in drug development.

The PD and efficacy endpoints being evaluated (sweat chloride, spirometry, and patient-reported outcomes) are widely accepted and generally recognized as reliable, accurate, and relevant to the study of individuals with CF. Sweat chloride was evaluated in the registration study of IVA (Kalydeco), and spirometry and CFQ-R assessments were evaluated in the registration studies of IVA (Kalydeco) and LUM/IVA combination therapy (Orkambi).

Rationales for other safety and PD assessments are listed below.

Spirometry

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

[redacted]

[redacted]

9.4 Study Restrictions

9.4.1 Prohibited Medications

Prohibited medications are shown in Table 9-1. VX-121, TEZ, VX-561, and IVA are metabolized extensively via CYP3A. Therefore, use of moderate and strong inducers or inhibitors of CYP3A, which have the potential to alter the exposure of VX-121, TEZ, VX-561, or IVA will be prohibited. VX-121 is a potential inhibitor of the hepatic transporter organic anion transporting polypeptide 1B1 (OATP1B1). Therefore, substrates of OATP1B1, such as HMG-Co-A Reductase Inhibitors ("statins") are prohibited during treatment.

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

Table 9-1 Prohibited Medications

	Timing of Restriction	
Medication[a]	**Start of Restriction**	**End of Restriction**
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of study drug	None allowed through the Safety Follow-up Visit
Moderate and strong CYP3A inhibitors (except ciprofloxacin)	None allowed within 14 days before the first dose of study drug	None allowed through the Safety Follow-up Visit
CFTR modulators other than study drug (e.g., Kalydeco, Orkambi, TEZ/IVA)	**Parts 1**[redacted] None allowed within 28 days before the first dose of study drug **Part 2:** None allowed after the first dose of study drug	**Parts 1**[redacted] None allowed through the Safety Follow-up Visit **Part 2:** None allowed through Day 57.
OATP1B1 substrates	None allowed within 14 days before the first dose of the study drug	None allowed through the Safety Follow-up Visit

IVA: ivacaftor; OATP1B1: organic anion transporting polypeptide 1B1; TEZ: tezacaftor
Notes: The first dose of study drug refers to the first dose of TEZ/IVA in the Run-in Period (Part 2) or the first dose of study drug in the Treatment Period (Parts 1[redacted]). The use of prohibited medication by subjects with medical needs will be addressed on a case-by-case basis with the medical monitor.
[a] See Section 9.5 for guidance on concomitant medications.

9.5 Prior and Concomitant Medications

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

- Subjects must remain on a stable CF medication (and supplement) regimen (other than protocol-specified changes in CFTR modulator regimen) for their CF from 28 days before

the start of the TEZ/IVA Run-in Period (Part 2) or 28 days before the Day 1 Visit (Parts 1 [redacted]) through the Safety Follow-up Visit. Stable CF medication regimen is defined as the current medication regimen for CF that subjects have been following for at least 28 days before the start of the TEZ/IVA Run-in Period (Part 2) or 28 days before the Day 1 Visit (Parts 1 [redacted]). Subjects must not initiate long-term treatment with new medication from 28 days before the start of the TEZ/IVA Run-in Period (Part 2) or 28 days before the Day 1 Visit (Parts 1 [redacted]) through the Safety Follow-up Visit unless discussed and approved by the medical monitor. Guidelines for stable CF medication regimens for CF are as follows:

  - Subjects who are taking daily inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.
  - Subjects who cycle onto and off an inhaled antibiotic should continue on their prior schedule. The timing of the first dose of study drug on the Day 1 Visit should be synchronized as closely as possible (and not more than ± 3 days) to the first day in the cycle onto the inhaled antibiotic.
  - Subjects who alternate between 2 different inhaled antibiotics should remain on the same cycling schedule during the study. The timing of the first dose of study drug on the Day 1 Visit should be synchronized as closely as possible (and not more than ± 3 days) to the first day in the cycle onto 1 of the inhaled antibiotics.

