

1 TITLE PAGE



*VERTEX PHARMACEUTICALS INCORPORATED*

## **Clinical Study Protocol**

**A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-121 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for *F508del* and a Minimal Function Mutation (F/MF)**

**Vertex Study Number: VX20-121-102**

**IND Number: 142001**

**EudraCT Number: 2021-000712-31**

**Date of Protocol:** 19 August 2021 (Version 3.0)

Replaces Version 2.0, dated 12 July 2021

Vertex Pharmaceuticals Incorporated  
50 Northern Avenue  
Boston, MA 02210-1862, USA

### **CONFIDENTIAL**

This document contains confidential information. Any use, distribution, or disclosure without the prior written consent of Vertex Pharmaceuticals Incorporated is strictly prohibited except to the extent required under applicable laws or regulations. Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

## Summary of Changes to the Protocol

The previous version of this protocol (Version 2.0, 12 July 2021) was amended to create the current version (Version 3.0, 19 August 2021). The protocol history is provided below.

Protocol History	
Version and Date of Protocol	Comments
Version 1.0, 27 April 2021	Original version
Version 2.0, 12 July 2021	Clarified definition of minimal function mutations eligible for enrollment; Added exclusion criteria that subjects cannot participate in an interventional study of a non-investigational treatment from screening through end of study participation; Updated acceptable methods of contraception based on supporting nonclinical data
Version 3.0, 19 August 2021	Current version

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

Change and Rationale	Affected Sections
Increased planned sample size and Treatment Period duration	Global
Study endpoints were updated to reflect the change in Treatment Period duration	Sections 2, 7, and 12.3.3
Liver function test elevations, creatine kinase elevations, rash, cataracts, hypoglycemia, and neuropsychiatric events were designated as adverse events of special interest	Section 12.3.4
Hemoglobin A1c was added to the hematology panel to assess pancreatic endocrine function	Section 9.3.4, Table 3-1, Table 3-2, and Table 11-2
Analysis of primary and key secondary endpoints through Week 24 will be estimated by averaging Weeks 16 and 24	Sections 2 and 12.3.3.1
Rationale for the non-inferiority margin for primary analysis of the primary endpoint was provided	Section 12.1
Clarified that it is the responsibility of the investigator to report unexpected serious adverse drug reactions to the local IRB/IEC if allowed by local regulations	Section 13.1.2.3
Clarified that definition of minimal function mutation is based on biological plausibility of no translated protein or in vitro testing that supports lack of responsiveness to TEZ, IVA, or TEZ/IVA	Appendix A

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

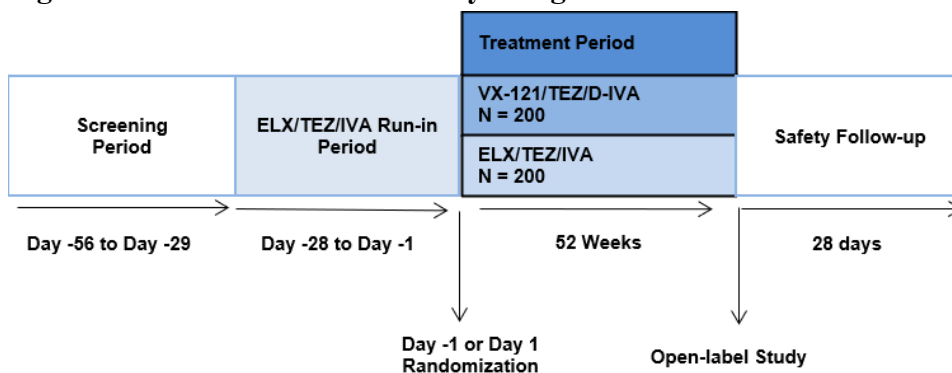
## 2 PROTOCOL SYNOPSIS

- Title** A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-121 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for *F508del* and a Minimal Function Mutation (F/MF)
- Brief Title** A Phase 3 Study of VX-121 Combination Therapy in Subjects With Cystic Fibrosis Heterozygous for *F508del* and a Minimal Function Mutation (F/MF)
- Clinical Phase and Clinical Study Type** Phase 3, efficacy and safety
- Objectives**
- Primary Objective**  
To evaluate the efficacy of VX-121/tezacaftor/deutivacaftor (VX-121/TEZ/D-IVA) in cystic fibrosis (CF) subjects who are heterozygous for *F508del* and a minimal function mutation (F/MF subjects)
- Secondary Objectives**
- To evaluate the safety of VX-121/TEZ/D-IVA
  - To evaluate the pharmacokinetics (PK) of VX-121/TEZ/D-IVA
- Endpoints**
- Primary Endpoint**  
Absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV<sub>1</sub>) through Week 24
- Key Secondary Endpoints**
- Absolute change from baseline in sweat chloride (SwCl) through Week 24
  - Proportion of subjects with SwCl <60 mmol/L through Week 24 (pooled with data from Study VX20-121-103)
  - Proportion of subjects with SwCl <30 mmol/L through Week 24 (pooled with data from Study VX20-121-103)
- Other Secondary Endpoints**
- Number of pulmonary exacerbations (PEX) through Week 52
  - Absolute change from baseline in Cystic Fibrosis Questionnaire – Revised (CFQ-R) Respiratory Domain (RD) score through Week 24
  - Absolute change from baseline in ppFEV<sub>1</sub> through Week 52
  - Absolute change from baseline in SwCl through Week 52
  - Proportion of subjects with SwCl <60 mmol/L through Week 24
  - Proportion of subjects with SwCl <30 mmol/L through Week 24
  - Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry
- Other Endpoints**
- Proportion of subjects with SwCl <60 mmol/L through Week 52
  - Proportion of subjects with SwCl <30 mmol/L through Week 52
  - Absolute change from baseline in body mass index (BMI) at Week 52
  - Absolute change from baseline in BMI z-score at Week 52
  - Absolute change from baseline in weight at Week 52

- Absolute change from baseline in CFQ-R RD score through Week 52
- PK parameters of VX-121, TEZ, and D-IVA

<b>Number of Subjects</b>	Approximately 400 subjects will be randomized (1:1) to the VX-121/TEZ/D-IVA group or the elxacaftor (ELX)/TEZ/ivacaftor (IVA) group.
<b>Study Population</b>	Male and female subjects with CF who are 12 years of age or older and heterozygous for <i>F508del</i> and an MF mutation (F/MF subjects)
<b>Investigational Drug</b>	<p>Study drug refers to VX-121/TEZ/D-IVA, ELX/TEZ/IVA, IVA, and their matching placebos.</p> <p>Active study drugs will be orally administered as either 2 fixed-dose combination (FDC) film-coated VX-121/TEZ/D-IVA tablets in the morning, or as 2 FDC film-coated ELX/TEZ/IVA tablets in the morning and as 1 film-coated IVA tablet in the evening.</p> <p><b>Active substance:</b> VX-121, TEZ (VX-661), and D-IVA (VX-561)</p> <p><b>Activity:</b> CFTR corrector, CFTR corrector, and CFTR potentiator (increased Cl<sup>-</sup> secretion)</p> <p><b>Strength and route of administration:</b> 10 mg VX-121/50 mg TEZ/125 mg D-IVA; oral administration</p> <p><b>Active substance:</b> ELX (VX-445), TEZ (VX-661), and IVA (VX-770)</p> <p><b>Activity:</b> CFTR corrector, CFTR corrector, and CFTR potentiator (increased Cl<sup>-</sup> secretion)</p> <p><b>Strength and route of administration:</b> 100 mg ELX/50 mg TEZ/75 mg IVA; oral administration</p> <p><b>Active substance:</b> IVA (ivacaftor; VX-770)</p> <p><b>Activity:</b> CFTR potentiator (increased Cl<sup>-</sup> secretion)</p> <p><b>Strength and route of administration:</b> 150 mg; oral administration</p>
<b>Study Duration</b>	The total study duration is approximately 64 weeks (4 weeks for the Screening Period, 4 weeks for the Run-in Period, 52 weeks for the Treatment Period, and 4 weeks for the Safety Follow-up Period).
<b>Study Design</b>	<p>This is a Phase 3, randomized, double-blind, ELX/TEZ/IVA-controlled, parallel-group, multicenter study.</p> <p>All subjects entering the Run-in Period will receive ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h). Following completion of the Run-in Period, approximately 400 subjects will be randomized (1:1) to the VX-121/TEZ/D-IVA group or ELX/TEZ/IVA group. The dosages to be evaluated are shown in the table below. Randomization will be stratified by age at the Screening Visit (&lt;18 versus ≥18 years of age), ppFEV<sub>1</sub> determined during the Run-in Period (Day -14 clinic assessment; &lt;70 versus ≥70), SwCl determined during the Run-in Period (Day -14 assessment; &lt;30 versus ≥30 mmol/L), and prior CFTR modulator use (yes versus no).</p>

**Figure 2-1 VX20-121-102 Study Design**



D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; N: number of subjects; TEZ: tezacaftor

Note: The figure is not drawn to scale.

**Treatment Groups and Dosages**

Treatment Group	VX-121	ELX	TEZ	D-IVA	IVA
VX-121/TEZ/D-IVA	20 mg qd	0 mg	100 mg qd	250 mg qd	0 mg
ELX/TEZ/IVA	0 mg	200 mg qd	100 mg qd	0 mg	150 mg q12h

D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor

**Assessments Efficacy:** Spirometry, SwCl, CFQ-R, documentation of events related to health outcomes (e.g., PEx), height, and weight

**Safety:** AEs, clinical laboratory assessments, ECGs, vital signs, pulse oximetry, physical examinations, and ophthalmologic examinations (for subjects <18 years of age on the date of informed consent)

**PK:** VX-121, TEZ, D-IVA, ELX, IVA, and relevant metabolite plasma concentrations

**Exploratory:** Treatment Satisfaction Questionnaire for Medication (TSQM), Cystic Fibrosis Impact Questionnaire (CF-IQ), DNA sample (optional), inflammatory mediators, blood biomarker sample, RNA sample (optional), and sputum samples

**Statistical Analyses** The primary efficacy endpoint is the absolute change from baseline in ppFEV<sub>1</sub> through Week 24 (estimated by averaging Weeks 16 and 24). The primary null hypothesis to be tested is that the mean absolute change from baseline in ppFEV<sub>1</sub> through Week 24 for VX-121/TEZ/D-IVA is inferior by >3 percentage points compared to ELX/TEZ/IVA. The null hypothesis will be tested at a 1-sided significance level of 0.025.

Assuming a within-group SD of 8 and 10% drop-out rate at Week 24 and a treatment difference of 0 between VX-121/TEZ/D-IVA and ELX/TEZ/IVA, a sample size of 200 subjects in each group for a total of 400 subjects will have more than 90% power to test the primary hypothesis for the primary endpoint, based on a 1-sided, 2-sample *t*-test at a significance level of 0.025.

The primary analysis of the primary endpoint will be conducted with clinic spirometry data only and will be performed using a mixed-effects model for repeated measures (MMRM) with absolute change from baseline in ppFEV<sub>1</sub> at Day 15, Week 4, Week 8, Week 16, and Week 24 as the dependent variable. The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects, with continuous baseline ppFEV<sub>1</sub>, continuous baseline SwCl, and age at screening (<18 versus ≥18 years of age) as covariates. An unstructured covariance structure will be used to model the within-subject errors.

The primary result obtained from the model will be the estimated treatment difference through Week 24. The primary null hypothesis will be rejected and non-inferiority demonstrated if the lower bound of the 95% CI is  $\geq -3.0$ .

