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-659 Combination Therapy in Subjects Aged 18 Years and Older With Cystic Fibrosis

Vertex Study Number: VX16-659-101

IND Number: 134285

EudraCT Number: 2016-003585-11

Date of Protocol: 01 September 2017 (Version 3.0)

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Summary of Changes to the Protocol

The previous version of this protocol (Version 2.0, 30 June 2017) was amended to create the current version (Version 3.0, 01September 2017). The protocol history is provided below.

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.0, 03 March 2017	Original version
Version 2.0, 30 June 2017	Added study drug doses, revised elements of the study design including treatment arms, sample size, and study duration, and revised inclusion/exclusion criteria.
Version 3.0, 01 September 2017	Current version

Key changes in the current version of the protocol are summarized below.

Change and Rationale	**Affected Sections**
Added Part 3 to evaluate VX-659 in triple combination with TEZ/VX-561 (deuterated IVA)	Global
Incorporated Administrative Letter #1 which clarified that the pretreatment (screening) $ppFEV_1$ value used for stratification refers to the last $ppFEV_1$ measurement before treatment with VX-659	Sections 9.1.3, 9.3.1, and Table 3-2
For Part 2, extended the window for the Day -14 Visit from Day -15 to Day -3 to allow scheduling flexibility	Table 3-2
Specified required pregnancy tests and clarified that additional testing may be needed per country-specific regulations, [redacted].	Section 11.7.2

Typographical and administrative changes were also made to improve the clarity of the document.

2 PROTOCOL SYNOPSIS

Title

A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety and Efficacy of VX-659 Combination Therapy in Subjects Aged 18 Years and Older With Cystic Fibrosis

Brief Title

A Study Evaluating the Safety and Efficacy of VX-659 Combination Therapy in Subjects With Cystic Fibrosis

Clinical Phase and Study Type

Phase 2 safety and efficacy

Objectives

Primary Objectives

Parts 1 and 2: To evaluate the safety and tolerability of VX-659 in triple combination (TC) with tezacaftor (TEZ) and ivacaftor (IVA)

Part 3 (optional): To evaluate the safety and tolerability of VX-659 in TC with TEZ and VX-561 (also known as CTP-656, deuterated IVA)

All parts: To evaluate the efficacy of VX-659 in TC with TEZ and either IVA or VX-561

Secondary Objectives

Parts 1 and 2: To evaluate the pharmacodynamic (PD) effects of VX-659 in TC with TEZ and IVA on CFTR function

Part 3 (optional): To evaluate the PD effects of VX-659 in TC with TEZ and VX-561 on CFTR function

All parts:

- To evaluate the pharmacokinetics (PK) of VX-659 when administered in TC with TEZ and either IVA or VX-561
- To evaluate the PK of TEZ, IVA, VX-561 and their respective metabolites when administered with VX-659 (as applicable)

Endpoints

Primary Endpoints

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

Secondary Endpoints

- Absolute change in sweat chloride concentrations from baseline through the Day 29 Visit
- Relative change in $ppFEV_1$ from baseline through the Day 29 Visit
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline at the Day 29 Visit
- PK parameters of VX-659, TEZ, M1-TEZ, IVA, M1-IVA, and VX-561

Number of Subjects

Up to approximately 105 subjects will be randomized: approximately 54 subjects in Part 1, approximately 27 subjects in Part 2, and approximately 24 subjects in Part 3.

Study Population

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

Part 1 and Part 3: heterozygous for *F508del* and a minimal *CFTR* function mutation that is not expected to respond to TEZ, IVA, or TEZ/IVA (F/MF genotypes)

Part 2: homozygous for *F508del* (F/F genotype)

Investigational Drug

Active substance: VX-659
Activity: CFTR corrector (increased Cl^- secretion)
Strength and route of administration: 80-mg VX-659 tablet for oral administration

Active substance: IVA (ivacaftor; VX-770)
Activity: CFTR potentiator (increased Cl^- secretion)
Strength and route of administration: 150-mg IVA film-coated tablet for oral administration

Active substance: TEZ (tezacaftor; VX-661) and IVA
Activity: CFTR corrector and potentiator (increased Cl^- secretion)
Strength and route of administration: 100-mg TEZ/150-mg IVA fixed-dose combination film-coated tablet for oral administration

Active substance: TEZ
Activity: CFTR corrector (increased Cl^- secretion)
Strength and route of administration: 50-mg TEZ tablet for oral administration

Active substance: VX-561 (deuterated ivacaftor)
Activity: CFTR potentiator (increased Cl^- secretion)
Strength and route of administration: 50-mg VX-561 tablet for oral administration

Study Duration

Part 1: Total duration is approximately 13 weeks. Subjects will receive study drug for approximately 5 weeks: 4 weeks in Period 1 followed by 4 days in Period 2.

Part 2: Total duration is approximately 20 weeks. Subjects will receive study drug for 12 weeks: 4 weeks during the Run-in Period, 4 weeks in Period 1, and 4 weeks in Period 2.

Part 3: Total duration is approximately 12 weeks. Subjects will receive study drug for 4 weeks in Period 1

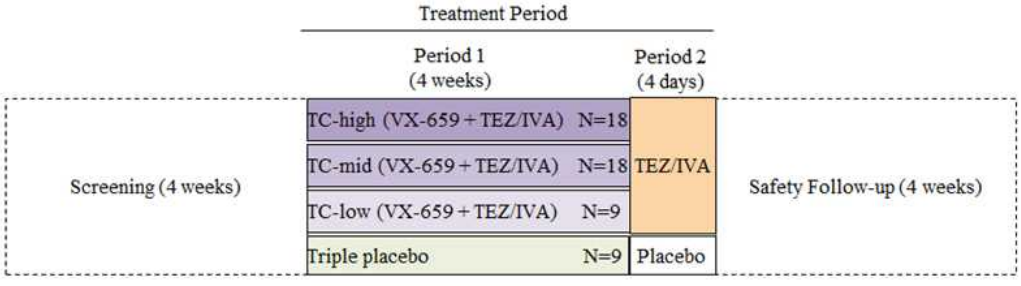
Study Design

This is a Phase 2, randomized, double-blind, placebo- and TEZ/IVA-controlled, 3-part, multicenter study. All parts will be conducted concurrently. Part 1 and Part 2 include a 4-week screening period, 2 dosing periods (a TC dosing period, Period 1, and a VX-659 washout period, Period 2), and a 4-week safety follow-up period. Part 2 also includes a 4-week Run-in Period prior to Period 1. Part 3 is optional and includes a 4-week screening period, a TC dosing period (Period 1), and a 4-week safety follow-up period. The treatment arms and doses of VX-659, TEZ, and IVA or VX-561 to be evaluated are shown below. Subjects may not participate in more than 1 part.

To maintain the blind, matching placebo tablets will be administered, as applicable, so that all subjects receive the same number of tablets within a given dosing period.

Randomization will be stratified by $ppFEV_1$. Schematics of the study design are shown below.

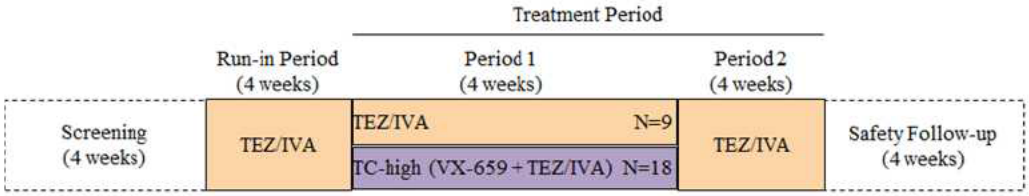
Part 1: Subjects With F/MF Genotypes



IVA: ivacaftor; TC: triple combination; TEZ: tezacaftor

Placebo is the control because efficacy has not been established for a corrector, potentiator, or any corrector/potentiator combination in subjects with F/MF genotypes. Period 2 is included to enable a more thorough evaluation of VX-659 exposure-response relationships by conducting PK and PD assessments during the VX-659 washout.

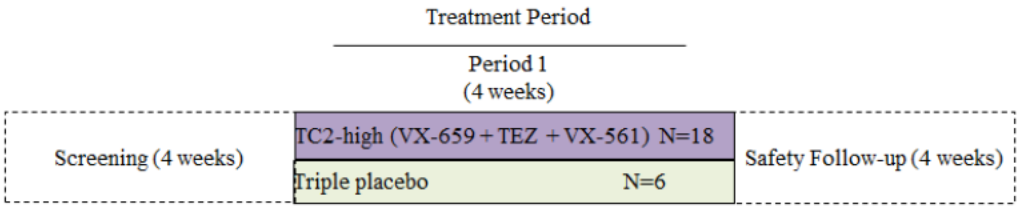
Part 2: Subjects With F/F Genotype



IVA: ivacaftor; TC: triple combination; TEZ: tezacaftor

TEZ/IVA is the control because results from a Phase 3 study (Study VX14-661-106) demonstrated a clinically meaningful benefit for TEZ/IVA treatment in subjects with the F/F genotype. Period 2 is 4 weeks to enable an assessment of PD and efficacy endpoints after VX-659 is washed out.

Part 3: Subjects With F/MF Genotype (optional)



TC: triple combination; TEZ: tezacaftor

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

Treatment Arms and Planned Doses by Part

	Period 1			Period 2	
	VX-659 Dosage	**TEZ Dosage**	**IVA Dosage**	**TEZ Dosage**	**IVA Dosage**
Part 1					
TC-high	400 mg qd	100 mg qd	150 mg q12h	100 mg qd	150 mg q12h
TC-mid	240 mg qd	100 mg qd	150 mg q12h	100 mg qd	150 mg q12h
TC-low	80 mg qd	100 mg qd	150 mg q12h	100 mg qd	150 mg q12h
Triple placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Part 2					
TEZ/IVA	Placebo	100 mg qd	150 mg q12h	100 mg qd	150 mg q12h
TC-high	400 mg qd	100 mg qd	150 mg q12h	100 mg qd	150 mg q12h

Part 3 (optional)			
	Period 1		
	VX-659 Dosage	**TEZ Dosage**	**VX-561 Dosage**
TC2-high	400 mg qd	100 mg qd	200 mg qd
Triple placebo	Placebo	Placebo	Placebo

IVA: ivacaftor; q12h: every 12 hours; qd: daily; TC: triple combination; TEZ: tezacaftor
Note: In Part 2, all subjects will also receive TEZ 100 mg qd/IVA 150 mg q12h during the Run-in Period

Assessments

Safety: AEs, clinical laboratory assessments, ECGs, vital signs, pulse oximetry, physical examinations (PEs)
Efficacy: spirometry, CFQ-R
PD: sweat chloride
PK: VX-659, TEZ, M1-TEZ, IVA, M1-IVA, VX-561
[redacted]

Statistical Analyses

Primary Objectives

The safety analysis will be descriptive only.