- Subjects may receive doses of prednisone or prednisolone of up to 10 mg/day or equivalent (chronically), or prednisone or prednisolone 60 mg/day for up to 5 days, without prior approval of the medical monitor.
- Information about bronchodilator use during the study will be collected and documented. Subjects who are using a bronchodilator must have their spirometry assessments performed according to the guidelines provided in Section 11.5.1.

9.6 Administration

Study drug will be administered orally, and subjects will swallow study drug whole, followed by 240 mL of water. Subjects may take additional water, as needed, to swallow tablets. Subjects will receive the same number of tablets each day to maintain the blind. Additional information is provided in the Pharmacy Manual.

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

1. It is recommended that the dose be taken within 30 minutes of the start of the meal or snack.
2. Study drug will be administered q12h or qd (± 2 hours). VX-121, TEZ, and VX-561 will be administered qd and IVA will be administered q12h. For each subject, all doses of study drugs will be taken at approximately the same time each day. For example, the morning dose could be taken at 08:00 every morning and the evening dose could be taken at 20:00 every evening throughout the study.
3. The date, amount taken, and time of study drug administration, including whether food was taken with each dose, will be recorded for the 2 doses before PK sample collection and the dose received on the morning of PK sample collection.

4. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. The meal or snack will be provided by the site for the morning dose of study drug. For the Day -14 Visit in Part 2, study drug does not need to be administered at the site for that visit.
5. A subject's morning dose can be delayed by up to 6 hours to accommodate predose assessments on clinic visit days.
6. For visits after the Day 1 Visit, subjects will be instructed to bring all used and unused study drug to the site; study drug will be dispensed at each visit, as appropriate.

Missed Doses

If a subject misses a dose and recalls the missed dose within 6 hours (q12h dosing) or within 12 hours (qd dosing), the subject should take the dose with food. If more than 6 hours (q12h dosing) or 12 hours (qd dosing) have elapsed after the usual dosing time, the subject should skip that dose and resume the 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 Modification for Toxicity

If any unacceptable toxicity arises, individual subjects will discontinue dosing (Section 9.1.6). No dose modifications for toxicity are allowed.

9.8 Study Drug Interruption and Stopping Rules

In subjects who have interrupted study drug for >72 hours for any reason, the investigator should resume study drug only after a thorough investigation of the cause for interruption. The investigator should evaluate the subject's clinical stability and only resume study drug after the subject is clinically stable and there is no comorbidity or condition 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.

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

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

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

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

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

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

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

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

If an alternative, reversible cause of transaminase elevation and/or increased bilirubin or clinical jaundice has been identified, study drug administration may be resumed once transaminases or bilirubin return to baseline or are ≤2 × ULN, whichever is higher. Regardless of the duration of interruption, the medical monitor should be notified prior to resumption of study drug. Upon resumption of study drug, transaminases and bilirubin should be assessed weekly until the Safety Follow-up Visit. If a protocol-defined transaminase or bilirubin elevation interruption threshold recurs with rechallenge with the study drug (with confirmation of the initial elevation by repeat testing within 48 to 72 hours), then the study drug must be permanently discontinued, regardless of the presumed etiology.

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

9.9 Removal of Subjects

Subjects may withdraw from the study at any time at their own request. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex

for safety, behavior, noncompliance with study procedures, or administrative reasons. A subject who withdraws from study drug treatment will continue to be followed unless the subject withdraws consent.

Subjects will discontinue from study drug dosing and the investigator will notify the medical monitor if any of the following occur

- Pregnancy
- Meets any of the stopping (discontinuation) criteria (Section 9.8) or has other unacceptable toxicity as determined by the investigator

Subjects who are withdrawn from study drug dosing will complete assessments as described in Section 9.1.6 and may have additional PK samples collected as deemed appropriate by the investigator in consultation with the Vertex medical monitor. Consideration should be given to the need for additional safety assessments as described in Section 9.1.6. The investigator will use clinical judgment to determine whether assessments after study drug discontinuation should occur while the subject remains confined in the clinical unit or can be completed as outpatient visits.

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

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a Safety Follow-up Visit, if applicable (see Section 9.1.5), and follow up with the subject regarding any unresolved AEs.

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

Stopping rules are presented in Section 9.8.