**DMC Reviews** A data monitoring committee (DMC) will conduct safety reviews of study data as outlined in the DMC Charter.

### 3 SCHEDULE OF ASSESSMENTS

Schedules of assessments are shown in [Table 3-1](#) and [Table 3-2](#).

All visits will be scheduled relative to the Day 1 Visit (first dose of randomized study drug in the Treatment Period).

Study visits should be performed in the clinic as specified in [Table 3-1](#) and [Table 3-2](#), if at all possible. The Screening Visit, Day -28 Visit, Day -14 Visit, Day 1 Visit, Week 24 Visit, and Week 52 Visit must be performed in clinic (Section [9.1.8](#)).

All questionnaires completed on the day of the study visit must be completed prior to any other assessments, with Cystic Fibrosis Questionnaire–Revised (CFQ-R) completed first. CF-IQ, PGIS, and PGIC must be completed on the same day, and CF-IQ must be performed before PGIS or PGIC (as applicable). Remaining 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 study drug dosing (Section [9.6.1](#)), unless noted otherwise.

**Table 3-1 Study VX20-121-102: Screening**

Event/Assessment	Screening Visit Day -56 Through Day -29	Comments
ICF and assent (when applicable)	X	
Demographics	X	
Medical history	X	
CFQ-R	X	Section <a href="#">11.5.3</a>
CF-IQ	X	Section <a href="#">11.4.6</a>
<i>CFTR</i> genotype	X	If the <i>CFTR</i> genotype result is not received before the first dose of ELX/TEZ/IVA in the Run-in Period, a previous <i>CFTR</i> genotype laboratory report may be used to establish eligibility (Section <a href="#">8.1</a> ). Subjects who have been enrolled and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section <a href="#">9.9</a> ).
FSH	X	Postmenopausal female subjects only; Section <a href="#">11.6.2</a>
Serum pregnancy test (all female subjects)	X	Section <a href="#">11.6.2</a>
Serum chemistry	X	Section <a href="#">11.6.2</a>
Hematology	X	Section <a href="#">11.6.2</a>
HbA1c	X	HbA1c will be collected as part of the hematology blood draw (Section <a href="#">11.6.2</a> )
Coagulation	X	Section <a href="#">11.6.2</a>
Urinalysis	X	Section <a href="#">11.6.2</a>
Height and weight	X	Measured with shoes off

**Table 3-1 Study VX20-121-102: Screening**

<b>Event/Assessment</b>	<b>Screening Visit Day -56 Through Day -29</b>	<b>Comments</b>
Ophthalmologic examination	X	Conducted by an ophthalmologist or optometrist, only for subjects <18 years of age on the date of informed consent (Section 11.6.6). The screening examination does not need to be conducted if there is documentation of an examination meeting the protocol requirements that was conducted within 3 months before the date of informed consent.
Complete physical examination	X	Section 11.6.3
Vital signs	X	Collected after the subject has been at rest for at least 5 minutes (Section 11.6.3)
Pulse oximetry	X	Collected after the subject has been at rest for at least 5 minutes (Section 11.6.4)
Standard 12-lead ECG	X	Collected after the subject has been at rest for at least 5 minutes (Section 11.6.5)
Spirometry	X	Performed pre- or post-bronchodilator (Section 11.5.1).
Sweat chloride	X	Section 11.5.2
Medications review	X	Section 9.5
AEs and SAEs	Continuous from signing of ICF (and assent form) through completion of study participation	Section 13.1; completion of study participation is defined in Section 9.1.7

AE: adverse event; CF-IQ: Cystic Fibrosis Impact Questionnaire; CFQ-R: Cystic Fibrosis Questionnaire – Revised; FSH: follicle-stimulating hormone; HbA1c: hemoglobin A1c; ICF: informed consent form; SAE: serious adverse event



**Table 3-2 Study VX20-121-102: Run-in Period, Treatment Period, and Safety Follow-up Visit**

Event/Assessment <sup>a</sup>	Run-in Period		Treatment Period <sup>b</sup>						ETT Visit <sup>c</sup>	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug (If Applicable) <sup>d</sup>	Comments
	Day -28 (± 1 Day)	Day -14 (Day -15 to Day -3)	Day 1	Day 15 (± 3 Days)	Weeks 4, 8, 12, 16 (± 5 Days)	Weeks 20, 28, 32, 40, 44, 48 (± 5 Days)	Weeks 24 and 36 (± 5 Days)	Week 52 (± 5 Days)			
Clinic visit	X	X	X	X	X <sup>e</sup>		X	X	X	X	See Section 9.1.8 for use of remote measures in extenuating circumstances.
Telephone contact						X					Assess the subject’s status, any AEs, concomitant medications, treatments, and procedures.
Inclusion and exclusion criteria review	X										Section 8
Randomization			X								Randomization may occur on either Day -1 or Day 1, after all eligibility criteria are confirmed (Section 9.1.3).
CFQ-R			X		Weeks 8 and 16		Week 24	X	X		Completed before the start of any other assessments on the day of the study visit (Section 11.5.3).

<sup>a</sup> All assessments will be performed before dosing unless noted otherwise.

<sup>b</sup> To enter the Treatment Period, conditions for entry must be satisfied (Section 9.1.3).

<sup>c</sup> If the subject prematurely discontinues study drug treatment, an ETT Visit should be scheduled as soon as possible after the decision to discontinue treatment (Section 9.1.5). Subjects who prematurely discontinue treatment during the Run-in Period will complete an ETT Visit and Safety Follow-up Visit, as applicable. Subjects who prematurely discontinue study drug treatment during the Treatment Period should continue to complete all scheduled study visits for assessments following completion of the ETT Visit (and Safety Follow-up Visit, if applicable).

<sup>d</sup> The Safety Follow-up Visit is required for all subjects, unless otherwise specified (Section 9.1.4). For subjects who complete an ETT Visit 3 weeks or later following the last dose of study drug, the ETT Visit will replace the Safety Follow-up Visit, and a separate Safety Follow-up Visit will not be required (Section 9.1.5).

<sup>e</sup> The Week 12 Visit may be performed either in the clinic or as a home health visit, if permitted by local regulations. See Section 9.1.8 for use of remote measures in extenuating circumstances. All home health visits must have a consultation between the subject and investigator (i.e., in person, phone, or telemedicine video conference). This consultation should occur within 2 business days before or after the home health visit and can be outside the visit window.

**Table 3-2 Study VX20-121-102: Run-in Period, Treatment Period, and Safety Follow-up Visit**

Event/Assessment <sup>a</sup>	Run-in Period		Treatment Period <sup>b</sup>						ETT Visit <sup>c</sup>	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug (If Applicable) <sup>d</sup>	Comments
	Day -28 (± 1 Day)	Day -14 (Day -15 to Day -3)	Day 1	Day 15 (± 3 Days)	Weeks 4, 8, 12, 16 (± 5 Days)	Weeks 20, 28, 32, 40, 44, 48 (± 5 Days)	Weeks 24 and 36 (± 5 Days)	Week 52 (± 5 Days)			
TSQM	X		X					X	X		May be completed within 5 days prior to the study visit. All questionnaires completed on the day of the study visit must be completed prior to any other assessments, with CFQ-R completed first. All subjects will complete the TSQM at the Day -28 Visit; only subjects <18 years of age on the date of informed consent will complete the TSQM at subsequent visits (Section 11.4.5).
CF-IQ	X		X		Week 4		Week 24	X			May be completed within 5 days prior to the study visit. CF-IQ, PGIS, and PGIC must be completed on the same day, and CF-IQ must be performed before PGIS and PGIC (as applicable). All questionnaires completed on the day of the study visit must be completed prior to any other assessments, with CFQ-R completed first (Section 11.4.6).
PGIS	X		X		Week 4						
PGIC			X		Week 4						
Height and weight	X		X	X	Weeks 4, 8, 16		X	X	X	X	Measured with shoes off. Following screening, height will be collected only for subjects ≤21 years of age on the date of informed consent

**Table 3-2 Study VX20-121-102: Run-in Period, Treatment Period, and Safety Follow-up Visit**

Event/Assessment <sup>a</sup>	Run-in Period		Treatment Period <sup>b</sup>						ETT Visit <sup>c</sup>	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug (If Applicable) <sup>d</sup>	Comments
	Day -28 (± 1 Day)	Day -14 (Day -15 to Day -3)	Day 1	Day 15 (± 3 Days)	Weeks 4, 8, 12, 16 (± 5 Days)	Weeks 20, 28, 32, 40, 44, 48 (± 5 Days)	Weeks 24 and 36 (± 5 Days)	Week 52 (± 5 Days)			
Ophthalmologic examination								X	X		Subjects <18 years of age on the date of informed consent and have completed at least 12 weeks of study drug treatment will have a single ophthalmologic examination conducted by a licensed ophthalmologist or optometrist within 4 weeks prior to completion of study participation (Section 11.6.6). This examination should be completed within 4 weeks before the Week 52 Visit, unless the subject prematurely discontinues study drug, in which case this examination should occur by the Safety Follow-up Visit (or ETT Visit for subjects who do not complete a Safety Follow-up Visit) (Section 9.1.5).
Physical examination	Abbrev		Complete					Complete	Complete		Symptom-directed PEs may be performed at any time if deemed necessary by the investigator (Section 11.6.3).
Pregnancy testing	Urine		Urine		Urine <sup>f</sup>	Urine <sup>f</sup>	Urine	Urine	Serum	Serum	All female subjects (Section 11.6.2)
FSH											Blood samples for FSH will be measured as needed as outlined in Section 11.6.2.
Standard 12-lead ECG	X		X	X	Weeks 4, 8, 16		X	X	X	X	After the subject has been at rest for at least 5 minutes, and before dosing (as applicable) (Section 11.6.5)
Vital signs	X		X	X	X		X	X	X	X	After the subject has been at rest for at least 5 minutes, and before dosing (as applicable) (Section 11.6.3)

<sup>f</sup> When there is no clinic visit (e.g., Week 12, Week 20), a urine pregnancy test will be performed with a home kit provided by the study site. Results will be reported to the site by telephone.

**Table 3-2 Study VX20-121-102: Run-in Period, Treatment Period, and Safety Follow-up Visit**

Event/Assessment <sup>a</sup>	Run-in Period		Treatment Period <sup>b</sup>						ETT Visit <sup>c</sup>	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug (If Applicable) <sup>d</sup>	Comments
	Day -28 (± 1 Day)	Day -14 (Day -15 to Day -3)	Day 1	Day 15 (± 3 Days)	Weeks 4, 8, 12, 16 (± 5 Days)	Weeks 20, 28, 32, 40, 44, 48 (± 5 Days)	Weeks 24 and 36 (± 5 Days)	Week 52 (± 5 Days)			
Pulse oximetry	X		X	X	X		X	X	X	X	After the subject has been at rest for at least 5 minutes, and before dosing (as applicable) (Section 11.6.4)
Spirometry (in-clinic)		X	X	X	Weeks 4, 8, 16		X	X	X	X	Should be performed pre-bronchodilator, before dosing, and at approximately the same time at each visit. If the visit is performed as a home health visit, spirometry may be performed using a mobile device (Section 9.1.8).
Spirometry (mobile device)		X	X								Spirometry with a mobile device should be performed at home and as applicable (Section 9.1.8)
Sweat chloride		X	X	X	Weeks 4 and 16		X	X	X		Will be performed before dosing (Section 11.5.2)
Serum chemistry	X		X <sup>g</sup>	X	X		X	X	X	X	Section 11.6.2
Hematology	X		X <sup>g</sup>	X	X		X	X	X	X	Section 11.6.2
HbA1c			X <sup>g</sup>		Week 12		Week 24	X			HbA1c will be collected as part of the hematology blood draw (Section 11.6.2)
Coagulation	X		X <sup>g</sup>		Week 12		X	X	X	X	Section 11.6.2
Urinalysis	X		X		Week 12		X	X	X	X	Section 11.6.2

<sup>g</sup> Blood samples will be collected before the first dose of study drug in the Treatment Period.