The primary efficacy endpoint is the absolute change from baseline through the Day 29 Visit for $ppFEV_1$

All $ppFEV_1$ hypothesis tests will be performed within the mixed-effects model for repeated measures (MMRM) framework at a 5% alpha level, with appropriate adjustment for baseline covariates. The null within-group hypothesis of no difference in the mean absolute change from baseline through the Day 29 Visit for $ppFEV_1$ in all treatment groups, by part, will be tested using MMRM. The adjusted means and 2-sided 95% confidence intervals of the average treatment effects through the Day 29 Visit for all within-group and between-group comparisons will be estimated within MMRM.

Secondary Objectives

The PD endpoint is the absolute change in sweat chloride from baseline through the Day 29 Visit. In Part 1, the null hypothesis of the lack of a decreasing dose-response trend in the mean absolute change from baseline through the Day 29 Visit for sweat chloride between the TC dose groups and placebo will be tested using a multiple comparisons procedure based on the 1-sided maximum *t*-statistic. The adjusted means and 2-sided 95% confidence intervals of the average treatment effects through the Day 29 Visit, for all within-group and between-group comparisons, will be estimated within MMRM.

Interim Analyses

Interim analyses (IAs) may be conducted for any part of the study after at least 50% of subjects in the part have completed the Day 15 Visit. Each IA will only include data for a single part of the study.

IDMC Reviews

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

3 SCHEDULE OF ASSESSMENTS

Schedules of Assessments are provided in Table 3-1 for Part 1, Table 3-2 for Part 2, and Table 3-3 for Part 3. All visits will be scheduled relative to the Day 1 Visit (first dose of VX-659 or VX-659 matched placebo).

Informed consent must be completed before any assessments are done at the Screening Visit. The Cystic Fibrosis Questionnaire-Revised (CFQ-R) assessment must be completed before any other assessment at the clinic visits when it is required. Other assessments may be performed in any order when more than 1 assessment is required at a particular time point. All assessments will be performed before dosing, unless noted otherwise.

Table 3-1 Study VX16-659-101 Part 1 (Subjects with F/MF genotypes): Schedule of Assessments

Event/Assessment[a]	Screening Period		Treatment Period (5 weeks)				ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
			Period 1[c] (4 weeks)			Period 2		
	Screening Visit Days -28 to -1	Stratification Visit[d] Day -27 to -1	Day 1	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 33 Visit[e]		
Informed consent	X							
Randomization[f]			X					
Study drug dosing[g]			Day 1 through Day 33 Visit					
Demographics	X							
Medical history	X							
CFTR genotype[h]	X							
Height[i]	X							
Weight[i]	X		X	X	X		X	X

[a] All assessments will be performed predose, unless noted otherwise. Assessments that are collected predose and postdose will only be collected once if study drug is not administered on the day of the visit (i.e., if subject prematurely discontinued study drug treatment).

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

[c] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 9.1.4.

[d] The spirometry assessment used for stratification must be performed at least 14 days after the last dose of any previous CFTR modulator treatment. Therefore, subjects being treated with 1 or more CFTR modulators (investigational or approved) within 14 days of the Screening Visit must have a separate Stratification Visit at least 14 days after the subject's last CFTR modulator dose. For subjects not being treated with any CFTR modulators within 14 days of the Screening Visit, the Screening Visit spirometry assessment can be used for stratification.

[e] The Day 33 Visit may occur 3 to 6 days after the actual date of the Day 29 Visit.

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

[g] On days of scheduled visits, the in-clinic dose of study drugs will be given in the morning, at least 6 hours apart from any other scheduled dose and after all predose assessments are complete. The last dose of VX-659 in Part 1 Period 1 will be the morning dose on the Day 29 Visit. The last dose of TEZ/IVA in Part 1 Period 2 will be the morning dose on the Day 33 Visit. Refer to Section 9.7 for details.

[h] *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 (see inclusion criterion 6).

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

Table 3-1 Study VX16-659-101 Part 1 (Subjects with F/MF genotypes): Schedule of Assessments

Event/Assessment[a]	Screening Period		Treatment Period (5 weeks)				ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
			Period 1[c] (4 weeks)			Period 2		
	Screening Visit Days -28 to -1	Stratification Visit[d] Day -27 to -1	Day 1	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 33 Visit[e]		
Physical examination[j]	Complete		Abbrev.	Abbrev.	Abbrev.		Abbrev.	Complete
Vital signs[k]	X		X	X	X	X	X	X
Pulse oximetry[k]	X		X	X	X	X	X	X
Standard 12-lead ECG[l]	X		X	X	X		X	X
Sweat chloride[m,p]	X		X	X	X	X	X	X
Spirometry[n]	X	X	X	X	X	X	X	X
CFQ-R[o,p]			X	X	X			
Urinalysis[p]	X		X	X	X		X	X
Pregnancy test (females of childbearing potential)	Serum		Urine		Urine		Serum	Serum
FSH[q]	X							

[j] Complete and abbreviated physical examinations (PEs) are described in Section 11.7.3. Symptom-directed PEs can be done at any time at the discretion of the investigator or healthcare provider.

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

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

[m] See inclusion criterion 5 for information about the sweat chloride assessment for study eligibility. Sweat chloride assessments should be done at approximately the same time at every study visit during the Treatment Period and follow-up.

[n] At the Screening Visit, spirometry may be done pre- or post-bronchodilator. At other study visits, spirometry will be done pre-bronchodilator, before the in-clinic dose of study drugs, and should be performed at approximately the same time at every visit. On the Day 1 and 15 Visits, spirometry will also be performed 5 hours (± 1 hour) after the in-clinic dose of study drugs.

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

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

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

Table 3-1 Study VX16-659-101 Part 1 (Subjects with F/MF genotypes): Schedule of Assessments

	Screening Period		Treatment Period (5 weeks)					
			Period 1[c] (4 weeks)			Period 2		
Event/Assessment[a]	**Screening Visit Days -28 to -1**	**Stratification Visit[d] Day -27 to -1**	**Day 1**	**Day 15 (± 2 days)**	**Day 29 (± 2 days)**	**Day 33 Visit[e]**	**ETT Visit[b]**	**Safety Follow-up 28 (± 7) Days After Last Dose**
G6PD activity test[r]	X							
Serum chemistry and hematology[p]	X		X	X	X	X	X	X
Coagulation[p]	X		X	X	X		X	X
PK sampling[s]			X	X	X	X	X	
[redacted]								
AEs, medications[u], treatments, and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit							

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

[s] Blood samples will be collected for PK analysis of study drugs and metabolites. On the Day 1 Visit, samples will be collected before (0 hours) and 1, 2, 4, and 6 hours after the in-clinic dose. On the Day 15 Visit, samples will be collected before (0 hours) and 1, 2, 4, 6, and 8 hours after the in-clinic dose. On the Day 29 and Day 33 Visits, a single sample will be collected before the in-clinic dose. At the ETT Visit, a single sample will be collected.

[redacted]

Refer to Section 9.5 for details.

Table 3-2 Study VX16-659-101 Part 2 (Subjects with F/F genotype): Schedule of Assessments

Event/Assessment[a]	Screening Period	Run-in (4 weeks)		Treatment Period (8 weeks)					ETT Visit[b]	Safety Follow-up
				Period 1 (4 weeks)[d]			Period 2 (4 weeks)			
	Screening Visit Days -56 to -29	Day -28 (± 1 day)	Day -14 (Days -15 to -3)	Day 1	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	Day 57 (± 3 days)		28 (± 7) Days After Last Dose[c]
Informed consent	X									
Randomization[e]				X						
Study drug dosing[f]		Day -28 to Day -1		Day 1 to 29			Day 29 to 57			
Demographics	X									
Medical history	X									
CFTR genotype[g]	X									
Height[h]	X									
Weight[h]	X	X		X	X	X	X	X	X	X
Physical examination[i]	Complete	Complete	Abbrev.	Abbrev.	Abbrev.	Abbrev.		Abbrev.	Abbrev.	Complete
Vital signs[j]	X	X		X	X	X	X	X	X	X

[a] All assessments will be performed predose, unless noted otherwise. Assessments that are collected predose and postdose will only be collected once if study drug is not administered on the day of the visit (i.e., if subject prematurely discontinued study drug treatment).

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

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

[d] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 9.1.4.

[e] Randomization may occur on the previous day (Day -1) after all inclusion and exclusion criteria and criteria for entry into the Treatment Period (see footnote d) have been confirmed.

[f] On days of scheduled visits, the in-clinic dose of study drug will be given in the morning, at least 6 hours apart from any other scheduled dose and after all predose assessments are complete. The last dose of VX-659 in Part 2 Period 1 will be the morning dose on the Day 29 Visit. The last dose of TEZ/IVA in Part 2 Period 2 will be the morning dose on the Day 57 Visit. Refer to Section 9.7 for details.

[g] *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 (see inclusion criterion 6).

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

[i] Complete and abbreviated PEs are described in Section 11.7.3. Symptom-directed PEs can be done at any time at the discretion of the investigator or healthcare provider.