9.10 Replacement of Subjects

Subjects who withdraw or are withdrawn 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-121, TEZ, VX-561, TEZ/IVA, IVA, and their matching placebos.

10.1 Preparation and Dispensing

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

10.2 Packaging and Labeling

Vertex will supply the VX-121 tablets, TEZ tablets, VX-561 tablets, TEZ/IVA fixed-dose combination (FDC) tablets, IVA tablets, and all matching placebos. Study drug labeling will be in compliance with applicable local and national regulations. Additional details regarding packaging, labeling, and dispensing will be included in the Pharmacy Manual.

10.3 Study Drug Supply, Storage, and Handling

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

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

TEZ and matching placebo will be supplied as white tablets of similar size and appearance containing 50 mg TEZ and 0 mg TEZ, respectively.

VX-561 and matching placebo will be supplied as tablets of similar size and appearance containing 50 mg VX-561 and 0 mg VX-561, respectively.

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

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

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

10.4 Drug Accountability

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

10.5 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

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

If a subject demonstrates continued noncompliance of study drug dosing despite educational efforts, the investigator should consider discontinuing the subject.

10.7 Blinding and Unblinding

This will be a double-blind study, with the exception of the Run-in and Washout Periods of Part 2, which will be open-label.

10.7.1 Blinding

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

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of the subject or the male subject's partner and her fetus in the event of a pregnancy
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy serious adverse event (SAE) processing and reporting regulations
- Unblinded statistician preparing the final (production) randomization list who is not part of the study team
- Vertex IWRS Manager
- Vertex Clinical Supply Chain
- IDMC
- Vendor performing the unblinded analysis for any needed reviews of safety, PD, and efficacy data
- Bioanalytical contract research organization (CRO) analyzing PK samples and Vertex Bioanalytical personnel who are not members of the SET but review raw data from the Bioanalytical CRO. The Vertex Bioanalytical SET member will continue to be blinded.
- Vertex 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.

Sweat Chloride and Spirometry Blinding:

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

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

10.7.2 Unblinding

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

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 unblinding. If investigators deem it unnecessary to unblind immediately, they will first attempt to contact the medical monitor to discuss 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.

Contact information for the medical monitor (and an appropriate backup) is included in the medical monitoring plan.

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 Vertex, the CRO, or any site personnel (other than the physician treating the subject). In addition, the investigator will consider whether the clinical event that prompted unblinding will be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to Vertex GPS or designee, per Section 13.1.2.

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

11 ASSESSMENTS

The schedule of assessments is shown in Table 3-1, Table 3-2, [redacted]

11.1 Subject and Disease Characteristics

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

11.2 Pharmacokinetics

11.2.1 Blood Sampling

Blood samples will be collected from subjects for the evaluation of plasma concentrations of VX-121, TEZ, VX-561, [redacted]. These samples may also be used for evaluation of metabolites of TEZ, [redacted] and VX-561 [redacted]

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

Based on emergent data, the number of sampling points for VX-121 plasma may be reduced and/or time points may be modified. Actual sampling times may change upon agreement of the clinical pharmacologist and investigator. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. Acceptable windows for sampling times are shown in Table 11-1.

Table 11-1 Acceptable Pharmacokinetic Sampling Windows

Sampling Time	Time From Scheduled Sampling Allowed
Predose	Within 60 minutes before dosing
Predose on Day 2 (Part 1)	24 hours (± 2 hours) after the first dose for subjects who participate in the Day 2 Visit
From 1 to ≤8 hours after study drug dosing	± 15 minutes

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

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

11.2.2 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 in the Laboratory Manual.

11.2.3 Bioanalysis

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

[redacted]

11.3 Pharmacodynamics: Sweat Chloride

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

At each time point, 2 samples will be collected, 1 from each arm (left and right). Additionally, sweat collections will be performed on any single day during screening. At the Washout Visit(s) for all Parts, sweat chloride assessments should be done within 2 hours before study drug dosing in the morning. Collection of sweat chloride will not overlap with any other study assessments.

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

Specific instructions for collection, handling, processing, and shipping of sweat chloride samples to the central laboratory will be provided in a separate Laboratory Manual.