**Table 3-2 Study VX20-121-102: Run-in Period, Treatment Period, and Safety Follow-up Visit**

Event/Assessment <sup>a</sup>	Run-in Period		Treatment Period <sup>b</sup>						ETT Visit <sup>c</sup>	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug (If Applicable) <sup>d</sup>	Comments	
	Day -28 (± 1 Day)	Day -14 (Day -15 to Day -3)	Day 1	Day 15 (± 3 Days)	Weeks 4, 8, 12, 16 (± 5 Days)	Weeks 20, 28, 32, 40, 44, 48 (± 5 Days)	Weeks 24 and 36 (± 5 Days)	Week 52 (± 5 Days)				
PK sampling			Predose and 2 hours postdose	Predose	Weeks 4, 8, 16		Week 24		X		Week 4, Week 16, Week 24: predose Week 8: <ul style="list-style-type: none"> <li>• Predose and 4 hours postdose for all subjects &lt;18 years of age on the date of informed consent.</li> <li>• Predose and 4, 5, 6, and 7 hours postdose for up to approximately 40 subjects ≥18 years of age on the date of informed consent.</li> <li>• Predose and 2 hours postdose for all other subjects ≥18 years of age on the date of informed consent.</li> </ul> Refer to <a href="#">Table 11-1</a> for acceptable PK sampling windows. If study drug is not administered at the Week 8 Visit (i.e., due to study drug interruption or permanent discontinuation), a single PK blood sample will be collected at the visit. At the ETT Visit, a single PK blood sample will be collected.	
DNA sample (optional)			X								If permitted by local regulations ( <a href="#">Section 11.4.1</a> )	
Inflammatory mediator samples	X		X		Week 4		Week 24	X			<a href="#">Section 11.4.2</a>	
Blood sample for RNA (optional)	X		X		Week 4		Week 24	X			If permitted by local regulations ( <a href="#">Section 11.4.3</a> )	
Blood biomarker samples	X		X		Week 4		Week 24	X			<a href="#">Section 11.4.3</a>	
Sputum samples	X		X				Week 24	X			Sputum samples will be collected from subjects who can produce a sample spontaneously ( <a href="#">Section 11.4.4</a> ).	
Run-in ELX/TEZ/IVA dosing	Day -28 through Day -1											<a href="#">Section 9.1.2</a>

**Table 3-2 Study VX20-121-102: Run-in Period, Treatment Period, and Safety Follow-up Visit**

Event/Assessment <sup>a</sup>	Run-in Period		Treatment Period <sup>b</sup>						ETT Visit <sup>c</sup>	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug (If Applicable) <sup>d</sup>	Comments
	Day -28 (± 1 Day)	Day -14 (Day -15 to Day -3)	Day 1	Day 15 (± 3 Days)	Weeks 4, 8, 12, 16 (± 5 Days)	Weeks 20, 28, 32, 40, 44, 48 (± 5 Days)	Weeks 24 and 36 (± 5 Days)	Week 52 (± 5 Days)			
Run-in ELX/TEZ/IVA drug count	X	X	X								
Randomized study drug dosing			Day 1 through evening before Week 52 Visit								Section 9.6
Randomized study drug count <sup>h</sup>			X	X	X		X	X	X		
Other events related to outcome	Continuous from signing of ICF through completion of study participation									Section 11.5.4; completion of study participation is defined in Section 9.1.7	
Medications review	Continuous from signing of ICF through completion of study participation									Section 9.5; completion of study participation is defined in Section 9.1.7	
Treatments and procedures review	Continuous from signing of ICF through completion of study participation									Completion of study participation is defined in Section 9.1.7	
AEs and SAEs	Continuous from signing of ICF through completion of study participation									Section 13.1; completion of study participation is defined in Section 9.1.7	

AE: adverse event; CF: cystic fibrosis; CF-IQ: Cystic Fibrosis Impact Questionnaire; CFQ-R: CF Questionnaire-Revised; ELX: elxacaftor; ETT: Early Termination of Treatment; FSH: follicle-stimulating hormone; HbA1c: hemoglobin A1c; ICF: informed consent form; IVA: ivacaftor; PE: physical examination; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PK: pharmacokinetic; SAE: serious adverse event; TEZ: tezacaftor; TSQM: Treatment Satisfaction Questionnaire for Medication

<sup>h</sup> Study drug count will be assessed at in-clinic visits.

## 4 TABLE OF CONTENTS

<b>1</b>	<b>Title Page</b> .....	<b>1</b>
	Summary of Changes to the Protocol.....	2
<b>2</b>	<b>Protocol Synopsis</b> .....	<b>3</b>
<b>3</b>	<b>Schedule of Assessments</b> .....	<b>7</b>
<b>4</b>	<b>Table of Contents</b> .....	<b>15</b>
	List of Tables.....	19
	List of Figures .....	19
	List of Appendices .....	19
	List of Abbreviations.....	20
<b>5</b>	<b>Introduction</b> .....	<b>23</b>
	5.1 Background.....	23
	5.2 Study Rationale .....	23
<b>6</b>	<b>Study Objectives</b> .....	<b>24</b>
	6.1 Primary Objective.....	24
	6.2 Secondary Objectives .....	24
<b>7</b>	<b>Study Endpoints</b> .....	<b>24</b>
	7.1 Primary Endpoint.....	24
	7.2 Secondary Endpoints .....	24
	7.2.1 Key Secondary Endpoints .....	24
	7.2.2 Other Secondary Endpoints .....	24
	7.3 Other Endpoints.....	25
<b>8</b>	<b>Study Population</b> .....	<b>25</b>
	8.1 Inclusion Criteria .....	25
	8.2 Exclusion Criteria.....	26
<b>9</b>	<b>Study Implementation</b> .....	<b>27</b>
	9.1 Study Design .....	27
	9.1.1 Screening .....	28
	9.1.1.1 Repetition of Screening Assessment(s).....	28
	9.1.1.2 Rescreening.....	28
	9.1.1.3 Extension of Screening Period Window .....	28
	9.1.2 ELX/TEZ/IVA Run-in Period .....	29
	9.1.3 Treatment Period .....	29
	9.1.4 Follow-up.....	29
	9.1.5 Early Termination of Treatment.....	30
	9.1.5.1 Discontinuation During the Run-in Period .....	30
	9.1.5.2 Discontinuation During the Treatment Period .....	30
	9.1.6 Lost to Follow-up .....	30
	9.1.7 Completion of Study Participation .....	31
	9.1.8 Use of Remote Measures in Extenuating Circumstances.....	31
	9.1.9 Data Monitoring Committee.....	32
	9.2 Method of Assigning Subjects to Treatment Groups .....	32
	9.3 Rationale for Study Elements.....	32
	9.3.1 Study Design.....	32
	9.3.2 Study Population.....	32

9.3.3	Study Drug Dose .....	33
9.3.4	Rationale for Study Assessments .....	34
9.4	Study Restrictions.....	34
9.4.1	Prohibited Medications.....	34
9.5	Prior and Concomitant Medications.....	35
9.6	Administration.....	36
9.6.1	Dosing.....	36
9.6.2	Missed Doses.....	37
9.7	Dose Modification for Toxicity.....	37
9.8	Study Drug Interruption and Stopping Rules .....	37
9.8.1	Liver Function Tests.....	37
9.8.2	Rash .....	38
9.9	Removal of Subjects.....	38
9.10	Replacement of Subjects .....	39
<b>10</b>	<b>Study Drug Information and Management.....</b>	<b>39</b>
10.1	Preparation and Dispensing.....	39
10.2	Packaging and Labeling .....	39
10.3	Study Drug Supply, Storage, and Handling .....	39
10.4	Drug Accountability .....	40
10.5	Disposal, Return, or Retention of Unused Drug.....	40
10.6	Compliance.....	41
10.7	Blinding and Unblinding .....	41
10.7.1	Blinding .....	41
10.7.2	Unblinding.....	42
<b>11</b>	<b>Assessments .....</b>	<b>43</b>
11.1	Subject and Disease Characteristics .....	43
11.2	Pharmacokinetics.....	43
11.2.1	Blood Sampling .....	43
11.2.2	Processing and Handling of Pharmacokinetic Samples .....	44
11.2.3	Bioanalysis.....	44
11.3	Pharmacodynamics.....	44
11.4	Exploratory Assessments.....	44
11.4.1	Pharmacogenomics.....	44
11.4.2	Inflammatory Mediators .....	44
11.4.3	Other Blood Biomarkers.....	44
11.4.4	Microbiology and Other Sputum Biomarkers .....	45
11.4.5	Treatment Satisfaction Questionnaire for Medication.....	45
11.4.6	Other Questionnaires .....	45
11.5	Efficacy.....	46
11.5.1	Spirometry .....	46
11.5.2	Sweat Chloride .....	47
11.5.3	Cystic Fibrosis Questionnaire-Revised .....	47
11.5.4	Other Events Related to Outcome .....	47
11.5.4.1	Antibiotic Therapy for Sinopulmonary Sign/Symptoms .....	47
11.5.4.2	Hospitalization for CF.....	48
11.5.5	Height and Weight.....	48



11.6	Safety	48
11.6.1	Adverse Events	48
11.6.2	Clinical Laboratory Assessments	48
11.6.3	Physical Examinations and Vital Signs	50
11.6.4	Pulse Oximetry	50
11.6.5	Electrocardiograms	50
11.6.6	Ophthalmologic Examination	51
11.6.7	Contraception and Pregnancy	51
11.6.7.1	Contraception	51
11.6.7.2	Pregnancy	53
<b>12</b>	<b>Statistical Analysis</b>	<b>53</b>
12.1	Sample Size and Power	53
12.2	Analysis Sets	54
12.3	Statistical Analysis	55
12.3.1	General Considerations	55
12.3.2	Background Characteristics	55
12.3.3	Efficacy Analysis	55
12.3.3.1	Analysis of Primary Endpoint	55
12.3.3.2	Analysis of Secondary Endpoints	56
12.3.3.3	Multiplicity Adjustment	57
12.3.3.4	Analysis of Other Endpoints	57
12.3.4	Safety Analysis	57
12.4	Interim Analysis	57
12.5	Data Monitoring Committee Analysis	57
12.6	Clinical Pharmacology Analysis	58
12.6.1	Pharmacokinetic Analysis	58
12.6.2	Pharmacokinetic/Pharmacodynamic Analyses	58
<b>13</b>	<b>Procedural, Ethical, Regulatory, and Administrative Considerations</b>	<b>58</b>
13.1	Adverse Event and Serious Adverse Event Documentation, Severity Grading, and Reporting	58
13.1.1	Adverse Events	58
13.1.1.1	Definition of an Adverse Event	58
13.1.1.2	Clinically Significant Assessments	58
13.1.1.3	Documentation of Adverse Events	59
13.1.1.4	Adverse Event Severity	59
13.1.1.5	Adverse Event Causality	60
13.1.1.6	Study Drug Action Taken	60
13.1.1.7	Adverse Event Outcome	61
13.1.1.8	Treatment Given	61
13.1.2	Serious Adverse Events	61
13.1.2.1	Definition of a Serious Adverse Event	61
13.1.2.2	Reporting and Documentation of Serious Adverse Events	62
13.1.2.3	Expedited Reporting and Investigator Safety Letters	63
13.2	Administrative Requirements	63
13.2.1	Product Complaints	63
13.2.2	Ethical Considerations	63