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

Table 3-2 Study VX16-659-101 Part 2 (Subjects with F/F genotype): Schedule of Assessments

	Screening Period	Run-in (4 weeks)		Treatment Period (8 weeks)						Safety Follow-up
				Period 1 (4 weeks)[d]			Period 2 (4 weeks)			
Event/Assessment[a]	Screening Visit Days -56 to -29	Day -28 (± 1 day)	Day -14 (Days -15 to -3)	Day 1	Day 15 (± 2 days)	Day 29 (± 2 days)	Day 43 (± 3 days)	Day 57 (± 3 days)	ETT Visit[b]	28 (± 7) Days After Last Dose[c]
Pulse oximetry[j]	X	X		X	X	X	X	X	X	X
Standard 12-lead ECG[k]	X	X		X	X	X	X	X	X	X
Sweat chloride[l,o]	X		X	X	X	X	X	X	X	
Spirometry[m]	X		X	X	X	X	X	X	X	X
CFQ-R[n,o]				X	X	X	X	X		
Urinalysis[o]	X	X		X	X	X	X	X	X	X
Pregnancy test (all females of childbearing potential)	Serum	Urine		Urine		Urine		Urine	Serum	Serum
FSH[p]	X									
G6PD activity test[q]	X									
Serum chemistry and hematology[o]	X	X		X	X	X	X	X	X	X
Coagulation[o]	X	X		X	X	X			X	X

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

[l] See inclusion criterion 5 for information about the sweat chloride assessment for study eligibility. Sweat chloride assessments should be done at approximately the same time at every study visit during the Treatment Period and follow-up.

[m] The ppFEV1 assessment for stratification of randomization will be done at the Day -14 Visit. See Section 9.3.1. At the Screening Visit, spirometry may be done pre- or post-bronchodilator. At other study visits, spirometry will be done pre-bronchodilator, before the in-clinic dose of study drugs, and should be performed at approximately the same time at every visit. On the Day 1 and 15 Visits, spirometry will also be performed 5 hours (± 1 hour) after the in-clinic dose of study drugs.

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

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

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

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

Table 3-2 Study VX16-659-101 Part 2 (Subjects with F/F genotype): Schedule of Assessments

	Screening Period	Run-in (4 weeks)		Treatment Period (8 weeks)						Safety Follow-up
				Period 1 (4 weeks)[d]			Period 2 (4 weeks)			
Event/Assessment[a]	**Screening Visit Days -56 to -29**	**Day -28 (± 1 day)**	**Day -14 (Days -15 to -3)**	**Day 1**	**Day 15 (± 2 days)**	**Day 29 (± 2 days)**	**Day 43 (± 3 days)**	**Day 57 (± 3 days)**	**ETT Visit[b]**	**28 (± 7) Days After Last Dose[c]**
PK sampling[r]				X	X	X	X		X	
[redacted]										
AEs, medications[t], treatments, and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit									

[r] Blood samples will be collected for PK analysis of study drugs and metabolites. On the Day 1 Visit, samples will be collected before (0 hours) and 1, 2, 4, and 6 hours after the in-clinic dose. On the Day 15 Visit, samples will be collected before (0 hours) and 1, 2, 4, 6, and 8 hours after the in-clinic dose. On the Day 29 and 43 Visits, a single sample will be collected before the in-clinic dose. At the ETT Visit, a single sample will be collected.

[redacted]

Refer to Section 9.5 for details.

Table 3-3 Study VX16-659-101 Part 3 (Subjects with F/MF genotypes): Schedule of Assessments

Event/Assessment[a]	Screening Period		Treatment Period (4 weeks)			ETT Visit[b]	Safety Follow-up 28 (± 7) Days After Last Dose
			Period 1[c] (4 weeks)				
	Screening Visit Days -28 to -1	Stratification Visit[d] Days -27 to-3	Day 1	Day 15 (± 2 days)	Day 29 (± 2 days)		
Informed consent	X						
Randomization[e]			X				
Study drug dosing[f]			Day 1 through Day 29 Visit				
Demographics	X						
Medical history	X						
CFTR genotype[g]	X						
Height[h]	X						
Weight[h]	X		X	X	X	X	X

[a] All assessments will be performed predose, unless noted otherwise. Assessments that are collected predose and postdose will only be collected once if study drug is not administered on the day of the visit (i.e., if subject prematurely discontinued study drug treatment).

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

[c] To be eligible to continue into the Treatment Period, subjects must have stable CF disease and have remained on stable CF medication regimen during the 28 days before the Day 1 Visit AND must not have had an acute non-CF illness within 14 days before the Day 1 Visit. See Section 9.1.4.

[d] The spirometry assessment used for stratification must be performed at least 14 days after the last dose of any previous CFTR modulator treatment. Therefore, subjects being treated with 1 or more CFTR modulators (investigational or approved) within 14 days of the Screening Visit must have a separate Stratification Visit at least 14 days after the subject's last CFTR modulator dose. For subjects not being treated with any CFTR modulators within 14 days of the Screening Visit, the Screening Visit spirometry assessment can be used for stratification.

[e] Randomization may occur on the previous day (Day -1) after all inclusion and exclusion criteria and criteria for entry into the Treatment Period (see footnote c) have been confirmed.

[f] On days of scheduled visits, the in-clinic dose of study drugs will be given in the morning, at least 6 hours apart from any other scheduled dose and after all predose assessments are complete. The last dose of VX-659 and TEZ/VX-561 in Part 3 Period 1 will be the morning dose on the Day 29 Visit. Refer to Section 9.7 for details.

[g] *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 (see inclusion criterion 6).

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

Table 3-3 Study VX16-659-101 Part 3 (Subjects with F/MF genotypes): Schedule of Assessments

	Screening Period		Treatment Period (4 weeks)				
			Period 1[c] (4 weeks)				
Event/Assessment[a]	**Screening Visit Days -28 to -1**	**Stratification Visit[d] Days -27 to-3**	**Day 1**	**Day 15 (± 2 days)**	**Day 29 (± 2 days)**	**ETT Visit[b]**	**Safety Follow-up 28 (± 7) Days After Last Dose**
Physical examination[i]	Complete		Abbrev.	Abbrev.	Abbrev.	Abbrev.	Complete
Vital signs[j]	X		X	X	X	X	X
Pulse oximetry[j]	X		X	X	X	X	X
Standard 12-lead ECG[k]	X		X	X	X	X	X
Sweat chloride[l,o]	X		X	X	X	X	X
Spirometry[m]	X	X	X	X	X	X	X
CFQ-R[n,o]			X	X	X		
Urinalysis[o]	X		X	X	X	X	X
Pregnancy test (females of childbearing potential)	Serum		Urine		Urine	Serum	Serum
FSH[p]	X						

[i] Complete and abbreviated physical examinations (PEs) are described in Section 11.7.3. Symptom-directed PEs can be done at any time at the discretion of the investigator or healthcare provider.

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

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

[l] See inclusion criterion 5 for information about the sweat chloride assessment for study eligibility. Sweat chloride assessments should be done at approximately the same time at every study visit during the Treatment Period and follow-up.

[m] At the Screening Visit, spirometry may be done pre- or post-bronchodilator. At other study visits, spirometry will be done pre-bronchodilator, before the in-clinic dose of study drugs, and should be performed at approximately the same time at every visit. On the Day 1 and 15 Visits, spirometry will also be performed 5 hours (± 1 hour) after the in-clinic dose of study drugs.

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

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

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

Table 3-3 Study VX16-659-101 Part 3 (Subjects with F/MF genotypes): Schedule of Assessments

	Screening Period		Treatment Period (4 weeks)				
			Period 1[c] (4 weeks)				
Event/Assessment[a]	**Screening Visit Days -28 to -1**	**Stratification Visit[d] Days -27 to-3**	**Day 1**	**Day 15 (± 2 days)**	**Day 29 (± 2 days)**	**ETT Visit[b]**	**Safety Follow-up 28 (± 7) Days After Last Dose**
G6PD activity test[q]	X						
Serum chemistry and hematology[o]	X		X	X	X	X	X
Coagulation[o]	X		X	X	X	X	X
PK sampling[r]			X	X	X	X	
[redacted]							
AEs, medications[t], treatments, and procedures	Continuous from signing of the ICF through the Safety Follow-up Visit						

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

[r] Blood samples will be collected for PK analysis of study drugs and metabolites. On the Day 1 Visit, samples will be collected before (0 hours) and 1, 2, 4, and 6 hours after the in-clinic dose. On the Day 15 Visit, samples will be collected before (0 hours) and 1, 2, 4, 6, and 8 hours after the in-clinic dose. On the Day 29 Visit, a single sample will be collected before the in-clinic dose. At the ETT Visit, a single sample will be collected.

[redacted]

[t] Refer to Section 9.5 for details.

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Glossary of Terms

Abbreviation	Term
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	cystic fibrosis transmembrane conductance regulator protein
CFTR	cystic fibrosis transmembrane conductance regulator gene
Cl^-	chloride ion
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DNA	deoxyribonucleic acid
EC_{90}	concentration at which effect is at 90% of the maximum
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
E_{max}	maximum effect
ETT	early termination of treatment
F/F	homozygous for *F508del*
F/MF	heterozygous for *F508del* and a minimal *CFTR* function mutation that is not expected to respond to TEZ, IVA, or TEZ/IVA
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
$FEF_{25\%-75\%}$	forced expiratory flow at 25%-75% of forced vital capacity
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
FVC	forced vital capacity
G6PD	glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GLI	Global Lung Function Initiative
GPS	Global Patient Safety (Vertex)
HBE	human bronchial epithelial (cells)
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
IA	interim analysis
ICF	informed consent form

Abbreviation	Term
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IPD	important protocol deviation
IRB	institutional review board
IVA	ivacaftor (VX-770)
IWRS	interactive web response system
LLN	lower limit of normal
LUM	lumacaftor (VX-809)
MCP	multiple comparisons procedure
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model for repeated measures
OATP1B1	organic anion transporting polypeptide 1B1
PD	pharmacodynamic, pharmacodynamics
PE	physical examination
PI	pancreatic insufficiency
PK	pharmacokinetics
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
PR	PR interval
q12h	every 12 hours
qd	daily
QRS	portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QTc	QT interval corrected
QTcB	QT interval corrected by Bazett's formula
QTcF	QT interval corrected by Fridericia's formula
RR	interval from the onset of 1 QRS complex to the next
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SI	International System
SUSAR	suspected, unexpected, serious adverse reaction
SwCl	sweat chloride
TBD	to be determined
TC	triple combination
TE	treatment emergent
TEAE	treatment-emergent adverse event
TEZ	tezacaftor (VX-661)
ULN	upper limit of normal
US	United States
UV	ultraviolet

5 INTRODUCTION

5.1 Background

Cystic fibrosis (CF) is an autosomal recessive chronic disease with serious morbidities and frequent premature mortality. At present, there is no cure. CF affects approximately 70,000 individuals worldwide[1] (approximately 30,000 in the US[1,2] and 32,000 in the European Union[3]). Based on its prevalence, CF qualifies as an orphan disease.[4, 5]

CF is caused by reduced quantity and/or function of the CFTR protein due to mutations in the *CFTR* gene. The CFTR protein is an epithelial chloride channel that aids in regulating salt and water absorption and secretion and pH balance in sweat glands and multiple organs, including the lungs, pancreas, and other gastrointestinal organs. Despite progress in the treatment of CF with antibiotics and mucolytics, the predicted median age of survival for a person with CF is approximately 40 years.[2,6] Progressive loss of lung function is the leading cause of mortality.[7] More effective treatments are needed for CF.