See Section 10.7.1 for information about blinding of sweat chloride results.

[redacted]

11.5 Efficacy

11.5.1 Spirometry

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

Spirometry will be performed as outlined below:

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

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

During the Screening Period, spirometry assessments may be performed pre- or post-bronchodilator. At all other visits, all spirometry assessments should be performed "pre-bronchodilator". During the Treatment Period, spirometry assessments must be performed before the morning dose of study drugs at approximately the same time at each visit. For the Day -14 Visit in Part 2, spirometry may be performed postdose.

As noted in Table 3-1, an optional cohort in Part 1 may have spirometry performed at 24 hours (± 2 hours) after the first dose (subjects will return to the site to complete the 24-hour postdose assessment; this assessment should be performed predose on Day 2). Vertex will work with study sites to manage the allocation of subjects participating in the 24-hour postdose spirometry assessment.

At the Washout Visit(s) for all Parts, spirometry assessments should be done within 2 hours before study drug dosing in the morning.

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

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

11.5.2 Cystic Fibrosis Questionnaire-Revised

Subjects will be asked to complete the CFQ-R in their native language, if validated translations are available.[16, 17] 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.[18, 19]

11.6 Safety

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

11.6.1 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.

11.6.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory with the exception of the urine pregnancy tests, which will be performed at the site.

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

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

Table 11-2 Safety Laboratory Test Panels

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

Note: Glomerular filtration rate will be calculated by the Modification of Diet in Renal Disease Study Equation for subjects ≥18 years of age (Section 8.2).

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

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

Other Clinical Laboratory Assessments as Described in Section 3:

Pregnancy Testing:

- Serum β-hCG tests will be done at screening for all female subjects (Table 3-1, Table 3-2, [redacted]
- Serum and urine β-hCG tests will be done at the noted visits subsequent to screening for women of childbearing potential only (Table 3-1, Table 3-2, [redacted]

The pregnancy tests at screening and Day 1 (Parts 1 [redacted] or screening and Day -28 (Part 2) must be negative before receiving the first dose of study drug for all women of childbearing potential.

If a urine pregnancy test is positive, the pregnancy will be confirmed with a serum β-hCG test. If pregnancy is confirmed, the procedures outlined in Section 11.6.7.2 will be followed.

FSH: Blood samples for FSH will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be within the postmenopausal reference range of the performing laboratory to be considered postmenopausal.

CFTR Genotype: *CFTR* genotyping will be performed for all subjects (Section 8.1).

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

For purposes of study conduct, the central laboratory must be used for all laboratory tests. 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.

11.6.3 Physical Examinations and Vital Signs

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

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

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

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

11.6.4 Pulse Oximetry

Pulse oximetry is a noninvasive measure of oxygen delivery to the tissues and has been correlated with clinical status and lung function. Arterial oxygen saturation by pulse oximetry will be measured after at least a 5-minute rest and before study drug dosing.

11.6.5 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout. Additional standard 12-lead ECGs will be performed at any other time if clinically indicated. The performance of all ECGs will adhere to the following guidelines:

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

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

If study sites cannot use QTcF they should discuss alternatives with the Medical Monitor.

To ensure safety of the subjects, a qualified individual at the study site will make comparisons to baseline measurements. If the QTcF is increased by >60 msec from the baseline or an absolute QTcF value is ≥500 msec for any scheduled ECG, 2 additional ECGs will be performed approximately 2 to 4 minutes apart to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (>60 msec from baseline or ≥500 msec), a single ECG will be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

11.6.6 Spirometry

Refer to Section 11.5.1.

11.6.7 Contraception and Pregnancy

The effects of VX-121 monotherapy or in TC with TEZ and IVA or VX-561 on conception, pregnancy, and lactation in humans are not known. VX-121, 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. In preliminary embryo-fetal developmental toxicity studies in rats and rabbits, VX-121 was determined to be non-teratogenic, and there were no adverse maternal and embryo/fetal developmental effects up to the highest dose evaluated.

11.6.7.1 Contraception

Study participation requires compliance with the contraception guidelines outlined below:

Contraception for the couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and post-ovulation 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/salpingo-oophorectomy) will be considered to be of childbearing potential.
- Same sex relationships.