13.2.3	Subject Information and Informed Consent .....	63
13.2.4	Investigator Compliance .....	63
13.2.5	Access to Records .....	64
13.2.6	Subject Privacy .....	64
13.2.7	Record Retention .....	64
13.2.8	Study Termination .....	64
13.2.9	End of Study .....	65
13.3	Data Quality Assurance .....	65
13.4	Monitoring .....	65
13.5	Electronic Data Capture .....	65
13.6	Confidentiality and Disclosure .....	66
13.7	Publications and Clinical Study Report .....	66
13.7.1	Publication of Study Results .....	66
13.7.2	Clinical Study Report .....	67
<b>14</b>	<b>References .....</b>	<b>68</b>
<b>APPENDIX A: Examples of Eligible MF Mutations .....</b>		<b>70</b>
<b>15</b>	<b>Protocol Signature Pages .....</b>	<b>72</b>
15.1	Sponsor Signature Page .....	72
15.2	Investigator Signature Page .....	73

**List of Tables**

Table 3-1	Study VX20-121-102: Screening.....	7
Table 3-2	Study VX20-121-102: Run-in Period, Treatment Period, and Safety Follow-up Visit.....	9
Table 9-1	Treatment Period Groups and Dosages.....	28
Table 9-2	Prohibited Medications .....	34
Table 10-1	Study Drug; Strength/Dosage Form/Route.....	40
Table 11-1	Acceptable Pharmacokinetic Sampling Windows .....	43
Table 11-2	Safety Laboratory Test Panels .....	49
Table 11-3	Acceptable Methods of Contraception.....	52
Table 13-1	Grading of AE Severity .....	59
Table 13-2	Classifications for AE Causality.....	60
Table 13-3	Classifications for Study Drug Action Taken With Regard to an AE .....	60
Table 13-4	Classifications for Outcome of an AE .....	61

**List of Figures**

Figure 2-1	VX20-121-102 Study Design .....	5
Figure 9-1	VX20-121-102 Study Design .....	27

**List of Appendices**

APPENDIX A	Examples of Eligible MF Mutations
------------	-----------------------------------

## List of Abbreviations

Abbreviation	Definition
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the concentration versus time curve
BA	bioavailability
BMI	body mass index
CBC	complete blood count
CD	compact disc
CF	cystic fibrosis
CF-IQ	Cystic Fibrosis Impact Questionnaire
CFQ-R	Cystic Fibrosis Questionnaire - Revised
CFTR	CF transmembrane conductance regulator protein
<i>CFTR</i>	CF transmembrane conductance regulator gene
CI	confidence interval
$C_{max}$	maximum observed concentration
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
D-IVA	deutivacaftor
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
ELX	elexacaftor
ETT	Early Termination of Treatment
EU	European Union
F/MF	heterozygous for <i>F508del</i> and a minimal function mutation
<i>F508del</i>	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FEF <sub>25%-75%</sub>	forced expiratory flow, midexpiratory phase
FEV <sub>1</sub>	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone

FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLI	Global Lung Function Initiative
GPS	Global Patient Safety
HbA1c	hemoglobin A1c
HBE	human bronchial epithelial
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IgG	immunoglobulin G
IL-8	interleukin-8
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	institutional review board
IV	intravenous
IVA	ivacaftor
IWRS	interactive web response system
LFT	liver function test
LUM	lumacaftor
max	maximum
MF	minimal function
min	minimum
MMRM	mixed-effects model for repeated measures
OATP1B1	organic anion transporting polypeptide 1B1
<i>P</i>	probability
PD	pharmacodynamic
PE	physical examination
PEx	pulmonary exacerbations
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
P-gp	P-glycoprotein
PIs	principal investigators
PK	pharmacokinetic(s)
ppFEV <sub>1</sub>	percent predicted forced expiratory volume in 1 second
PPS	Per-protocol Set
PRO	patient-reported outcome
q12h	every 12 hours
qd	once daily
QTcF	QT interval corrected by Fridericia's formula
RD	Respiratory Domain
RNA	ribonucleic acid

SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SUSAR	suspected, unexpected, serious adverse reaction
SwCl	sweat chloride
TC	triple combination
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
TSQM	Treatment Satisfaction Questionnaire for Medication
<i>t</i> -test	statistical test used when the independent variable is binary and the dependent variable is continuous
ULN	upper limit of normal
US	United States
USA	United States of America
WBC	white blood cell

---

## 5 INTRODUCTION

### 5.1 Background

Cystic fibrosis (CF) is an autosomal recessive genetic disease with serious morbidities and frequent premature mortality. CF affects more than 80,000 individuals worldwide (approximately 31,000 in the US and 49,000 in the EU).<sup>1-4</sup>

CF is caused by decreased quantity and/or function of the CFTR protein due to mutations in the *CFTR* gene.<sup>5</sup> CFTR is a channel that regulates the flow of chloride and other anions across epithelia in multiple organs and tissues, including the lungs, pancreas and other gastrointestinal organs, and sweat glands.<sup>6</sup> Despite progress in the treatment of CF with antibiotics and mucolytics, the current median age at death among people with CF is approximately 30 years, and the predicted median age of survival is approximately 47 years.<sup>1,2</sup> More effective treatments are needed for CF.

The most common disease-causing mutation is *F508del*: approximately 85.3% of people with CF in the US and 80.6% in Europe have at least one *F508del* allele.<sup>1,2</sup>

At present CF does not have a cure. CFTR modulators (i.e., correctors and potentiators) represent a major advancement in the treatment of CF because they are systemic therapies that target the underlying cause of the disease and have been shown to improve CF survival by modifying the course of disease.<sup>7,8</sup> The clinical testing and regulatory approval of CFTR modulators in certain countries for the treatment of people with CF caused by specific *CFTR* genotypes have established the therapeutic value of specific regimens developed by Vertex. These treatment regimens include ivacaftor (IVA) monotherapy (Kalydeco™), lumacaftor (LUM)/IVA dual combination therapy (Orkambi™), tezacaftor (TEZ)/IVA dual combination therapy (Symdeko™, Symkevi™), and elexacaftor (ELX)/TEZ/IVA triple combination (TC) therapy (Trikafta™, Kaftrio™).

Deutivacaftor (D-IVA, VX-561) is a CFTR potentiator and is a deuterated isotope of IVA with a specific pattern of 9 substituted deuteriums. In vitro data indicate similar potency of D-IVA in human bronchial epithelial (HBE) cells relative to IVA. Nonclinical and clinical data demonstrate a similar safety profile relative to IVA, and pharmacokinetic (PK) data support once daily (qd) dosing (refer to VX-121/TEZ/D-IVA Investigator's Brochure).

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

### 5.2 Study Rationale

This study will evaluate the efficacy and safety of VX-121/TEZ/D-IVA in CF subjects who are heterozygous for *F508del* and a minimal function mutation (F/MF) (refer to Appendix A for a non-exhaustive list of MF mutations). While ELX/TEZ/IVA is approved in certain regions for

subjects with F/MF genotypes, there remains a need for more highly effective CFTR modulators that can restore CFTR function (e.g., CFTR-mediated chloride transport) toward levels seen in carriers (who do not develop CF) in as many patients with CF as possible. The potential for benefit in these patients is supported by in vitro data and clinical data in F/MF subjects; in addition, VX-121/TEZ/D-IVA is generally safe and well tolerated (refer to VX-121/TEZ/D-IVA Investigator's Brochure).

## **6 STUDY OBJECTIVES**

### **6.1 Primary Objective**

To evaluate the efficacy of VX-121/TEZ/D-IVA in CF subjects who are heterozygous for *F508del* and a minimal function mutation (F/MF subjects)

### **6.2 Secondary Objectives**

- To evaluate the safety of VX-121/TEZ/D-IVA
- To evaluate the PK of VX-121/TEZ/D-IVA

## **7 STUDY ENDPOINTS**

### **7.1 Primary Endpoint**

Absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV<sub>1</sub>) through Week 24

### **7.2 Secondary Endpoints**

#### **7.2.1 Key Secondary Endpoints**

- Absolute change from baseline in sweat chloride (SwCl) through Week 24
- Proportion of subjects with SwCl <60 mmol/L through Week 24 (pooled with data from Study VX20-121-103)
- Proportion of subjects with SwCl <30 mmol/L through Week 24 (pooled with data from Study VX20-121-103)

#### **7.2.2 Other Secondary Endpoints**

- Number of pulmonary exacerbations (PEx) through Week 52
- Absolute change from baseline in Cystic Fibrosis Questionnaire – Revised (CFQ-R) Respiratory Domain (RD) score through Week 24
- Absolute change from baseline in ppFEV<sub>1</sub> through Week 52
- Absolute change from baseline in SwCl through Week 52
- Proportion of subjects with SwCl <60 mmol/L through Week 24
- Proportion of subjects with SwCl <30 mmol/L through Week 24
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry



### 7.3 Other Endpoints

- Proportion of subjects with SwCl <60 mmol/L through Week 52
- Proportion of subjects with SwCl <30 mmol/L through Week 52
- Absolute change from baseline in body mass index (BMI) at Week 52
- Absolute change from baseline in BMI z-score at Week 52
- Absolute change from baseline in weight at Week 52
- Absolute change from baseline in CFQ-R RD score through Week 52
- PK parameters of VX-121, TEZ, and D-IVA

## 8 STUDY POPULATION

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

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

### 8.1 Inclusion Criteria

1. Subject (or his or her legally appointed and authorized representative) will sign and date an informed consent form (ICF), and when appropriate, an assent form.
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Subjects aged 12 years or older, on the date of informed consent
4. Confirmed diagnosis of CF as determined by the investigator
5. Heterozygous for *F508del* and an MF mutation, defined as a mutation that either results in no translated CFTR protein or that is non-responsive to TEZ, IVA, or TEZ/IVA based on in vitro testing (F/MF genotypes, see Appendix A for examples of eligible MF mutations). If the screening *CFTR* genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used to establish eligibility. Subjects who have been enrolled and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9).
6. For subjects currently receiving ELX/TEZ/IVA, FEV<sub>1</sub> value  $\geq 40\%$  and  $\leq 90\%$  of predicted mean for age, sex, and height (equations of the Global Lung Function Initiative [GLI])<sup>9</sup> at the Screening Visit. All subjects not currently receiving ELX/TEZ/IVA must have an FEV<sub>1</sub> value  $\geq 40\%$  and  $\leq 80\%$  of predicted mean. Spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria<sup>10</sup> for acceptability and repeatability.
7. Stable CF disease as judged by the investigator.
8. Willing to remain on a stable CF treatment regimen (as defined in Section 9.5) through completion of study participation.