More than 2000 mutations of the *CFTR* gene have been identified.[8] Most of these mutations are not associated with CF disease or are very rare. Currently, the CFTR2 database contains information on only 322 of these identified mutations, with sufficient evidence to define 281 mutations as disease-causing.[9] The most common disease-causing *CFTR* mutation, *F508del*, accounts for 70% of the identified alleles in people with CF, with nearly half of all people with CF are homozygous for *F508del*.

Based on the understanding of the molecular defects caused by *CFTR* mutations, 2 complementary approaches have been developed to address the decreased quantity and/or function of CFTR in order to enhance chloride transport in patients with CF. Correctors facilitate the cellular processing and trafficking to increase the quantity of functional CFTR at the cell surface. Potentiators increase the channel open probability of the CFTR protein delivered to the cell surface to enhance ion transport. Depending on the amount of residual CFTR channel activity in the membrane, and the pathophysiology of that activity (reflecting the *CFTR* genotype of the patient and possibly other factors), both approaches may be required.

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

VX-659 is a next-generation CFTR corrector. In vitro, VX-659 improves the processing and trafficking of F508del-CFTR, thereby increasing the quantity of functional F508del-CFTR protein at the cell surface.[10] The effect of VX-659 was additive to the effect of TEZ. The CFTR protein delivered to the cell surface by VX-659 alone or in combination with TEZ (VX-659/TEZ) was potentiated by IVA.[10] In human bronchial epithelial (HBE) cells studied in vitro, the triple combination (TC) of VX-659, TEZ, and IVA (VX-659/TEZ/IVA) increased CFTR chloride transport more than any of the dual combinations (VX-659/TEZ, VX-659/IVA, and TEZ/IVA) or individual components (VX-659, TEZ, and IVA) under most conditions studied.[10]

VX-561 (also known as CTP-656 and C-10355) is a deuterated isotope of IVA with a specific pattern of 9 substituted deuteriums. In vitro data indicate similar potency of VX-561 in HBE cells relative to IVA.[11] 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.

5.2 Rationale for This Study

This is the second clinical study of VX-659 and is designed to evaluate the safety and efficacy of VX-659 in TC with TEZ and either IVA or VX-561 in subjects with CF who are heterozygous for *F508del* with a second *CFTR* allele carrying a minimal function (MF) mutation that is not expected to respond to TEZ, IVA, or TEZ/IVA (F/MF genotypes) and homozygous for *F508del* (F/F genotype).

Data from nonclinical studies of VX-659, TEZ, IVA, and VX-561 and the current unmet medical need for new treatments for CF support clinical development of VX-659 in combination with other CFTR modulators for the treatment of CF.

6 STUDY OBJECTIVES

6.1 Primary Objectives

Parts 1 and 2: To evaluate the safety and tolerability of VX-659 in TC with TEZ and IVA

Part 3 (optional): To evaluate the safety and tolerability of VX-659 in TC with TEZ and VX-561

All parts: To evaluate the efficacy of VX-659 in TC with TEZ and either IVA or VX-561

6.2 Secondary Objectives

Parts 1 and 2: To evaluate the pharmacodynamic (PD) effects of VX-659 in TC with TEZ and IVA on CFTR function

Part 3 (optional): To evaluate the PD effects of VX-659 in TC with TEZ and VX-561 on CFTR function

All parts:

- To evaluate the pharmacokinetics (PK) of VX-659 when administered in TC with TEZ and either IVA or VX-561
- To evaluate the PK of TEZ, IVA, VX-561 and their respective metabolites when administered with VX-659 (as applicable)

7 STUDY ENDPOINTS

7.1 Primary Endpoints

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

7.2 Secondary Endpoints

- Absolute change in sweat chloride concentrations from baseline through the Day 29 Visit
- Relative change in $ppFEV_1$ from baseline through the Day 29 Visit
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline at the Day 29 Visit
- PK parameters of VX-659, TEZ, M1-TEZ, IVA, M1-IVA, and VX-561

8 STUDY POPULATION

Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects are randomized (Part 1 and Part 3) or receive TEZ/IVA in the Run-in Period (Part 2).

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 will be aged 18 years or older on the date of informed consent.
4. Body weight ≥35 kg.
5. Subjects must be able to produce a valid (quantity-sufficient) sweat sample at screening. If the initial screening collection results in insufficient sweat volume, then the sweat chloride collection may be repeated once, after approval by the medical monitor.
    - Parts 1 and 3: Subjects must have a sweat chloride value ≥60 mmol/L at screening or documented in the form of a laboratory report in the subject's medical record. If the sweat chloride value cannot be determined from the screening test for a reason other than insufficient sweat volume (i.e., because of laboratory error, damaged specimen, or equipment malfunction), it is acceptable to use a sweat chloride value that was obtained before previous treatment with IVA, LUM/IVA, or an investigational CFTR modulator.
    - Part 2: For subjects with a sweat chloride value ≥60 mmol/L at screening or documented in the form of a laboratory report in the subject's medical record, medical monitor approval is not required. For subjects with a sweat chloride value <60 mmol/L at screening and no documented historical value ≥60 mmol/L, medical monitor approval is required based on documented evidence of chronic sinopulmonary disease manifested by at least 1 of the following:

- Persistent colonization/infection with typical CF pathogens, including but not limited to, *Staphylococcus aureus*, *Haemophilus influenzae*, and/or *Pseudomonas aeruginosa*
- Chronic cough and sputum production
- Persistent chest radiograph abnormalities (e.g., bronchiectasis, atelectasis, infiltrates, hyperinflation)
- Nasal polyps, chronic sinusitis, or radiographic or computed tomographic abnormalities of the paranasal sinuses

6. Subjects must have an eligible *CFTR* genotype as noted below. If the screening *CFTR* genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used as a source document to establish eligibility and avert the risk of screening period expiration. Note: Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.10).
   - Part 1 and Part 3: Heterozygous for *F508del* with a second *CFTR* allele carrying an MF mutation that is not expected to respond to TEZ, IVA, or TEZ/IVA (Appendix A)
   - Part 2: Homozygous for *F508del*
7. FEV_1 value ≥40% and ≤90% of predicted mean for age, sex, and height (equations of the Global Lung Function Initiative [GLI])[12] at the Screening Visit. Spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria[13] for acceptability and repeatability.
8. Stable CF disease as judged by the investigator.
9. Willing to remain on a stable CF treatment regimen through the planned end of treatment or, if applicable, the Safety Follow-up Visit.

8.2 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, 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. Current or past history of peptic ulcer disease.
5. History of hemolysis.
6. Glucose-6-phosphate dehydrogenase (G6PD) deficiency, defined as G6PD activity less than the lower limit of normal (LLN) or 70% of the mean of the LLN and the upper limit of normal (ULN), whichever is greater.

7. Any of the following abnormal laboratory values at screening:
   - Hemoglobin <10 g/dL
   - Total bilirubin ≥2 × ULN
   - Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transpeptidase, or alkaline phosphatase ≥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)[14, 15]
8. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for sinopulmonary disease within 28 days before the first dose of study drug.
9. Lung infection with organisms associated with a more rapid decline in pulmonary status (e.g., *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*). For subjects who have had a history of a positive culture in the past, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
   - The subject has had 2 respiratory tract cultures negative for these organisms within the 12 months before the screening visit, with no subsequent positive cultures.
   - These 2 respiratory tract cultures were separated by at least 3 months, and 1 of them was obtained within 6 months before the screening visit.
10. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug.
11. A standard digital ECG demonstrating QTc >450 msec at screening. If QTc exceeds 450 msec for the screening ECG, the ECG should be repeated 2 more times during the Screening Period, and the subject will be excluded if the average of the 3 QTc values is >450 msec. Study sites should use QTcF unless they receive approval in advance from the medical monitor to use QTcB (Section 11.7.5).
12. History of solid organ or hematological transplantation.
13. History of alcohol or drug of abuse in the past year, including but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator.
14. Ongoing or prior participation in a study of an investigational treatment other than a CFTR modulator within 28 days or 5 terminal half-lives (whichever is longer) before screening. The duration of the elapsed time may be longer if required by local regulations.
15. Use of prohibited medications as defined in Table 9-3, within the specified window before the first dose of study drug.
16. Pregnant or nursing females. Females of childbearing potential must have a negative pregnancy test at screening and the Day 1 Visit (Part 1 and Part 3) or Day -28 Visit (Part 2).
17. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of

the study. An adult (aged 18 years or older) who is a relative of a study staff member may be randomized in the study provided that

- the adult lives independently of and does not reside with the study staff member, and
- the adult participates in the study at a site other than the site at which the family member is employed.

9 STUDY IMPLEMENTATION

9.1 Study Design

This is a Phase 2, randomized, double-blind, placebo- and TEZ/IVA-controlled, parallel-group, 3-part, multicenter study. All parts will be conducted concurrently. Subjects may not participate in more than 1 part.

Key study elements of each part are summarized in Table 9-1, treatment arms and planned doses are shown in Table 9-2, and a schematic of the study design is shown in Figure 9-1. Study visits and assessments are shown in Table 3-1 (Part 1), Table 3-2 (Part 2), and Table 3-3 (Part 3).