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

Table 11-3 Acceptable Methods of Contraception

Method	Male Subjects and Their Female (Non-study) Partners	Female Subjects and Their Male (Non-study) Partners
Vasectomy 6 months or more previously, with a documented negative postvasectomy semen analysis for sperm	Yes	Yes
Documented tubal ligation 4 weeks or more previously	Yes	Yes
Male or female condom with or without spermicide[a]	Yes	No
Female barrier contraception (such as diaphragm, cervical cap, or sponge) with spermicide	Yes	No
Continuous use of an intrauterine device for at least 90 days before the first dose of study drug.	Yes	Yes
Oral, patch, implanted, or injected hormonal contraceptives, if used consistently and correctly for at least 60 days before the first dose of study drug	Yes	See footnote b

Notes: At least 1 acceptable method of contraception must be used by couples not exempt from the contraception requirement. Methods of contraception must be in successful use from signing of consent, approximately 28 days before the first dose of study drug (unless otherwise noted), and until 90 days following the last dose of study drug. Additional contraception requirements may need to be followed according to local regulations and/or requirements. The first dose of study drug refers to the first dose of TEZ/IVA in the Run-in Period (Part 2) or the first dose of study drug in the Treatment Period (Parts 1 [redacted]

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

[b] Combination (estrogen and progestogen containing) and implantable or injectable progestogen-only hormonal contraception are considered acceptable methods of contraception. Progestogen-only oral hormonal contraception is NOT considered an acceptable method of contraception.

Additional notes:

- Male and female subjects who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study if they become sexually active with a partner of the opposite sex.
- Male subjects must not donate sperm during the period starting from the first dose of TEZ/IVA in the Run-in Period (Part 2) or the first dose of study drug in the Treatment Period (Parts 1 [redacted] until 90 days after the last dose of study drug.
- Female subjects of childbearing potential should not plan to become pregnant during the study or within 90 days after the last dose of study drug. For male subjects with a female partner of childbearing potential, the couple should not plan to become pregnant during the study or within 90 days after the last dose of study drug, with the exception of couples who plan to become pregnant by artificial insemination using sperm banked by the male subject before the first dose of study drug or sperm from another source.
- Male subjects whose female partner becomes pregnant through well-documented in vitro fertilization (donated sperm) or banked sperm (collected before the subject received study drug), or is otherwise already pregnant before the male subject's first dose of study drug, must be compliant with the contraception requirements. In this scenario, the male subject and

his female partner must commit to using a male condom (to ensure there is no exposure of the fetus to study drug) from signing consent through 90 days after the last dose of study drug.

- Female subjects should not nurse a child from signing consent through 90 days following the last dose of study drug.
- Unique situations that may not fall within the above specifications may be discussed with the Vertex medical monitor or authorized designee on an individual basis.

11.6.7.2 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 subject or the female partner of a male subject becomes pregnant while participating in the study, study drug will be permanently discontinued immediately. The investigator will notify the medical monitor and Vertex GPS within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy using the Pregnancy Information Collection Form.

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

12 STATISTICAL AND ANALYTICAL PLANS

This section presents a summary of the planned analyses on safety, efficacy, and clinical pharmacology for this study. Statistical analysis details on safety and efficacy 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

The primary objectives of Parts 1, 2, [redacted] are the evaluation of safety, tolerability, and efficacy of VX-121 in TC with TEZ/VX-561 [redacted] 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 endpoints are safety and tolerability. Approximately 108 subjects with CF will be enrolled in the study with approximately 81 subjects receiving VX-121 in TC with either TEZ/VX-561 [redacted]. 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. A sample size of 18 subjects per treatment group provides at least 90% power to detect a mean

within-treatment change of 7 percentage points. These calculations assumed a standard deviation of 8 percentage points for the absolute change from baseline in $ppFEV_1$ and were based on EAST, Version 6.4.1.