## 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(s) to the subject. This includes, but is not limited to, the following:
  - Hepatic cirrhosis with portal hypertension, moderate hepatic impairment (Child Pugh Score 7 to 9), or severe hepatic impairment (Child Pugh Score 10 to 15).
  - Solid organ or hematological transplantation.
  - Alcohol or drug abuse in the past year, including, but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator.
  - Cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years).
2. History of intolerance to study drug that would pose an additional risk to the subject in the opinion of the investigator. (e.g., subjects with a history of liver function test [LFT] elevations requiring treatment interruption or discontinuation, allergy or hypersensitivity to the study drug).
3. Any of the following abnormal laboratory values at screening:
  - Hemoglobin <10 g/dL
  - Total bilirubin  $\geq 2 \times$  upper limit of normal (ULN)
  - Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP)  $\geq 3 \times$  ULN
  - Abnormal renal function defined as glomerular filtration rate  $\leq 50$  mL/min/1.73 m<sup>2</sup> (calculated by the Modification of Diet in Renal Disease Study Equation)<sup>11,12</sup> for subjects  $\geq 18$  years of age and  $\leq 45$  mL/min/1.73 m<sup>2</sup> (calculated by the Counahan-Barratt equation)<sup>13</sup> for subjects aged 12 to 17 years (inclusive).
4. An acute upper or lower respiratory infection, PEx, or changes in therapy (including antibiotics) for sinopulmonary disease within 28 days before the first dose of ELX/TEZ/IVA in the Run-in Period (Day -28).
5. Lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*). For subjects who have had a history of a positive culture, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
  - The subject has not had a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent.
  - The subject has had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent one within the 6 months before the date of informed consent.

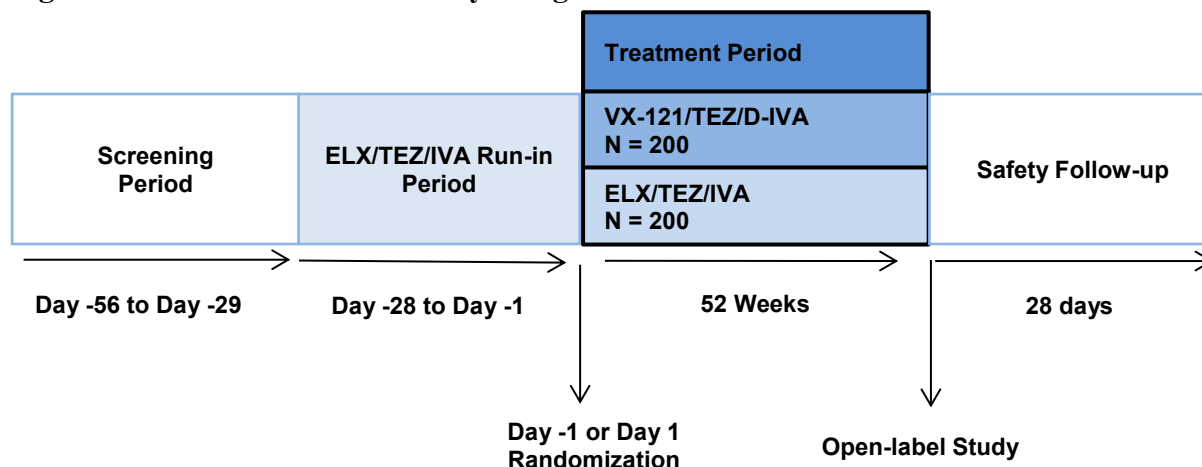
6. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of ELX/TEZ/IVA in the Run-in Period (Day -28).
7. Ongoing or prior participation in a study of an investigational treatment other than a Vertex CFTR modulator within 28 days or 5 terminal half-lives (whichever is longer) before screening, or participation in an interventional study of a non-investigational treatment from screening through end of study participation. The duration of the elapsed time may be longer if required by local regulations.
8. Use of prohibited medications as defined in [Table 9-2](#), within the specified window before the first dose of ELX/TEZ/IVA in the Run-in Period (Day -28).
9. Pregnant or breast-feeding females. Female subjects must have a negative pregnancy test at screening (serum test) and Run-in Period/Day -28 (urine test).
10. 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 at that site. However, an adult (aged 18 years or older) who is a relative of a study staff member may be enrolled in the study provided that
  - the adult lives independently of and does not reside with the study staff member, and
  - the adult participates in the study at a site other than the site at which the family member is employed.

## 9 STUDY IMPLEMENTATION

### 9.1 Study Design

This is a Phase 3, randomized, double-blind, ELX/TEZ/IVA-controlled, parallel-group, multicenter study. A schematic of the study design is shown in [Figure 9-1](#).

**Figure 9-1 VX20-121-102 Study Design**



D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; N: number of subjects; TEZ: tezacaftor  
 Note: The figure is not drawn to scale.

Approximately 400 subjects will be enrolled. Study drug is defined in Section 10.

All subjects entering the Run-in Period will receive ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h). Following completion of the Run-in Period, approximately 400 subjects will be randomized 1:1 to the VX-121/TEZ/D-IVA group or the ELX/TEZ/IVA group for the Treatment Period. The dosages to be evaluated are shown in [Table 9-1](#). Randomization will be stratified; details are provided in [Section 9.2](#).

**Table 9-1 Treatment Period Groups and Dosages**

Treatment Group	VX-121	ELX	TEZ	D-IVA	IVA
VX-121/TEZ/D-IVA	20 mg qd	0 mg	100 mg qd	250 mg qd	0 mg
ELX/TEZ/IVA	0 mg	200 mg qd	100 mg qd	0 mg	150 mg q12h

D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor

Note: Study drug administration is described in [Section 9.6](#).

Study visits and assessments to be conducted are shown in [Table 3-1](#) and [Table 3-2](#). All visits will occur within the windows specified.

### 9.1.1 Screening

Screening Visit assessments are listed in [Table 3-1](#).

The Screening Period (Day -56 through Day -29) will occur within 28 days before the first dose of ELX/TEZ/IVA in the Run-in Period.

Screening assessments will be used to confirm that subjects meet the eligibility criteria. The investigator (or an appropriate authorized designee) will obtain informed consent and assent, if applicable, from each subject before any study procedure takes place.

#### 9.1.1.1 Repetition of Screening Assessment(s)

Screening assessments may be repeated once to establish study eligibility. If repeat values of the individual assessment(s) are within the eligibility criteria and completed within the screening window, then the subject is eligible for the study.

#### 9.1.1.2 Rescreening

Subjects may be rescreened once. If a subject is rescreened, all screening assessments will be repeated, except for:

- *CFTR* genotyping
- Follicle-stimulating hormone (FSH) level (if serum FSH level was in the postmenopausal range as determined by the laboratory performing the test during prior screening)
- Ophthalmologic examination (if performed within 3 months of the date of informed consent, for subjects <18 years of age on the date of informed consent)

If a subject is rescreened, a new screening window will begin when 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 for the following reasons:

- Repetition of the Screening Period assessments ([Section 9.1.1.1](#))

- Unexpected operational or logistic delays, or to meet the eligibility criteria
- Scheduling of ophthalmologic examination (for subjects <18 years of age on the date of informed consent, Section 11.6.6)

### 9.1.2 ELX/TEZ/IVA Run-in Period

The Run-in Period has a 4-week duration and is designed to establish a reliable on-treatment (ELX/TEZ/IVA) baseline for the Treatment Period. The first dose of open-label ELX/TEZ/IVA will be administered at the Day -28 Visit. Female subjects must have a negative pregnancy test at Day -28 before receiving study drug. The last dose of open-label ELX/TEZ/IVA will be administered on Day -1 (1 day before the Day 1 Visit).

On Day -14, spirometry (clinic and mobile) and SwCl will be assessed. The Day -14 clinic spirometry and SwCl assessments will be used for stratification of randomization (Section 9.2).

Subjects who prematurely discontinue study drug treatment during the Run-in Period will not be randomized or participate in the Treatment Period (Section 9.1.5.1).

### 9.1.3 Treatment Period

Treatment Period assessments are listed in Table 3-2.

The Treatment Period will be randomized, double-blind, and ELX/TEZ/IVA-controlled. It will last approximately 52 weeks (Day 1 through Week 52). Study drug administration details are provided in Section 9.6.

Randomization will occur before the first dose of study drug during the Treatment Period and may occur on either Day 1 or Day -1. Randomization and stratification details are provided in Section 9.2.

To enter the Treatment Period, subjects must have stable CF disease (as judged by the investigator) and have remained on a stable CF treatment regimen during the Run-in Period. Female subjects also must have a negative pregnancy test at Day 1 before receiving randomized study drug. If these conditions are not met (for example, if the subject has an acute upper or lower respiratory infection, PEx, or changes in therapy [including antibiotics] for sinopulmonary disease within 28 days before the Day 1 Visit [first dose of study drug in the Treatment Period]), the subject is considered a run-in failure and cannot enter the Treatment Period or rescreen.

The Week 12 Visit may be performed either in the clinic or as a home health visit, if permitted by local regulations. All home health visits must have a consultation between the subject and investigator (i.e., in person, phone, or telemedicine video conference). This consultation should occur within 2 business days before or after the home health visit and can be outside the visit window. Additional details regarding home health visits will be provided in the Study Reference Manual.

Subjects who prematurely discontinue study drug treatment will remain in the study from the time of discontinuation of study drug treatment through the last scheduled study visit (Section 9.1.5).

### 9.1.4 Follow-up

The Safety Follow-up Visit will occur approximately 28 ( $\pm$  7) days after the last dose of study drug for subjects who complete study drug dosing and for subjects who prematurely discontinue

study drug dosing, as described in Section 9.1.5. The assessments performed at the Safety Follow-up Visit are listed in Table 3-2.

An open-label study will be available for subjects who complete the Week 52 Visit and are eligible. The Safety Follow-up Visit is not required for subjects who complete the Treatment Period and transition within 28 days of the last dose of study drug to either:

- a commercially available Vertex CFTR modulator regimen,
- a managed access program-supplied Vertex CFTR modulator regimen,
- or, an open-label study or other qualified Vertex study.

### **9.1.5 Early Termination of Treatment**

If a 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 treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 ( $\pm$  7) 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 consent for the study, no further assessments will be performed. Vertex may retain and continue using the study data and samples after the study ends, and may use the samples and information in the development of the study compound, for other drugs and diagnostics, in publications and presentations, and for education purposes. If a subject withdraws from the study, the study data and samples collected will remain part of the study (Section 9.9).

#### **9.1.5.1 Discontinuation During the Run-in Period**

Subjects who prematurely discontinue study drug treatment during the Run-in Period will not be randomized or participate in the Treatment Period. These subjects will complete an ETT Visit and Safety Follow-up Visit (as applicable).

#### **9.1.5.2 Discontinuation During the Treatment Period**

Subjects who prematurely discontinue study drug treatment during the Treatment Period should continue to complete all scheduled study visits for assessments following completion of the ETT Visit (and Safety Follow-up Visit, if applicable), as detailed in Table 3-2.

### **9.1.6 Lost to Follow-up**

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

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

### 9.1.7 Completion of Study Participation

Completion of study participation for each individual subject is defined as one of the following:

- For subjects who complete the Treatment Period and transition to either an open-label study or other qualified Vertex study, a commercially available Vertex CFTR modulator regimen, or a managed access program-supplied Vertex CFTR modulator regimen within 28 days of the Week 52 Visit: the Week 52 Visit
- For subjects who complete the Treatment Period and do not transition to either an open-label study or other qualified Vertex study, a commercially available Vertex CFTR modulator regimen, or a managed access program-supplied Vertex CFTR modulator regimen within 28 days of the Week 52 Visit: the Safety Follow-up Visit
- For subjects who prematurely discontinue study drug treatment but do not withdraw consent (and assent, as applicable): the latest completed study visit up to and including the Week 52 Visit, ETT Visit, or Safety Follow-up Visit (if required)
- For subjects who withdraw consent or assent: date of withdrawal of consent or assent, whichever is earlier (Section 9.9)

If subjects are lost to follow-up (Section 9.1.6), the date of completion of study participation will be defined as the date of the last contact.

The end of study is defined in Section 13.2.9.