Table 9-1 Key Study Elements by Part

Element	Part 1	Part 2	Part 3 (optional)
Study population			
Genotype(s)	F/MF	F/F	F/MF
Age	≥18 years	≥18 years	≥18 years
$ppFEV_1$ criteria	≥40 to ≤90	≥40 to ≤90	≥40 to ≤90
Number of subjects	Approximately 54	Approximately 27	Approximately 24
Randomization			
Ratio	1:1:2:2 (placebo:TC-low: TC-mid:TC-high)	1:2 (TEZ/IVA:TC-high)	1:3 (placebo:TC2-high)
Stratification	$ppFEV_1$ (<70, ≥70)	$ppFEV_1$ (<70, ≥70)	$ppFEV_1$ (<70, ≥70)
Study design	Parallel group	Parallel group	Parallel group
Control	Placebo	TEZ/IVA	Placebo

F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a minimal *CFTR* function mutation that is not expected to respond to TEZ, IVA, or TEZ/IVA; IVA: ivacaftor; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TC: triple combination; TEZ: tezacaftor

Table 9-2 Treatment Arms and Planned Doses by Part

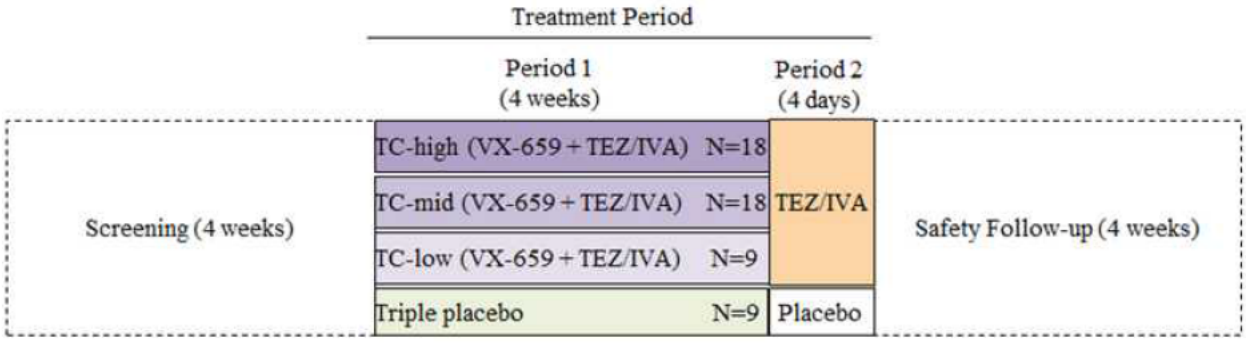
	Period 1			Period 2	
	VX-659 Dosage	TEZ Dosage	IVA Dosage	TEZ Dosage	IVA Dosage
Part 1					
TC-high	400 mg qd	100 mg qd	150 mg q12h	100 mg qd	150 mg q12h
TC-mid	240 mg qd	100 mg qd	150 mg q12h	100 mg qd	150 mg q12h
TC-low	80 mg qd	100 mg qd	150 mg q12h	100 mg qd	150 mg q12h
Triple placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Part 2[a]					
TEZ/IVA	Placebo	100 mg qd	150 mg q12h	100 mg qd	150 mg q12h
TC-high	400 mg qd	100 mg qd	150 mg q12h	100 mg qd	150 mg q12h

Part 3 (optional)			
		Period 1	
	VX-659 Dosage	TEZ Dosage	VX-561 Dosage
TC2-high	400 mg qd	100 mg qd	200 mg qd
Triple placebo	Placebo	Placebo	Placebo

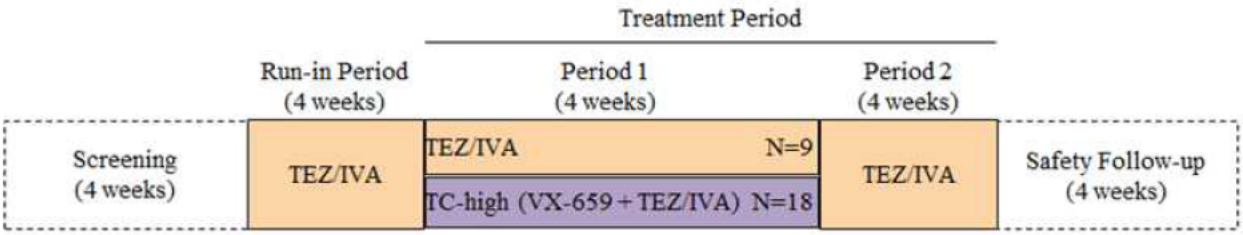
IVA: ivacaftor; q12h: every 12 hours; qd: daily; TC: triple combination; TEZ: tezacaftor
[a] In Part 2, all subjects will also receive TEZ 100 mg qd/IVA 150 mg q12h during the Run-in Period

Figure 9-1 Schematic of Study Design

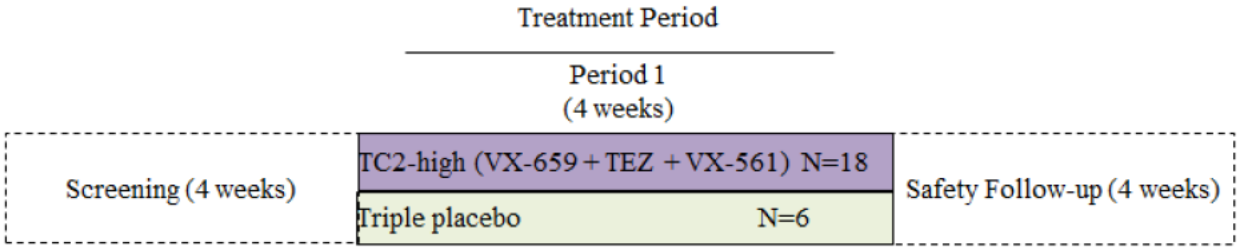
Part 1: Subjects With F/MF Genotypes



Part 2: Subjects With F/F Genotype



Part 3: Subjects with F/MF Genotypes (optional)



F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a minimal *CFTR* function mutation that is not expected to respond to TEZ, IVA, or TEZ/IVA; IVA: ivacaftor; N: number of subjects; TEZ: tezacaftor; TC: triple combination
Note: To maintain the blind, matching placebo tablets will be administered, as applicable, so that all subjects receive the same number of tablets within a given dosing period.

9.1.1 Screening

The Screening Period will occur within 28 days before the first dose of study drug. Screening assessments will be used to confirm that subjects meet the study eligibility criteria.

9.1.1.1 Repetition of Screening Assessment(s)

If screening spirometry measurements fail to meet acceptability and repeatability criteria as specified by American Thoracic Society/European Respiratory Society guidelines[13], repeat spirometry may be performed.

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

- If there is clear evidence of a damaged sample, laboratory error, or equipment malfunction, collection of a repeat sample for the appropriate laboratory test or assessment may be permitted.
- Exclusionary liver function tests results, which may be retested once within 14 days of the original screening date.
- Assessments required for eligibility that may be repeated as described in Sections 8.1 and 8.2.

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

9.1.1.2 Rescreening

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

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

- Repetition of Screening Period assessments (Section 9.1.1.1)
- Unexpected operational or logistic delays, or to meet the eligibility criteria
- To enable a subject's eligibility for this study to be determined before the subject discontinues previous CFTR modulator treatment (e.g., so that subjects can have screening assessments done while they are continuing to receive CFTR modulator treatment but have a washout period of at least 2 weeks before performing spirometry for stratification of randomization in this study and a washout period of at least 4 weeks before the Day 1 Visit in Part 1 and Part 3) (see Section 9.1.3 and Section 9.1.4).

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

9.1.2 Run-in Period (Part 2)

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

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

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

9.1.3 Randomization

For all parts, randomization will be stratified by $ppFEV_1$ values (<70 vs ≥70).

For subjects in Part 1 and Part 3, the spirometry assessment used for stratification must be performed at least 14 days after the last dose of any previous CFTR modulator treatment. Therefore, subjects being treated with 1 or more CFTR modulators (investigational or approved) within 14 days of the Screening Visit must have a separate Stratification Visit at least 14 days after the subject's last CFTR modulator dose. For subjects not being treated with any CFTR modulators within 14 days of the Screening Visit, the Screening Visit spirometry assessment can be used for stratification.

For subjects in Part 2, the $ppFEV_1$ assessment for stratification of randomization will be done at the Day -14 Visit. See Section 9.3.1.

Randomization will occur before the first dose of VX-659/control and may be done on either Day -1 or the Day 1 Visit, after all inclusion and exclusion criteria have been satisfied and the criteria for entry into the Treatment Period have been confirmed (see Section 9.1.4).

For Part 2, 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 a 4-week Run-in Period (Section 9.1.2).

9.1.4 Treatment Period

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

The total duration of treatment with study drug is approximately 5 weeks for Part 1 (Period 1 + Period 2), 12 weeks for Part 2 (Run-in + Period 1 + Period 2), and 4 weeks for Part 3 (Period 1 only). The duration of treatment with TC or placebo (Parts 1 and 3, Period 1) or TC or TEZ/IVA (Part 2, Period 1) is approximately 4 weeks. Study drug administration details are provided in Section 9.7.

9.1.5 Follow-up

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

A subject who was enrolled in Study VX14-661-110 and then enrolled in Part 2 of this study can re-enroll in Study 661-110 after completing this study. If the subject completes the Day 57 Visit of this study and then re-enters Study 661-110, the subject will not have a Safety Follow-up Visit in this study.

9.1.6 Early Termination of Treatment

If a subject prematurely discontinues treatment at any time after enrollment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the decision to terminate study drug treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 days after their last dose of study drug.

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

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

9.1.7 Independent Data Monitoring Committee

This study will be monitored by an independent data monitoring committee (IDMC), which will conduct reviews of safety data from all parts of the study as outlined in the IDMC charter. 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

An interactive web response system (IWRS) will be used to assign subjects to treatment. The randomization code list will be produced by Vertex Biometrics or a qualified randomization vendor.

9.3 Rationale for Study Design and Study Drug Regimens

9.3.1 Study Design

Stratification of Randomization

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 study drug dosing. Therefore, randomization in all parts will be stratified by pretreatment $ppFEV_1$ values, defined as the last $ppFEV_1$ measurement before treatment with VX-659. For Parts 1 and 3, this value is determined at screening, except for those subjects who require a Stratification Visit, in which case the value is determined at that visit. For Part 2, the pretreatment $ppFEV_1$ value is determined at the Day -14 Visit during the Run-In Period.

Control Treatments

Part 1 and Part 3: Efficacy has not been demonstrated for a corrector, potentiator, or any corrector/potentiator combination in subjects with F/MF genotypes. A Phase 3 study of TEZ/IVA in subjects with F/MF genotypes (Study VX14-661-107) was terminated following a planned interim futility analysis, which showed that the combination of TEZ/IVA did not result in a prespecified improvement in $ppFEV_1$. Because there is no effective treatment for this population, a placebo arm will be included as the control in Part 1 and Part 3.