12.2 Analysis Sets

12.2.1 All Subjects Set

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

12.2.2 Full Analysis Set

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

12.2.3 Safety Set

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

12.2.4 Pharmacokinetic Set

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

12.3 Statistical Analysis

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

12.3.1 General Considerations

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

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

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. 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. Further details on baseline definition will be provided in SAP.

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

The **Treatment-Emergent (TE) Period** will be from first dose date of TC to 28 days after the last dose date of study drug, or the completion date of study participation, whichever comes earlier. An additional TE Period related to the Run-in Period for Part 2 will be defined in the SAP, as appropriate.

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

All data will be summarized for each part, separately, unless specified otherwise.

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

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

12.3.2.2 Demographics and Baseline Characteristics

Demographic and other baseline characteristics will include, but are not limited to age, sex, race, weight, height, body mass index (BMI), medical history, baseline spirometry parameters, and baseline sweat chloride. These characteristics will be summarized for the FAS. No statistical tests will be done to evaluate baseline imbalances between groups.

12.3.2.3 Prior and Concomitant Medications

Medications used in this study will be coded using the WHO-DD 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 2 will be defined in the SAP, as appropriate.

12.3.2.4 Study Drug Exposure

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 study drug exposure, as primary, will be summarized for the FAS, and will be derived as 100 × [1 - (total number of days of study drug interruption) / (duration of study drug exposure in days)].

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

12.3.2.5 Important Protocol Deviations

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

IPDs will be provided in an individual subject data listing.

12.3.3 Safety Analysis

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

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

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

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.

12.3.3.1 Adverse Events

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

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

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

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

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

Summaries will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT) 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.

12.3.3.2 Clinical Laboratory Assessments

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

The number and percentage of subjects meeting 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. This listing will include data from scheduled and unscheduled visits.

12.3.3.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided overall and by treatment group for each part, at each scheduled visit and time point, as applicable, for the following ECG interval measurements (in msec): RR, PR, QT, and QT corrected for heart rate (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 may be described in the SAP.

12.3.3.4 Vital Signs

For the treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized overall and by treatment group at each scheduled visit. The following vital signs parameters will be summarized: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (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 may be described in the SAP.

12.3.3.5 Pulse Oximetry

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

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

12.3.3.6 Physical Examination

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

[redacted]

12.3.4 Efficacy Analysis

12.3.4.1 Spirometry

The absolute change from baseline for $ppFEV_1$ through Day 29 is a primary endpoint in Parts 1, 2, [redacted]. The within-group comparisons in the absolute change from baseline for $ppFEV_1$ through Day 29 will be the primary analysis. A mixed-effects model for repeated measures (MMRM) with change from baseline for $ppFEV_1$ at Days 15 and 29 as the dependent variable will be performed for the FAS for each part. 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. 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. A compound symmetry covariance structure will be used to model the within-subject errors. Conditional on the fixed effects, missing data due to treatment or study discontinuation will be assumed to be missing at random.

Adjusted means and 95% CIs of the average treatment effects through Day 29 (averaged over Days 15 and 29), as applicable, will be estimated within MMRM using least squares (LS) means via PROC MIXED in SAS, for all within-group comparisons in all parts. *P* values will also be provided for these comparisons. In addition, adjusted means and 95% CIs for the absolute change from baseline for $ppFEV_1$ through Day 29 will be estimated for between-group comparisons.

[redacted]

For endpoints other than primary, no multiplicity adjustments will be made and the corresponding *P* values for these endpoints will be considered as nominal.

12.3.4.2 Analysis of CFQ-R

One of the secondary efficacy variables is absolute change in the CFQ-R respiratory domain score from baseline at Day 29. Analysis of this secondary efficacy variable will be similar to that for the absolute change from baseline in $ppFEV_1$. Additional details of these analyses will be provided in the SAP.

12.3.5 Pharmacodynamic 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. Analysis of sweat chloride will be similar to that for the absolute change from baseline in $ppFEV_1$. Adjusted means and 95% CIs of the average treatment effects through Day 29, for all within-group and between-group comparisons for each part, separately, will be estimated within MMRM, with appropriate adjustment for covariates. *P* values will also be provided for all within-group comparisons.