### 9.1.8 Use of Remote Measures in Extenuating Circumstances

Study visits should be performed in the clinic as specified in Section 3, Table 3-1, and Table 3-2, if at all possible. However, under extenuating circumstances, specific alternative measures may be implemented (e.g., if a subject is unable to travel to the study site due to safety concerns and/or local restrictions related to COVID-19 or other emerging events) in order to ensure the safety of subjects, site investigators, and site personnel while maintaining compliance with GCP and minimizing impact to the integrity of the study. The decision whether to conduct study visits remotely or in clinic will be at the discretion of the investigator; if the investigator determines that study visits will be conducted remotely, the medical monitor should be notified. The Screening Visit, Day -28 Visit, Day -14 Visit, Day 1 Visit, Week 24 Visit, and Week 52 Visit must be performed in clinic.

The following remote measures may be implemented. Additional details can be found in the Study Reference Manual.

- Consent or re-consent may be obtained remotely in writing (or verbally, with follow-up written confirmation), as allowed by local regulations.
- Study drug may be shipped directly from the site to the subject, as applicable and as allowed by local regulations.
- Study visits (except for those noted above) may be conducted as in-home visits by qualified personnel.
- Study assessments to evaluate safety and efficacy may be performed or overseen by qualified personnel conducting the in-home visits.



### 9.1.9 Data Monitoring Committee

Safety and tolerability data will be reviewed by a data monitoring committee (DMC) to ensure the safety of the subjects. Procedural details of the DMC's structure and function, frequency of meetings, and data planned for review will be in the DMC charter. The DMC charter will be finalized before the first subject is screened.

## 9.2 Method of Assigning Subjects to Treatment Groups

Subjects will be randomized (1:1) to the VX-121/TEZ/D-IVA group or the ELX/TEZ/IVA group. Randomization will be stratified by age at the Screening Visit (<18 versus  $\geq$ 18 years of age), ppFEV<sub>1</sub> determined during the Run-in Period (Day -14 clinic assessment; <70 versus  $\geq$ 70), SwCl determined during the Run-in Period (Day -14 assessment; <30 versus  $\geq$ 30 mmol/L), and prior CFTR modulator use (yes versus no). If the Day -14 ppFEV<sub>1</sub> and/or SwCl values are not valid or not available, the most recent available clinic-assessed ppFEV<sub>1</sub> and/or SwCl value will be used for stratification.

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 Elements

### 9.3.1 Study Design

This Phase 3 study will assess the efficacy and safety of VX-121/TEZ/D-IVA therapy in F/MF subjects.

A randomized, double-blind, ELX/TEZ/IVA-controlled study design was selected to ascertain the effects of VX-121/TEZ/D-IVA while avoiding observer bias. ELX/TEZ/IVA is considered an appropriate active control since it is an approved standard of care for treatment of patients with at least one *F508del* allele in some regions.

A 4-week Run-in Period was incorporated into this study to establish a reliable on-treatment (ELX/TEZ/IVA) baseline for comparison during the Treatment Period.

A 52-week treatment duration was selected to characterize the safety and efficacy of VX-121/TEZ/D-IVA compared to ELX/TEZ/IVA. The primary endpoint is absolute change from baseline in ppFEV<sub>1</sub> through Week 24. Based on prior experience with CFTR modulators, 24 weeks is adequate to compare the efficacy of VX-121/TEZ/D-IVA versus ELX/TEZ/IVA on the endpoints being evaluated.

### 9.3.2 Study Population

This study will enroll F/MF subjects to evaluate the treatment effect in subjects with a single *F508del* allele and a second allele that either results in no translated CFTR protein or that is non-responsive to TEZ, IVA, or TEZ/IVA based on in vitro testing. As described in Section 9.3.3, F/MF subjects are expected to respond to VX-121/TEZ/D-IVA based on results from a Phase 2 study conducted in F/MF subjects.

Given the progressive nature of CF, there is a strong rationale for treating patients earlier in life. Experience with CFTR modulators in adolescent subjects  $\geq$ 12 to <18 years of age, including with ELX/TEZ/IVA, suggests that the exposures and safety profile of VX-121/TEZ/D-IVA will



be similar in adolescents and adults, which supports evaluation of VX-121/TEZ/D-IVA in adolescents in the present study.

### **9.3.3 Study Drug Dose**

#### **ELX/TEZ/IVA**

ELX/TEZ/IVA will be administered as ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h, which is the approved dosing regimen for Trikafta (Kaftrio) in subjects 12 years of age and older.

#### **VX-121**

The VX-121 dose of 20 mg qd was selected for Phase 3 based on an assessment of the benefit-risk profile from the Phase 2 Study VX18-121-101 (Study 121-101) Part 1 and the relative bioavailability (BA) of VX-121 Form A compared to Form D in Study VX19-121-003 (Study 121-003).

Study 121-101 evaluated a range of VX-121 (Form A) doses (5 mg qd, 10 mg qd, and 20 mg qd) in TC with TEZ 100 mg qd/D-IVA 150 mg qd for 4 weeks in F/MF subjects. Treatment with VX-121 10 mg qd in TC with TEZ/D-IVA resulted in clinically meaningful improvements in ppFEV<sub>1</sub> and SwCl compared to the placebo group, with minimal additional improvement at a higher dose of VX-121 20 mg in TC with TEZ/D-IVA. VX-121/TEZ/D-IVA was generally safe and well tolerated in all dose groups, and no differences in the safety profile of VX-121/TEZ/D-IVA were observed across the dose groups.

In addition to the Phase 2 efficacy study, Study 121-003 evaluated the relative BA of a fixed-dose combination (FDC) of VX-121 (Form D) 20 mg/TEZ 100 mg/D-IVA 150 mg compared to separate tablets of VX-121 (Form A), TEZ, and D-IVA at the same dose. Results showed that VX-121 Form D had ~55% lower C<sub>max</sub> and ~50% lower AUC compared to VX-121 Form A. Therefore, a dose of VX-121 20 mg qd Form D was selected for Phase 3 to achieve similar exposures as the VX-121 10 mg (Form A) dose.

#### **TEZ**

Based on results from Studies VX17-121-001 and 121-101, exposures of TEZ and its metabolites at the approved dose of TEZ 100 mg qd in combination with VX-121/IVA or VX-121/D-IVA were similar to historical exposures. The dose of TEZ to be evaluated in Phase 3 will be 100 mg qd, which is part of the approved dosing regimens for Symdeko (Symkevi) and Trikafta (Kaftrio).

#### **D-IVA**

The D-IVA dose of 250 mg qd was selected for Phase 3 based on assessment of the benefit-risk profile from the Phase 2 Study VX18-561-101 (Study 561-101) as well as PK data and exposure-response modeling.

A Phase 2 monotherapy dose-ranging study (Study 561-101) was conducted that evaluated D-IVA at 25 mg qd, 50 mg qd, 150 mg qd, and 250 mg qd for 12 weeks in subjects with a gating mutation who were receiving stable IVA treatment. Treatment with D-IVA 250 mg qd resulted in similar ppFEV<sub>1</sub> and SwCl values as the IVA 150 mg q12h group, with greater improvements in SwCl compared to the D-IVA 150 mg qd group. Treatment with D-IVA 150 mg qd and

250 mg qd was safe and well tolerated, and D-IVA exposures seen at 250 mg qd are consistent with prior IVA clinical experience.

### 9.3.4 Rationale for Study Assessments

The efficacy endpoints being evaluated (spirometry, SwCl, CFQ-R, PEx, and anthropometric measurements) are widely accepted and generally recognized as reliable, accurate, and relevant to the study of individuals with CF. On the Day -14 and Day 1 Visits, spirometry will be collected using a mobile device to establish baseline values on the mobile device. SwCl was evaluated in the registration study of IVA (Kalydeco), TEZ/IVA combination therapy (Symdeko, Symkevi), and ELX/TEZ/IVA (Trikafta, Kaftrio). Spirometry and CFQ-R assessments were evaluated in the registration studies of IVA (Kalydeco), LUM/IVA combination therapy (Orkambi), TEZ/IVA combination therapy (Symdeko, Symkevi), and ELX/TEZ/IVA (Trikafta, Kaftrio).

All safety and PK assessments are standard measurements for clinical studies in drug development. Hemoglobin A1c (HbA1c) is included to assess pancreatic endocrine function.

Obstruction of airways with thick mucus, chronic bacterial infection of the airways, and the inflammatory response all play a role in causing lung damage in CF. Therefore, assessment of inflammatory mediators and other biomarkers is included.

The Treatment Satisfaction Questionnaire for Medication (TSQM) is included as an additional endpoint, and is a widely used generic measure of satisfaction with medication and has been demonstrated to be a valid and reliable measure of satisfaction in patients with CF.<sup>14</sup> The domains of the TSQM measure effectiveness, side effects, convenience, and global satisfaction. Because treatment satisfaction is not measured with the other health-related quality-of-life measures in this study, the TSQM is included as a study assessment. CF-IQ is also included as an additional endpoint to assess life impacts of CF and complement the CFQ-R and TSQM. Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) are included to assess a subject's perceived severity/change of disease.

## 9.4 Study Restrictions

### 9.4.1 Prohibited Medications

Table 9-2 lists prohibited medications. A non-exhaustive list of study prohibitions and cautions for medication will be provided in the Study Reference Manual.

**Table 9-2 Prohibited Medications**

Medication	Timing of Restriction		Rationale
	Start of Restriction	End of Restriction	
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of ELX/TEZ/IVA on Day -28	None allowed through completion of study participation	VX-121, ELX, TEZ, IVA, and D-IVA are metabolized extensively via CYP3A4. Therefore, use of moderate and strong inducers and inhibitors of CYP3A, which have the potential to alter the exposure of VX-121, ELX, TEZ, IVA, and D-IVA, will be prohibited.

**Table 9-2 Prohibited Medications**

Medication	Timing of Restriction		Rationale
	Start of Restriction	End of Restriction	
Non-Vertex CFTR modulators (investigational or approved)	None allowed within 28 days or 5 terminal half-lives (whichever is longer) before screening	None allowed through completion of study participation	These agents may confound the results of this study.
Vertex CFTR modulators (investigational or approved), except for study drugs	None allowed from the first dose of ELX/TEZ/IVA on Day -28	None allowed until after the last dose of study drug	These agents may confound the results of this study.

D-IVA: deutivacaftor; ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor

## 9.5 Prior and Concomitant Medications

Information regarding prior and concomitant medications, including CF medications, other medications, and herbal and naturopathic remedies, will be collected from each subject's source documentation for medications taken within 56 days before the Screening Visit through completion of study participation, as defined in Section 9.1.7.

- Subjects should remain on a stable treatment regimen for their CF from 28 days before the Run-in/Day -28 through completion of study participation. Stable treatment regimen is defined as the current treatment regimen for CF that subjects have been following for at least 28 days before the Run-in/Day -28. Subjects may remain on Vertex CFTR modulators (investigational or approved) during the Screening Period and may transition directly to the Run-in/Day -28 without a washout (Table 9-2). Subjects should not initiate long-term treatment with new medication from 28 days before the Run-in/Day -28 through completion of study participation. Guidelines for stable treatment regimens for CF are as follows:
  - o Subjects who are taking inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.
  - o Subjects who cycle onto and off of an inhaled antibiotic should continue on their prior schedule. The timing of the first dose of ELX/TEZ/IVA in the Run-in Period should be synchronized as closely as possible (e.g., not more than  $\pm 3$  days) to the first day in the cycle onto the inhaled antibiotic.
  - o 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 ELX/TEZ/IVA in the Run-in Period should be synchronized as closely as possible (e.g., not more than  $\pm 3$  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. Subjects cannot receive prednisone or prednisolone at doses  $>60$  mg qd for longer than a 5-day period.