Part 2: A Phase 3 study of TEZ/IVA (Study VX14-661-106) demonstrated a clinically meaningful benefit in subjects with the F/F genotype[16]; therefore, TEZ/IVA is the active control.

Run-in Period

Part 2 will have a 4-week run-in period to establish a reliable on-treatment (TEZ/IVA) baseline for comparison to Period 1, when subjects will additionally receive VX-659 or placebo.

Period 2

Part 1 and Part 2 include a second dosing period (Period 2), during which subjects will be administered TEZ/IVA. In Part 1, Period 2 is 4 days and is included to enable a more thorough evaluation of VX-659 exposure-response relationships by conducting PK and PD assessments during the VX-659 washout. In Part 2, Period 2 is 4 weeks to enable an assessment of PD and efficacy endpoints after VX-659 is washed out.

9.3.2 Study Drug Dose and Duration

VX-659 Dosage

Part 1 will evaluate 3 dose levels of VX-659 in TC with TEZ/IVA in subjects with F/MF genotypes. The high dose of VX-659 to be evaluated as part of the TC is 400 mg qd. In healthy subjects in Study VX16-659-001, VX-659 monotherapy was shown to be safe and well tolerated at multiple doses up to 400 mg qd for 10 days, and VX-659 was safe and well tolerated at multiple doses up to 200 mg q12h in TC with TEZ 100 mg qd/IVA 150 mg q12h for 14 days.

The dose levels evaluated in Part 1 are expected to provide clinical benefit (based on in vitro data) and will provide a range of exposure for exposure-response analyses of efficacy and safety. The TC-high dose will also be used in Part 2 and Part 3. 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 *F508del*, including F/F, based on the similar potency of the TC in HBE cells that have 1 copy or 2 copies of *F508del*.[10]

TEZ Dosage

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

IVA Dosage

When administered in combination with VX-659, the IVA dosage will be 150 mg q12h. A dosage of 150 mg q12h is being used in Phase 3 studies of TEZ/IVA and is also the approved IVA monotherapy dosage for patients aged 12 years and older (150 mg q12h).

VX-561 Dosage

The VX-561 dosage will be 200 mg qd, based on preliminary PK and safety results for VX-561 from Study VX16-770-018, which evaluated the relative bioavailabity of the 50-mg tablet of VX-561 being used in the current study, and Study VX16-659-001, which is evaluating VX-561 200 mg qd in combination with VX-659 (400 mg qd) and TEZ (100 mg qd). A VX-561 dose of 200 mg qd in TC with VX-659 and TEZ is predicted to provide similar exposure of deuterated IVA relative to that of IVA following a dose of 150 mg q12h.

Treatment Duration

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

9.3.3 Rationale for Study Population

The study will include subjects with F/MF (Parts 1 and 3) and F/F (Part 2) genotypes based on in vitro data that indicate the potential for significant improvements in chloride transport for CF patients with 1 or 2 copies of *F508del* in response to treatment with TC. Each genotype group will be evaluated in a different part of the study because of the potential for differences in the magnitude of treatment response across the genotype categories, and also because of the differences in current standard of care, which informs the use of active control or triple placebo in the control arm.

9.3.4 Rationale for Study Assessments

All safety and PK assessments are common assessments for clinical studies, with the exception of the G6PD activity test to be performed at screening in this study. [redacted] prospective subjects will be screened for G6PD deficiency, and individuals who are G6PD deficient will be excluded as a precaution.

The PD and efficacy assessments are widely accepted and are relevant to the study of patients 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).

9.4 Prohibited Medications

[redacted]

9.5 Prior and Concomitant Medications

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

- Subjects must remain on a stable medication (and supplement) regimen for their CF from 28 days before the Day 1 Visit through the Safety Follow-up Visit. Stable medication regimen is defined as the current medication regimen for CF that subjects have been following for at least 28 days before the Day 1 Visit. Subjects must not initiate long-term treatment with new medication from 28 days before the Day 1 Visit through the Safety Follow-up Visit unless discussed and approved by the medical monitor. Guidelines for stable medication regimens for CF are as follows:

- Subjects who are taking daily inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.
- Subjects who cycle onto and off of an inhaled antibiotic should continue on their prior schedule. The timing of the first dose of study drug on 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 (chronically), or prednisone or prednisolone 60 mg qd for up to 5 days without prior approval of the medical monitor.
- Information about bronchodilator use during the study will be collected and documented. Subjects who are using a bronchodilator must have their spirometry assessments performed according to the guidelines provided in Section 11.6.1.

9.6 Study Restrictions

9.6.1 Exposure to Sunlight

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

9.7 Study Drug Administration

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

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

1. It is recommended that the dose be taken within 30 minutes of the start of the meal or snack.
2. Study drug will be administered qd (± 2 hours) or q12h (± 2 hours). For each subject, doses of study drugs will be taken at approximately the same time each day. For example, if dosing is q12h, the morning dose could be taken at 08:00 every morning and the evening dose could be taken at 20:00 every evening throughout the study.
3. The date, amount taken, and time of study drug administration, including whether food was taken with each dose, will be recorded for the 2 doses before PK sample collection and the dose received on the morning of PK sample collection.
4. On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. A meal or snack will be provided by the site for the morning dose of study drug.
5. 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 his/her dose with food. If more than 6 hours (q12h dosing) or 12 hours (qd dosing) have elapsed after his/her usual dosing time, the subject should skip that dose and resume his/her normal schedule for the following dose. Examples are provided below:

If study drug is administered q12h:

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

If study drug is administered qd:

- if the dose of study drug should have been taken at approximately 08:00, and the subject remembers before 20:00 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.

9.8 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.

9.9 Stopping Rules

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

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

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

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

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

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

- Subsequent ALT or AST values confirm the initial elevation that satisfied the interruption rule (above), and no convincing alternative etiology (e.g., acetaminophen use, viral hepatitis, or alcohol ingestion) is identified, regardless of whether transaminase levels have improved
- Subsequent indirect bilirubin values confirm the initial value as >2 × ULN (defined as ULN for total bilirubin minus ULN for direct bilirubin), in association with decreased haptoglobin

If an alternative, reversible cause of transaminase elevation and/or increased bilirubin or clinical jaundice has been identified, study drug administration may be resumed once transaminases or bilirubin return to baseline or are ≤2 × ULN, whichever is higher. Approval of the medical monitor is required before resumption of study drug. Upon resumption of study drug, transaminases and bilirubin should be assessed weekly for 4 weeks. If a protocol-defined transaminase or bilirubin elevation interruption threshold recurs during Period 1 or Period 2 (with confirmation of the initial elevation by repeat testing within 48 to 72 hours), then study drugs must be permanently discontinued, regardless of the presumed etiology.

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

9.10 Removal of Subjects

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

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

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

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a Safety Follow-up Visit, if applicable (see Section 9.1.6), and follow up with the subject regarding any unresolved AEs.

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

9.11 Replacement of Subjects

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

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

10 STUDY DRUG ADMINISTRATION AND MANAGEMENT

Study drug refers to VX-659, TEZ, TEZ/IVA, IVA, VX-561, 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

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

10.3 Study Drug Supply, Storage, and Handling

VX-659 and matching placebo will be supplied as tablets of similar size and appearance containing 80 mg VX-659 and 0 mg VX-659, respectively (Table 10-1).

TEZ/IVA (100 mg/150 mg) and matching placebo will be supplied as film-coated tablets of similar size and appearance containing 100 mg TEZ/150 mg IVA and 0 mg TEZ/0 mg IVA, respectively (Table 10-1).

IVA (150 mg) and matching placebo will be supplied as film-coated tablets of similar size and appearance containing 150 mg IVA and 0 mg IVA, respectively (Table 10-1).

TEZ and matching placebo will be supplied as tablets of similar size and appearance containing 50 mg TEZ and 0 mg TEZ, respectively (Table 10-1).

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 (Table 10-1).

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

Table 10-1 Study Drug: Strength/Formulation/Route

Drug Name	Strength/Formulation/ Route
VX-659	80-mg tablet, oral
VX-659-matching placebo	0-mg tablet, oral
TEZ/IVA fixed-dose	100-mg/150-mg tablet; oral
TEZ/IVA-matching placebo	0-mg/0-mg tablet; oral
IVA	150-mg tablet, oral
IVA-matching placebo	0-mg tablet, oral

Table 10-1 Study Drug: Strength/Formulation/Route

Drug Name	Strength/Formulation/ Route
TEZ	50-mg tablet, oral
TEZ-matching placebo	0-mg tablet, oral
VX-561	50-mg tablet, oral
VX-561-matching placebo	0-mg tablet, oral

IVA: ivacaftor; TEZ: tezacaftor

10.4 Drug Accountability

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

10.5 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 will contact the medical monitor to discuss discontinuing the subject from the study.

10.7 Blinding and Unblinding

This will be a double-blind study.

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 and her fetus in the event of a pregnancy
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy serious adverse event (SAE) processing and reporting regulations
- Unblinded statistician preparing the final (production) randomization list who is not part of the study team
- Vertex IWRS Manager
- Vertex Clinical Supply Chain
- IDMC
- Vendor performing the interim analyses (IAs) and preparing the unblinded analysis for the ongoing reviews of efficacy and safety data, and the IDMC
- Bioanalytical contract research organization (CRO) analyzing PK samples and Vertex Bioanalytical personnel who are not members of the study team may review raw data from Bioanalytical CRO.
- 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

Blinding of Sweat Chloride and Spirometry Results:

- The Vertex study team will not have access to sweat chloride or spirometry results after a subject receives the first dose of study drug on the Day 1 Visit until after the data are unblinded for full review per Section 12.3.6.1.
- Sites, subjects, and their parents/caregivers/companions should not be informed of a subject's study-related sweat chloride results until after the subject's last study visit, even if the subject prematurely discontinues treatment.
- Subjects and their parents/caregivers/companions should not be informed of the subject's study-related spirometry results until after the subject's last study visit, even if the subject prematurely discontinues treatment.