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

[redacted]

12.3.7 Interim and Independent Data Monitoring Committee Analyses

12.3.7.1 Interim Analysis

Not applicable

12.3.7.2 Independent Data Monitoring Committee Analysis

The IDMC (Section 9.1.7) will conduct safety review of study data. IDMC analyses will be conducted as outlined in the IDMC Charter.

12.4 Clinical Pharmacology Analysis

12.4.1 Pharmacokinetic Analysis

Individual concentration values of VX-121, TEZ, [redacted], VX-561, and respective metabolites will be listed, and summary statistics for concentrations of VX-121, TEZ, [redacted] and VX-561 by treatment will be provided. Population PK analyses will be presented in a separate report.

12.4.2 Pharmacokinetic/Pharmacodynamic Analyses

PD assessments to be included in PK/PD analyses may include sweat chloride, $ppFEV_1$, as well as 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-121, TEZ, VX-561, [redacted], 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 population PK/PD analysis will be presented in the Modeling and Simulation Plan.

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 the ICF is signed until the following times:

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit, the earliest of
  - 35 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 9.1.6)

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

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

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed November 2017). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." The severity of an AE that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

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

13.1.1.5 Adverse Event Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug(s). Causality will be classified using the categories 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 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 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 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, 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 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 Reporting and 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 **within 24 hours of identification**. 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 of identification**.

For SAEs that occur after obtaining informed consent and assent (where applicable) through the Safety Follow-up Visit, the SAE Form will be completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (preferred choice)

Fax: [redacted]

For questions, contact telephone: [redacted]

SAEs that occur after the Safety Follow-up Visit and are considered related to study drug(s) 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 the outcome to Vertex using the SAE Form.

13.1.2.3 Expedited Reporting and Investigator Safety Letters

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

It is the responsibility of the investigator or designee to promptly notify the local IRB/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 be conducted only 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 will be limited to the site and the study physician and will 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 US, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated regulations, an executed HIPAA authorization will be obtained by the site from each subject (or the legal representative of the subject) before research activities may begin. Each HIPAA authorization will comply with all HIPAA requirements including authorization allowing the site access to and use of the subject's personally identifiable health information, authorization for the site to disclose such information to Vertex, the FDA, and other parties requiring access under the protocol, and statements as to the purpose for which such information may be used and for how long.

13.2.6 Record Retention

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

13.2.7 Study Termination

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

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

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

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

13.2.8 End of Study

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

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

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

13.4 Monitoring

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

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

13.5 Electronic Data Capture

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

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

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

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

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

13.6 Publications and Clinical Study Report

[redacted]

13.6.2 Clinical Study Report

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

14 REFERENCE

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13 Vertex Pharmaceuticals Incorporated. Lumacaftor (VX-809) Investigator's Brochure, Version 7.0. Report date: 27 March 2014.

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20 Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good publication practice for communicating company-sponsored medical research: GPP3. Ann Intern Med. 2015;163(6):461-4.
21 International Committee of Medical Journal Editors (ICMJE). December 2017. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. Available at: http://www.icmje.org/recommendations/. Accessed 03 August 2018.

APPENDIX A Eligible MF *CFTR* Mutations

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

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

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

Inclusion of MF Mutations Based on In Vitro Testing

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

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

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

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

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

Eligible MF Mutations

The list below represents acceptable mutations, which are detectable by an FDA-cleared genotyping assay or other method (e.g., sequencing); however, this list may not include every eligible mutation, and investigators should contact the medical monitor regarding other mutations that may also meet study eligibility criteria.

CFTR Mutations Eligible for VX18-121-101 (Parts 1 [redacted]