- TEZ/IVA is a weak inhibitor of OATP1B1, and ELX and M23-ELX are potential inhibitors of OATP1B1 and OATP1B3. Administration of VX-121/TEZ/D-IVA or ELX/TEZ/IVA may increase systemic exposure of substrates of OATP1B1/1B3, which may increase or prolong their therapeutic effect and adverse reactions; therefore, caution and appropriate monitoring should be used when coadministration of study drugs with medicinal products that are substrates of OATP1B1/1B3, such as statins, glyburide, nateglinide, and repaglinide, is required.
- IVA and D-IVA are weak inhibitors of P-glycoprotein (P-gp). Administration of IVA or D-IVA may increase systemic exposure of medicinal products that are sensitive substrates of P-gp, which may increase or prolong their therapeutic effect and adverse reactions. Digoxin or other substrates of P-gp with a narrow therapeutic index, such as cyclosporine, everolimus, sirolimus, and tacrolimus, should be used with caution and appropriate monitoring.
- IVA and D-IVA may inhibit CYP2C9; therefore, during coadministration with warfarin, additional monitoring of the international normalized ratio is recommended. Other medicinal products that are CYP2C9 substrates for which exposure may be increased include glimepiride and glipizide; these should be used with caution.
- Subjects who are using a bronchodilator must have their spirometry assessments performed according to the guidelines provided in Section 11.5.1.

## 9.6 Administration

### 9.6.1 Dosing

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

Study drug will be administered with a fat-containing meal or snack, such as a standard “CF” meal or snack or a standard meal.

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 as FDC tablets (e.g., 2 VX-121/TEZ/D-IVA or matching placebo tablets; 2 ELX/TEZ/IVA or matching placebo tablets) in the morning and as 1 IVA or matching placebo tablet in the evening. For each subject, doses of study drugs will be taken at approximately the same time ( $\pm 2$  hours) each day.
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. If a subject’s scheduled visit is to occur in the afternoon, the following guidelines must be used:
  - If the dose in the clinic will be within 6 hours of the subject’s scheduled morning dose, the subject should withhold their morning dose of study drug and the morning dose will be administered in the clinic.

- If the dose in the clinic will be more than 6 hours after the subject's scheduled morning dose, the subject should take the morning dose of study drug at home.
  - At the Day 1 and Week 8 Visits, the morning dose of study drug must be administered in the clinic to enable predose and/or postdose PK sampling relative to the morning dose.
6. Subjects will be instructed to bring all used and unused materials associated with the study drug to the site; study drug will be dispensed at each visit, as appropriate.

### 9.6.2 Missed Doses

If 6 hours or less have passed since the missed morning or evening dose, the subject should take the missed dose as soon as possible and continue on the original schedule.

**Morning dose:** If more than 6 hours have passed since the missed morning dose, the subject should take the missed dose as soon as possible and should not take the evening dose.

**Evening dose:** If more than 6 hours have passed since the missed evening dose, the subject should not take the missed dose. The next scheduled morning dose should be taken at the usual time.

Morning and evening doses should not be taken at the same time.

### 9.7 Dose Modification for Toxicity

No dose modifications for toxicity are allowed. Treatment may be interrupted as outlined in Section 9.8. If any unacceptable toxicity arises, individual subjects will discontinue dosing (Section 9.9).

### 9.8 Study Drug Interruption and Stopping Rules

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

#### 9.8.1 Liver Function Tests

The central laboratory will notify the medical monitor of ALT or AST  $>3 \times \text{ULN}$  and total bilirubin  $>2 \times \text{ULN}$  that are derived from centrally submitted samples.

Subjects with new treatment-emergent ALT or AST elevations of  $>3 \times \text{ULN}$ , with or without total bilirubin  $>2 \times \text{ULN}$ , must be followed closely, including confirmatory testing performed by the central laboratory within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT, AST, and bilirubin levels, as clinically indicated.

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

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

- ALT or AST  $>8 \times \text{ULN}$
- ALT or AST  $>5 \times \text{ULN}$  for more than 2 weeks
- ALT or AST  $>3 \times \text{ULN}$ , in association with total bilirubin  $>2 \times \text{ULN}$  and/or clinical jaundice

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

Study drug administration **must be discontinued** if the following criterion 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, alcohol ingestion) is identified, regardless of whether transaminase levels have improved

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

If an alternative, reversible cause of transaminase elevation with or without increased bilirubin or clinical jaundice has been identified, study drug administration may be resumed once transaminases return to baseline or are  $\leq 2 \times$  ULN, whichever is higher. Regardless of the duration of interruption, the medical monitor should be notified prior to resumption of study drug. Upon resumption of study drug, transaminases and bilirubin should be assessed weekly for 4 weeks. If a protocol-defined transaminase elevation interruption threshold recurs within 4 weeks of rechallenge with the study drug (with confirmation of the initial elevation by repeat testing within 48 to 72 hours), then the study drug must be permanently discontinued, regardless of the presumed etiology.

### 9.8.2 Rash

Individuals who develop a generalized rash will be monitored closely. Study drug dosing should be interrupted if a subject develops a generalized rash of Grade 3 or higher, or a rash that is considered a serious adverse event (SAE). The investigator will notify the medical monitor of any rash that results in interruption of study drug, is Grade 3 or higher (Section 13.1.1.4), or is an SAE. Investigators should consider additional evaluation including laboratory testing (e.g., complete blood count [CBC] with differential, LFTs), photographs of the rash, and dermatology consultation. The investigator may consider resumption of study drug if considered clinically appropriate.

### 9.9 Removal of Subjects

Subjects may withdraw from the study at any time at their own request. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. A subject who withdraws from study drug treatment will continue to be followed unless the subject withdraws consent (and assent, as applicable).

In addition, a subject must be discontinued from study drug treatment if the subject meets any of the following criteria:

- Has a screening *CFTR* genotype that does not confirm study eligibility if a previous *CFTR* genotype laboratory report was used to establish eligibility. These subjects must be discontinued from the study (Section 8.1)
- Meets any of the stopping (discontinuation) criteria (Section 9.8)
- Becomes pregnant (Section 11.6.7.2)

Subjects who discontinue study treatment early should continue to return for study assessments, as noted in Section 9.1.5.

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 an ETT Visit and Safety Follow-up Visit, if applicable (see Section 9.1.4), and follow up with the subject regarding any unresolved AEs.

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

### **9.10 Replacement of Subjects**

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

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

## **10 STUDY DRUG INFORMATION AND MANAGEMENT**

During the Run-in Period, study drug refers to ELX/TEZ/IVA and IVA.

During the Treatment Period, study drug refers to VX-121/TEZ/D-IVA and matching placebo, ELX/TEZ/IVA and matching placebo, and IVA and matching placebo.

### **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 about packaging, labeling, and dispensing for study drug will be in the Pharmacy Manual.

### **10.3 Study Drug Supply, Storage, and Handling**

VX-121/TEZ/D-IVA will be supplied as FDC film-coated tablets containing 10 mg VX-121/50 mg TEZ/125 mg D-IVA. Matching VX-121/TEZ/D-IVA placebo tablets will be of similar size and appearance and contain 0 mg VX-121/0 mg TEZ/0 mg D-IVA (Table 10-1).

ELX/TEZ/IVA will be supplied as FDC film-coated tablets containing 100 mg ELX/50 mg TEZ/75 mg IVA. Matching ELX/TEZ/IVA placebo tablets will be of similar size and appearance and contain 0 mg ELX/0 mg TEZ/0 mg IVA (Table 10-1).



IVA will be supplied as a tablet containing 150 mg IVA. Matching IVA placebo tablets will be of similar size and appearance and contain 0 mg IVA (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/Dosage Form/Route**

<b>Drug Name, Dosage Form, Route</b>	<b>Strength</b>
VX-121/TEZ/D-IVA, FDC tablet, oral	
VX-121	10 mg
TEZ	50 mg
D-IVA	125 mg
VX-121/TEZ/D-IVA-matching placebo, tablet, oral	0 mg
ELX/TEZ/IVA, FDC tablet, oral	
ELX	100 mg
TEZ	50 mg
IVA	75 mg
ELX/TEZ/IVA-matching placebo, tablet, oral	0 mg
IVA, tablet, oral	150 mg
IVA-matching placebo, tablet, oral	0 mg

D-IVA: deutivacaftor; ELX: elexacaftor; FDC: fixed-dose combination; IVA: ivacaftor; TEZ: tezacaftor

#### **10.4 Drug Accountability**

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

If a site uses a site-specific drug accountability system and/or process, including processes associated with the destruction of returned materials, the process must be documented and approved by Vertex. Additional details will be provided in the Pharmacy Manual. The study monitor must review the drug accountability documentation on a regular basis. The study monitor will promptly communicate to Vertex any discrepancies he/she is unable to resolve with the site.

#### **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. 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.



The principal investigator (PI), study site staff, including pharmacy personnel will assist Vertex with any recall activities (as applicable) and place impacted investigational medicinal product (IMP) in quarantine when requested.

## **10.6 Compliance**

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

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

## **10.7 Blinding and Unblinding**

This is a double-blind study.

### **10.7.1 Blinding**

All subjects (and their parents/caregivers/companions), site personnel (including the investigator, the site monitor, and the study team), and members of the Vertex study team will be blinded to the treatment codes.

Individuals who may be unblinded include only 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 SAE processing and reporting regulations
- Vendor preparing the final (production) randomization list
- Vertex IWRS Manager
- Vertex Clinical Supply Chain
- DMC
- Vendor preparing the unblinded analysis of safety data for review by the DMC
- Analysts or vendor for modeling and simulations performing population PK modeling in preparation for regulatory submission(s)
- Bioanalytical contract research organization (CRO) analyzing PK samples and the Vertex Bioanalytical personnel who is not a member of the study team but reviews raw data from the Bioanalytical CRO. The Vertex Bioanalytical study team member will continue to be blinded.

### Access to Spirometry and SwCl Results:

During the conduct of the study, the Vertex study team will not have access to the spirometry or SwCl results after the first dose of study drug on Day 1 of the Treatment Period, with the exception of spirometry related to adverse event reporting.

Shortly before any planned efficacy analysis is conducted, the spirometry and SwCl data will be reviewed for data cleaning purposes by a limited Vertex team that does not have access to the treatment codes.

Individual SwCl test results will not be disclosed to the study sites with the exception of the Screening Visit and Day -14 values. Subjects and their parents/caregivers/companions should not be informed of study-related spirometry results until Vertex has determined that the study has completed (i.e., clinical study report [CSR] finalization), regardless of whether the subject has prematurely discontinued treatment.

### **10.7.2 Unblinding**

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

Unblinding of the individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, investigators will use their best judgment as to whether to unblind without first attempting to contact the medical monitor to discuss unblinding. If investigators deem it unnecessary to unblind immediately, they will first attempt to contact the medical monitor to discuss unblinding. If investigators have tried but are unable to reach the medical monitor, they will use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding.

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

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

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

## 11 ASSESSMENTS

The schedule of assessments is shown in [Table 3-1](#) and [Table 3-2](#).

### 11.1 Subject and Disease Characteristics

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

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

Height and weight will be measured with shoes off. Height will be collected at screening for all subjects. Following screening, height will be collected only for subjects  $\leq 21$  years of age on the date of informed consent.