10.7.2 Unblinding

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

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

Unblinding of the individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, investigators will use their best judgment as to

whether to unblind without first attempting to contact the medical monitor to discuss and agree to the need for unblinding. If investigators deem it not necessary to unblind immediately, they will first attempt to contact the medical monitor to discuss and agree to the need for unblinding. If investigators have tried but are unable to reach the medical monitor, they will use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding without having successfully reached and discussed the situation with the medical monitor.

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

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

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor will be notified within 24 hours of the unblinding event. The reason and the date of the unblinding will be documented clearly in the subject's study file. Information about the treatment assignment obtained from the unblinding will be maintained in a secure location with controlled access and will not be shared with the sponsor (Vertex), CRO, or any site personnel (other than the physician treating the subject). In addition, the investigator will consider whether the clinical event that prompted unblinding will be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to Vertex GPS or designee, per Section 13.1.2.

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

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

Unblinded Reviews of Data by Vertex for Administrative Purposes (Planning, Decision-making, and Regulatory Submission)

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

Unblinding: Interim Analysis Results

Interim analyses may be conducted for any part of the study after at least 50% of subjects in the part have completed the Day 15 Visit (see Section 12.3.6.1). Each IA will only include data for a single part of the study. The results of these analyses will be reviewed by a limited Vertex team. When an IA is performed after all subjects in a part have completed the Safety Follow-up Visit, results from that part will be unblinded for full review by the Vertex study team.

11 ASSESSMENTS

The Schedules of Assessments are shown in Table 3-1 (Part 1), Table 3-2 (Part 2), and Table 3-3 (Part 3).

11.1 Timing of Assessments

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

11.2 Subject and Disease Characteristics

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

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

Height and weight will be measured with shoes off.

11.3 Pharmacokinetics

11.3.1 Blood Sampling

Blood samples will be collected to determine plasma concentrations of VX-659, TEZ, M1-TEZ, IVA, M1-IVA, and VX-561. These samples may also be used for evaluation of VX-659 or VX-561 metabolites, for evaluation of additional TEZ or IVA metabolites, for further evaluation of the bioanalytical method, and for exploratory analyses that provide information on the metabolic pathways used by or affected by VX-659; these results may not be included in the clinical study report.

All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. Acceptable windows for sampling times are shown in Table 11-1. Samples collected outside of these acceptable windows will be considered protocol deviations.

Table 11-1 Acceptable Pharmacokinetic Sampling Windows

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

For each visit with a PK blood draw, a record of study drug administration will be collected as described in Section 9.7. The collection date and exact time that each PK blood sample is drawn will also be recorded.

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

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

11.3.2 Processing and Handling of Pharmacokinetic Samples

Detailed procedures for the collection of blood samples and further procedures for processing and handling of samples for PK analysis will be provided in the PK Sample Handling Guidelines.

11.3.3 Bioanalysis

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

11.4 Pharmacodynamics

Collection of sweat samples will be done with an approved collection device. At each time point, 2 samples will be collected, 1 from each arm (left and right). Sweat samples will be sent to a central laboratory for testing and interpretation of results. Individual sweat chloride test results will not be disclosed to the study sites after those from pre-dose on the Day 1 Visit. Specific instructions for collection, handling, processing, and shipping of sweat chloride samples to the central laboratory will be provided separately. See Section 10.7.1 for information about blinding of sweat chloride results.

[redacted]

11.6 Efficacy

11.6.1 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines/European Respiratory Society Guidelines[13] and the following additional guidelines:

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

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

During the Screening Period, spirometry assessments may be performed pre- or post-bronchodilators. At all other visits, all spirometry assessments should be performed

"pre-bronchodilator." During the Treatment Period, spirometry assessments must be performed before the in-clinic dose of study drug, at approximately the same time at each visit.

If 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 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.

The measured spirometric values listed below will be converted to percent predicted values using the GLI standards.[12]

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

11.6.2 Cystic Fibrosis Questionnaire-Revised

Subjects will be asked to complete the CFQ-R in their native language, if validated translations are available.[18, 19] 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.[20, 21]

11.7 Safety

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

11.7.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with ICH GCP guidelines. Section 13.1 outlines the definitions, collection periods, criteria, and procedures for

documenting, grading, and reporting AEs. A separate document that details AE case report form (CRF) completion guidelines for investigators as well as training will be provided.

11.7.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory, with the exception of the urine pregnancy tests which will be performed and analyzed at the site. Fasting is not required. The safety laboratory test panels are shown in Table 11-2.

Laboratory test results that are abnormal and considered clinically significant will be reported as AEs.

Table 11-2 Safety Laboratory Test Panels

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

[a] Blood smears will be saved for future evaluation, if needed.
[b] If urine is positive for leukocyte esterase, nitrite, protein, or blood, microscopic examination of urine will be performed for leukocytes, erythrocytes, crystals, bacteria, and casts.
[c] If blood urea nitrogen cannot be collected, urea may be substituted.
[d] Haptoglobin will be analyzed only if there is evidence of possible hemolysis as determined by the site.

Pregnancy (β-human chorionic gonadotropin) Tests for Females of Childbearing Potential: Serum samples will be analyzed for β-human chorionic gonadotropin at the central laboratory. Urine pregnancy tests will be performed at the site. The urine pregnancy test must be negative before the first dose of study drug (Day 1 Visit for Part 1 and Part 3; Day -28 Visit for Part 2). Pregnancy tests shown in Table 3-1, Table 3-2, and Table 3-3 are required in all countries.
s. Additional urine pregnancy tests may be required according to country-specific regulations and/or requirements.

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

CFTR genotype (Screening Period only): *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used to establish eligibility. Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.10).

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

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

For purposes of study conduct, the central laboratory must be used for all laboratory tests with the exception of the G6PD activity test. Local laboratories may be used at the discretion of the local investigator for management of urgent medical issues. If a local laboratory test value is found to be abnormal and clinically significant, it will be verified by the central laboratory as soon as possible after the investigator becomes aware of the abnormal result. If it is not possible to send a timely specimen to the central laboratory (e.g., the subject was hospitalized elsewhere), the investigator may base the assessment of an AE on the local laboratory value.

11.7.3 Physical Examinations and Vital Signs

A PE of all body systems will be done at screening and select study visits. At other visits, symptom-directed PEs can be done at the discretion of the investigator or healthcare provider.

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

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

Vital signs include blood pressure (systolic and diastolic), temperature (oral), pulse rate, and respiration rate. These will be assessed following at least a 5-minute rest in the seated position. Vital signs will be assessed according to Table 3-1, Table 3-2, and Table 3-3.

11.7.4 Pulse Oximetry

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

11.7.5 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout according to the Table 3-1, Table 3-2, and Table 3-3. Additional standard 12-lead ECGs will be performed at any other time if clinically indicated.

A subject should be rested for at least 5 minutes before an ECG is performed.

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

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

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

11.7.6 Pregnancy and Contraception

The effects of VX-659 monotherapy or in TC with TEZ and IVA or VX-561 on conception, pregnancy, and lactation in humans are not known. VX-659, TEZ, IVA, and VX-561 did not show genotoxic potential in a standard battery of in vitro (Ames test or micronucleus in cultured mammalian cells) and in vivo (rodent micronucleus) studies. VX-659, TEZ, and IVA also did not show genotoxic potential in chromosomal aberration studies. Reproductive toxicology studies of VX-659, TEZ, and IVA have not shown teratogenicity in rats and rabbits.

11.7.6.1 Contraception

Contraception requirement for the couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. True abstinence must be practiced from the Screening Visit through 90 days after the last dose of study drug.
- If the male is infertile (e.g., bilateral orchiectomy). If a male subject is assumed to have complete bilateral absence of the vas deferens, infertility must be documented before the first

dose of study drug (e.g., examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound).

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

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

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

Table 11-3 Acceptable Methods of Contraception

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

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

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

Additional notes:

- Male subjects must not donate sperm during the period starting from the first dose of study drug until 90 days after the last dose of study drug.

- Female subjects should not nurse a child during the period starting from the first dose of study drug until 90 days after the last dose of study drug.
- For male subjects with a female partner of childbearing potential, the couple must not plan to become pregnant during the study or within 90 days after the last study drug dose.

11.7.6.2 Pregnancy

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

If a female subject or the female partner of a male subject becomes pregnant while participating in the study, other than a female partner as the result of artificial insemination using sperm banked by the male subject before the first dose of study drug, study drug will be permanently discontinued immediately. The investigator will notify the medical monitor and Vertex GPS within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy using the Pregnancy Information Collection Form.

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

12 STATISTICAL AND ANALYTICAL PLANS

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

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

12.1 Sample Size and Power

12.1.1 Primary Objectives

The primary objectives of the study are the evaluation of safety and tolerability, and efficacy of VX-659 in TC with TEZ and either IVA or VX-561. The sample size calculations described below are deemed adequate to evaluate the objectives of the study, based on clinical and statistical considerations.

12.1.1.1 Safety and Tolerability

The primary safety endpoint is the incidence of AEs. Approximately 105 subjects will be randomized in the study with approximately 81 subjects receiving VX-659 in TC. The sample size for each treatment group will provide sufficient data for a descriptive analysis of AEs.

12.1.1.2 Efficacy

The primary efficacy endpoint is the absolute change from baseline in $ppFEV_1$ through the Day 29 Visit in all parts. A sample size of 18 subjects per treatment group provides at least 90% power to detect a mean within-group change of 7 percentage points.

12.1.2 Secondary Objectives

A secondary objective of the study is the evaluation of the PD effect of VX-659 in TC with TEZ and either IVA or VX-561.

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

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

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

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

E_{max}: maximum effect; TC: triple combination

A total sample size of 54 subjects in Part 1 will provide at least 90% power to detect a dose-response trend with MCP.

12.2 Analysis Sets

The following analysis sets are defined: All Subjects Set, Full Analysis Set (FAS), and Safety Set. An additional analysis set related to the Run-in Period in Part 2 will be defined in the statistical analysis plan (SAP), as appropriate.

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

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

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

12.3 Statistical Analysis

This section presents a summary of the planned statistical analyses of the PD, efficacy, and safety endpoints of the study. Statistical analysis details will be provided in the SAP.

12.3.1 General Considerations

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

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

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

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

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

The Treatment-emergent (TE) Period will include the time from the first dose in Period 1 to the Safety Follow-up Visit or 28 days after the last dose of the study drug for subjects who do not complete the Safety Follow-up Visit. Only data collected up to the end of study for a subject will be included in the analysis. An additional TE period related to the Run-in Period for Part 2 will be defined in the SAP, as appropriate.