MF Mutation Category	Mutation				
Nonsense mutations	Q2X	L218X	Q525X	R792X	E1104X
	S4X	Q220X	G542X	E822X	W1145X
	W19X	Y275X	G550X	W882X	R1158X
	G27X	C276X	Q552X	W846X	R1162X
	Q39X	Q290X	R553X	Y849X	S1196X
	W57X	G330X	E585X	R851X	W1204X
	E60X	W401X	G673X	Q890X	L1254X
	R75X	Q414X	Q685X	S912X	S1255X
	L88X	S434X	R709X	Y913X	W1282X
	E92X	S466X	K710X	Q1042X	Q1313X
	Q98X	S489X	Q715X	W1089X	Q1330X
	Y122X	Q493X	L732X	Y1092X	E1371X
	E193X	W496X	R764X	W1098X	Q1382X
	W216X	C524X	R785X	R1102X	Q1411X
Canonical splice mutations	185+1G→T	711+5G→A	1717-8G→A	2622+1G→A	3121-1G→A
	296+1G→A	712-1G→T	1717-1G→A	2790-1G→C	3500-2A→G
	296+1G→T	1248+1G→A	1811+1G→C	3040G→C (G970R)	3600+2insT
	405+1G→A	1249-1G→A	1811+1.6kbA→G		3850-1G→A
	405+3A→C	1341+1G→A	1811+1643G→T	3120G→A	4005+1G→A
	406-1G→A	1525-2A→G	1812-1G→A	3120+1G→A	4374+1G→T
	621+1G→T	1525-1G→A	1898+1G→A	3121-2A→G	
	711+1G→T		1898+1G→C		
Small (≤3 nucleotide) insertion/deletion (ins/del) frameshift mutations	182delT	1078delT	1677delTA	2711delT	3737delA
	306insA	1119delA	1782delA	2732insA	3791delC
	306delTAGA	1138insG	1824delA	2869insG	3821delT
	365-366insT	1154insTC	1833delT	2896insAG	3876delA
	394delTT	1161delC	2043delG	2942insT	3878delG
	442delA	1213delT	2143delT	2957delT	3905insT
	444delA	1259insA	2183AA→G[a]	3007delG	4016insT
	457TAT→G	1288insTA	2184delA	3028delA	4021dupT
	541delC	1343delG	2184insA	3171delC	4022insT
	574delA	1471delA	2307insA	3171insC	4040delA
	663delT	1497delGG	2347delG	3271delGG	4279insA
	849delG	1548delG	2585delT	3349insT	4326delTC
	935delA	1609del CA	2594delGT	3659delC	
Non-small (>3 nucleotide) insertion/deletion (ins/del) frameshift mutations	CFTRdele1	CFTRdele16-17b	1461ins4		
	CFTRdele2	CFTRdele17a,17b	1924del7		
	CFTRdele2,3	CFTRdele17a-18	2055del9→A		
	CFTRdele2-4	CFTRdele19	2105-2117del13insAGAAA		
	CFTRdele3-10,14b-16	CFTRdele19-21	2372del8		
	CFTRdele4-7	CFTRdele21	2721del11		
	CFTRdele4-11	CFTRdele22-24	2991del32		
	CFTR50kbdel	CFTRdele22,23	3667ins4		
	CFTRdup6b-10	124del23bp	4010del4		
	CFTRdele11	602del14	4209TGTT→AA		
	CFTRdele13,14a	852del22			
	CFTRdele14b-17b	991del5			

CFTR Mutations Eligible for VX18-121-101 (Parts 1 [redacted]

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

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

Source: CFTR2.org [Internet]. Baltimore (MD): Clinical and functional translation of CFTR. The Clinical and Functional Translation of CFTR (CFTR2), US Cystic Fibrosis Foundation, Johns Hopkins University, the Hospital for Sick Children. Available at: http://www.cftr2.org/. Accessed 15 May 2018.

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

[a] Also known as 2183delAA→G.

[b] Unpublished data.

15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX18-121-101	Version #: 4.0	Version Date: 09 May 2019
Study Title: A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety and Efficacy of VX-121 Combination Therapy in Subjects Aged 18 Years and Older With Cystic Fibrosis		

This clinical study protocol has been reviewed and approved by the sponsor.

[redacted]

15.2 Investigator Signature Page

Protocol #: VX18-121-101	Version #: 4.0	Version Date: 09 May 2019
Study Title: A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety and Efficacy of VX-121 Combination Therapy in Subjects Aged 18 Years and Older With Cystic Fibrosis		

I have read Protocol VX18-121-101, Version 4.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-121, tezacaftor, VX-561, and ivacaftor and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date