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

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

All data will be summarized for 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, completed Treatment Period, completed study/Safety Follow-up Visit, and discontinued treatment or study with a breakdown of the reasons for discontinuation) will be summarized overall and by treatment group.

12.3.2.2 Demographics and Baseline Characteristics

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

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

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

12.3.2.3 Prior and Concomitant Medications

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

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

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

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

An additional classification of concomitant medications related to the Run-in Period for Part 2 will be defined in the SAP, as appropriate.

12.3.2.4 Study Drug Exposure and Compliance

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

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

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

12.3.2.5 Important Protocol Deviations

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

IPDs will be provided in an individual subject data listing.

12.3.3 Efficacy Analysis

12.3.3.1 Analysis of Primary Efficacy Variables

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

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

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

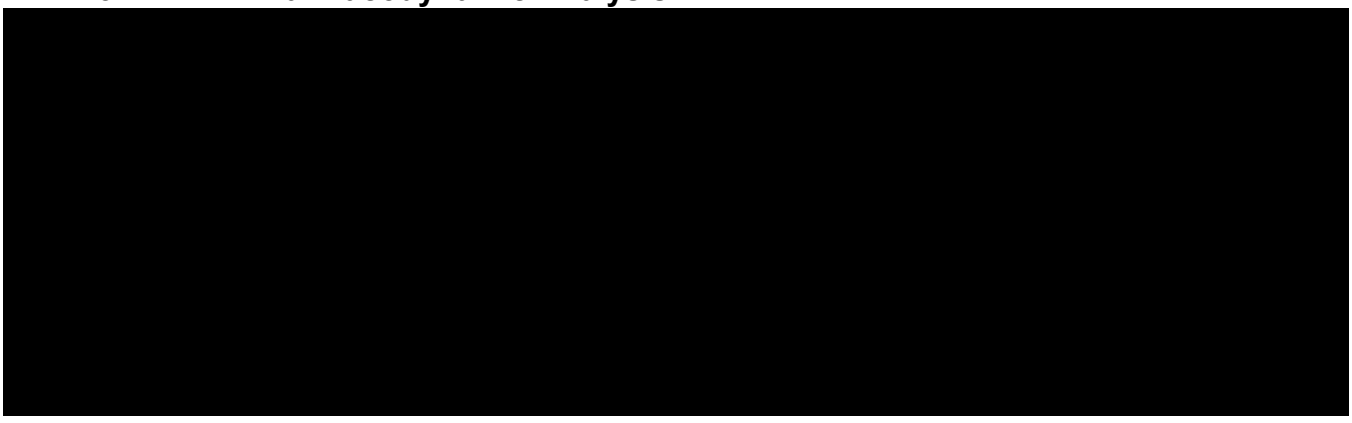
Additional supportive analyses using Period 2 in Parts 1 and 2 will be described in the SAP. Subgroup analyses will also be described in the SAP.

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

12.3.3.2 Analysis of Secondary Efficacy Variables

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

12.3.4 Pharmacodynamic Analysis



Estimation of Treatment Effects

In a separate MMRM model, adjusted means and 95% confidence intervals of the average treatment effects through the Day 29 Visit, with 2-sided *P* values, for all within-group and

between-group comparisons will be estimated within MMRM, with appropriate adjustment for covariates.

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

12.3.5 Safety Analysis

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

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

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

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

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

12.3.5.1 Adverse Events

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

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

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

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

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

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

12.3.5.2 Clinical Laboratory Assessments

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

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

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

12.3.5.3 Electrocardiogram

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 (QTcF), QRS duration, and heart rate (beats per minute).

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

Additional ECG analyses will be described in the SAP.

12.3.5.4 Vital Signs

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 will be described in the SAP.

12.3.5.5 Pulse Oximetry

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

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

12.3.5.6 Physical Examination

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

12.3.5.7 Other Safety Analysis

Not applicable.

12.3.6 Interim and IDMC Analyses

12.3.6.1 Interim Analysis

Interim analyses may be conducted for any part of the study after at least 50% of subjects in the part have completed the Day 15 Visit. Each IA will only include data for a single part of the study. The results of these analyses will be reviewed by a limited Vertex team. When an IA is performed after all subjects in a part have completed the Safety Follow-up Visit, results from that part will be unblinded for full review by the Vertex study team.

12.3.6.2 IDMC Analyses

IDMC analyses will be conducted as outlined in the IDMC Charter.

12.4 Clinical Pharmacology Analyses

12.4.1 Pharmacokinetic Analysis

The PK analysis of VX-659, TEZ and metabolite M1-TEZ, IVA and metabolite M1-IVA, and VX-561 may be performed using nonlinear mixed effects modeling. Standard noncompartmental analysis may also be performed as data allow. Descriptive statistics will be used to summarize PK parameter values for all analytes.

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

12.4.2 Pharmacokinetic/Pharmacodynamic Analyses

[redacted]

[redacted]

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

13.1.1.2 Clinically Significant Assessments

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

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

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

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

A laboratory value that is Grade 4 will not automatically be an SAE. A Grade 4 laboratory value will be an SAE if the subject's clinical status indicates a life-threatening AE.

13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time ICF is signed until the following time points:

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

- For enrolled subjects who do not have a Safety Follow-up Visit, the earliest of
  - 28 days after the last dose of study drug, or
  - the ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (see Section 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 in the study will be recorded only in the subject's source documents. The following data will be documented for each AE:

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

13.1.1.4 Adverse Event Severity

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

Table 13-1 Grading of AE Severity

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

13.1.1.5 Adverse Event Causality

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

Table 13-2 Classifications for AE Causality

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

13.1.1.6 Study Drug Action Taken

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

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

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

AE: adverse event

13.1.1.7 Adverse Event Outcome

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

Table 13-4 Classifications for Outcome of an AE

Classification	Definition
Recovered/Resolved	Resolution of an AE with no residual signs or symptoms
Recovered/Resolved With Sequelae	Resolution of an AE with residual signs or symptoms
Not Recovered/Not Resolved (Continuing)	Either incomplete improvement or no improvement of an AE, such that it remains ongoing

Table 13-4 Classifications for Outcome of an AE

Classification	Definition
Fatal	Outcome of an AE is death. "Fatal" will be used when death is at least possibly related to the AE.
Unknown	Outcome of an AE is not known (e.g., a subject lost to follow-up)

AE: adverse event

13.1.1.8 Treatment Given

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

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

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

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

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

Clarification will be made between the terms "serious" and "severe" because they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event, as in mild, moderate, or severe myocardial infarction. The event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as

"serious," which is based on subject/event outcome or action described above, and is usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining expedited regulatory reporting obligations.

13.1.2.2 Documentation of Serious Adverse Events

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

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

13.1.2.3 Reporting Serious Adverse Events

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

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (preferred choice)

Fax: [redacted]

Contact Telephone: [redacted]

13.1.2.4 Expedited Reporting and Investigator Safety Letters

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

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

13.2 Administrative Requirements

13.2.1 Ethical Considerations

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

13.2.2 Subject Information and Informed Consent

The investigator (or an appropriate authorized designee) will obtain informed consent from each subject before any study procedure takes place. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

13.2.3 Investigator Compliance

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

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

13.2.4 Access to Records

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

13.2.5 Subject Privacy

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

review of the data collection process. The FDA and regulatory authorities in other jurisdictions, including the IRB/IEC, may also request access to all study records, including source documentation, for inspection.

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

13.2.6 Record Retention

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

13.2.7 Study Termination

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

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

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

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

13.3 Data Quality Assurance

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

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data for each enrolled subject will be entered into a CRF by study site

personnel using a secure, validated, web-based electronic data capture (EDC) application. Vertex will have read-only access to site-entered clinical data in the EDC application.

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

13.4 Monitoring

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

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

13.5 Electronic Data Capture

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

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

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

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

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

13.6 Publications and Clinical Study Report

13.6.1 Publication of Study Results

Any and all scientific, commercial, and technical information disclosed by Vertex in this protocol or elsewhere will be considered the confidential and proprietary property of Vertex. The investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The investigator shall not use such information for any purpose other than determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The investigator understands that the information developed from this clinical study will be used by Vertex in connection with the development of the study drug and other drugs and diagnostics, and therefore may be disclosed as required to other clinical investigators, business partners and associates, the FDA, and other government agencies. The investigator also understands that, to allow for the use of the information derived from the clinical study, the investigator has the obligation to provide Vertex with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between Vertex and the investigator and/or the investigator's institution.

13.6.2 Clinical Study Report

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

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Appendix A *CFTR* Mutations That Are Predicted to Result in a CFTR Protein With Minimal Function (Part 1 and Part 3)

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

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

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

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

CFTR Mutations Eligible for VX16-659-101, Part 1 and Part 3

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

CFTR Mutations Eligible for VX16-659-101, Part 1 and Part 3

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

Source: CFTR2.org [Internet]. Baltimore (MD): Clinical and functional translation of CFTR. The Clinical and Functional Translation of CFTR (CFTR2), US Cystic Fibrosis Foundation, Johns Hopkins University, the Hospital for Sick Children. Available at: http://www.cftr2.org/. Accessed 15 February 2016.
CFTR: cystic fibrosis transmembrane conductance regulator; IVA: ivacaftor; LUM: lumacaftor; PI: pancreatic insufficiency; SwCl: sweat chloride; TEZ: tezacaftor
Note: %PI: percentage of *F508del-CFTR* heterozygous patients in the CFTR2 patient registry who are pancreatic insufficient; $SwCl^-$: mean sweat chloride of *F508del-CFTR* heterozygous patients in the CFTR2 patient registry
[a] Also known as 2183delAA→G.
[b] Unpublished data.

15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX16-659-101	Version #: 3.0	Version Date: 01 September 2017
Study Title: A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety and Efficacy of VX-659 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 #: VX16-659-101	Version #: 3.0	Version Date: 01 September 2017
Study Title: A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety and Efficacy of VX-659 Combination Therapy in Subjects Aged 18 Years and Older With Cystic Fibrosis		

I have read Protocol VX16-659-101, Version 3.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-659, tezacaftor, ivacaftor, and VX-561 (CTP-656) and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date