### 11.2 Pharmacokinetics

#### 11.2.1 Blood Sampling

Blood samples will be collected to determine plasma concentrations of VX-121, TEZ, D-IVA, ELX, IVA, and relevant metabolites. These samples may also be used for further evaluation of the bioanalytical method, or for exploratory analyses that provide information on the metabolic pathways used by or affected by any study drugs.

For PK sampling at the Week 8 Visit, all subjects  $< 18$  years of age on the date of informed consent will have 1 postdose sample taken at 4 hours after the morning clinic dose. Approximately 40 subjects  $\geq 18$  years of age on the date of informed consent will have a total of 4 postdose samples taken at 4, 5, 6, and 7 hours after the morning clinic dose. All other subjects  $\geq 18$  years of age on the date of informed consent will have 1 postdose sample taken at 2 hours after the morning clinic dose. Vertex will manage the allocation of the 40 subjects providing more intensive PK sampling across study sites. If study drug is not administered at the Week 8 visit (i.e., due to study drug interruption or permanent discontinuation), a single PK blood sample will be collected at the visit.

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. The exact time of the sample collection will be noted.

**Table 11-1 Acceptable Pharmacokinetic Sampling Windows**

Sampling Time	Time From Scheduled Sampling Allowed
Predose	-60 minutes
From 2 up to $\leq 7$ hours after study drug dosing	$\pm 15$ minutes

Blood samples will be collected as shown in [Table 3-2](#).

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

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

### **11.2.2 Processing and Handling of Pharmacokinetic Samples**

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

### **11.2.3 Bioanalysis**

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

### **11.3 Pharmacodynamics**

While SwCl is a pharmacodynamic measure of CFTR function, it is also a measure of efficacy and is discussed in Section 11.5.2.

### **11.4 Exploratory Assessments**

These data will be used for internal exploratory purposes. Detailed procedures for the collection of blood samples and additional procedures for processing and handling samples for pharmacogenomics analysis will be provided in a separate document.

#### **11.4.1 Pharmacogenomics**

An optional single blood sample (DNA Sample) will be collected for potential exploratory evaluation of associations between DNA markers with PK, pharmacodynamics (PD), treatment response, AEs, and health and disease, especially CF, for subjects who choose to participate in this assessment (if permitted by local regulations).

#### **11.4.2 Inflammatory Mediators**

Blood samples (inflammatory mediator samples) will be collected at the time points noted in Table 3-2 and tested to assess markers related to inflammation. These may include, but are not limited to, C-reactive protein (CRP), immunoglobulin G (IgG), white blood cell (WBC, leukocyte) count, and interleukin-8 (IL-8). Specific instructions for the collection, processing, storage, and shipment of inflammatory mediator samples will be provided in the Laboratory Manual.

#### **11.4.3 Other Blood Biomarkers**

Additional blood samples for plasma and serum will be collected and banked for potential future exploratory evaluation of other blood biomarkers (e.g., proteins, peptides, lipids, metabolites, etc.) in relation to PK, PD, treatment response, AEs, and various disease manifestations of CF.

Optional blood samples (RNA Sample) may be collected (if permitted by local regulations) for potential exploratory evaluation of associations between RNA markers with PK, PD, treatment response, and AEs.

#### **11.4.4 Microbiology and Other Sputum Biomarkers**

Sputum samples will be collected at the time points noted in [Table 3-2](#) from subjects who can produce a sample spontaneously. Each sample will be processed and frozen for potential exploratory evaluation of microbiology analysis and sputum biomarkers (which may include, but are not limited to, qualitative and quantitative bacterial and viral assessments including genomic analyses, analysis of immune cells, inflammatory markers, proteins, peptides, lipids, and endogenous metabolites) in relation to PK, PD, treatment response, AEs, and various disease manifestations of CF.

Specific instructions for the collection, processing, aliquoting, storage, and shipment of sputum samples will be provided in the Laboratory Manual.

#### **11.4.5 Treatment Satisfaction Questionnaire for Medication**

The TSQM is a widely used generic measure of satisfaction with medication. The domains of the TSQM measure effectiveness, side effects, convenience, and global satisfaction. Because treatment satisfaction is not measured with the other health-related quality-of-life measures in this study, the TSQM will be included as an assessment for this purpose. Translations of the TSQM will be provided for participating centers with non-English-speaking populations.

All subjects should be instructed to complete the TSQM questionnaire on the Day -28 Visit based on their experience of their current medication regimen over the prior 2 to 3 weeks. Only subjects <18 years of age on the date of informed consent will complete the TSQM at subsequent visits; these subjects should be instructed to complete the TSQM based on their experience of the study drug over the prior 2 to 3 weeks. Subjects who discontinue study drug prematurely or who have interrupted study drug will still complete the TSQM basing their experience of the study drug if taken during the prior 2 to 3 weeks. If study drug was not taken during this period, the responses should be based on their experience of their current medication regimen.

TSQM may be completed within 5 days prior to the study visit. All questionnaires completed on the day of the study visit must be completed prior to any other assessments, with CFQ-R completed first.

#### **11.4.6 Other Questionnaires**

The CF-IQ is a 23-item measure of patient-reported life impacts of CF across 5 domains: control and burden of CF treatment, physical activity, social activity, emotional, and work/school limitations. The CF-IQ measures each concept using a 5- or 7-point verbal rating scale and specifies a 7-day recall period for retrospective questions. The CF-IQ was developed to characterize the patients' experience of living with CF and to measure the impact of CF and CF treatment on patients' lives. The CF-IQ is designed to complement existing, more symptom-focused, CF-specific patient-reported outcome (PRO) measures like the CFQ-R. Translations of the CF-IQ will be provided for participating centers with non-English-speaking populations.

For purposes of validating CF-IQ, PGIS and PGIC will be performed per [Table 3-2](#) in order to assess a subject's perceived severity/change of disease. Details regarding CF-IQ validation will be provided in a separate document.

CF-IQ, PGIS, and PGIC may be completed within 5 days prior to the study visit. CF-IQ, PGIS, and PGIC must be completed on the same day, and CF-IQ must be performed before PGIS or

PGIC (as applicable). All questionnaires completed on the day of the study visit must be completed prior to any other assessments, with CFQ-R completed first.

## **11.5 Efficacy**

### **11.5.1 Spirometry**

Spirometry will be performed according to the American Thoracic Society Guidelines/European Respiratory Society Guidelines<sup>10</sup> and according to the additional guidelines that follow.

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

- withheld their short-acting bronchodilators (e.g., albuterol) or anticholinergic (e.g., ipratropium bromide [Atrovent<sup>®</sup>]) 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<sup>®</sup>]) for more than 24 hours before the spirometry assessment.

During the Screening Period, spirometry assessments may be performed pre- or post-bronchodilator. At all other visits, all spirometry assessments should be performed pre-bronchodilator. During the Treatment Period, spirometry assessments must be performed before study drug dosing (Section 9.6.1) at approximately the same time at each visit. In the event that a subject forgets to withhold bronchodilator(s), spirometry should be performed according to the following:

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

Spirometers will be provided to be used for all study assessments. During study visits, spirometry assessments will be conducted per Table 3-1 and Table 3-2 and will be performed on more than one spirometer as applicable. All spirometry data will be transmitted to a centralized spirometry service for quality review. The investigator's assessment of the spirometry results will be used for the screening assessment and determination of eligibility.

See Section 10.7.1 for information about access to spirometry results.

The measured spirometric values listed below will be converted to percent predicted values using the standard equations of GLI.<sup>9</sup>

- FEV<sub>1</sub> (L)
- Forced vital capacity (FVC) (L)

- FEV<sub>1</sub>/FVC (ratio)
- Forced expiratory flow, midexpiratory phase (FEF<sub>25%-75%</sub>) (L/s)

### **11.5.2 Sweat Chloride**

SwCl samples will be collected with an approved collection device. Each collection will occur before study drug dosing (Section 9.6.1). 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. Specific instructions for the collection, handling, processing, and shipping of SwCl samples to the central laboratory will be provided separately.

See Section 10.7.1 for information about access to SwCl results.

### **11.5.3 Cystic Fibrosis Questionnaire-Revised**

The CFQ-R provides information about demographics; general quality of life, school, work, or daily activities; and symptom difficulties (pertaining to CF).

Subjects will be asked to complete the CFQ-R in their native language, if validated translations are available.<sup>15, 16</sup> If there is no validated translation available in the subject's native language, the subject will not complete the questionnaire. Copies of the CFQ-R used will be provided in the Study Reference Manual. Validated translations of the CFQ-R, if available, will be provided for participating centers with non-English-speaking populations.<sup>17, 18</sup>

The CFQ-R will be completed before any other assessments are performed on the day of the study visit.

Subjects who are either 12 or 13 years of age on the date of informed consent will complete the CFQ-R Child version themselves, and their parents/caregivers will complete the CFQ-R Parent version, at all visits, regardless of whether the subject subsequently turns 14 years of age during the study. Subjects 14 years of age and older on the date of informed consent will complete the Adolescent/Adult version of the questionnaire themselves at all visits.

### **11.5.4 Other Events Related to Outcome**

#### **11.5.4.1 Antibiotic Therapy for Sinopulmonary Sign/Symptoms**

New or changed antibiotic therapy (intravenous [IV], inhaled, or oral) for the following sinopulmonary signs/symptoms will be determined and documented at visits as indicated in [Table 3-2](#):

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature above 38°C (equivalent to approximately 100.4°F)
- Anorexia or weight loss
- Sinus pain or tenderness



- Change in sinus discharge
- Change in physical examination (PE) of the chest
- Decrease in pulmonary function by 10%
- Radiographic changes indicative of pulmonary infection

**For this study, PEx is defined as a new or change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the above signs/symptoms.** This definition is based on the definition of a PEx used in previous clinical studies, including IVA clinical studies.<sup>19, 20</sup>

It is recommended that the study drug not be interrupted during a PEx unless, in the opinion of the investigator, it would be in the best interest of the subject.

#### **11.5.4.2 Hospitalization for CF**

Subjects will be queried about planned and unplanned hospitalizations lasting  $\geq 24$  hours that occurred during the study. The dates of hospitalizations and the reasons for hospitalizations will be documented.

For any hospitalization (planned and unplanned), the procedures for safety reporting should also be followed.

#### **11.5.5 Height and Weight**

Height and weight will be measured with shoes off. Height will be collected at screening for all subjects. Following screening, height will be collected only for subjects  $\leq 21$  years of age on the date of informed consent.

#### **11.6 Safety**

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

##### **11.6.1 Adverse Events**

All AEs will be assessed, documented, and reported in accordance with current ICH E6 GCP Guidelines. Section 13.1 outlines the definitions, collection periods, criteria, and procedures for documenting, grading, and reporting AEs.

##### **11.6.2 Clinical Laboratory Assessments**

Blood and urine samples will be analyzed at a central laboratory, with the exception of the urine pregnancy tests. As described below, urine pregnancy tests will either be analyzed by the site or at home using a home kit. On Day 1, blood samples will be collected before the first dose of study drug in the Treatment Period. Specific instructions for the collection, processing, and shipment of samples will be provided in a separate Laboratory Manual.

Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1).

The safety laboratory test panels are shown in [Table 11-2](#).



**Table 11-2 Safety Laboratory Test Panels**

Serum Chemistry	Hematology	Urinalysis <sup>a</sup>
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen <sup>b</sup>	Hemoglobin A1c <sup>c</sup>	Nitrite
Creatinine	Erythrocytes	Urobilinogen
Sodium	Mean corpuscular volume	Urine protein
Potassium	Platelets	pH
Calcium	Reticulocytes	Urine blood
Chloride	Leukocytes	Specific gravity
Magnesium	Differential (absolute and percent):	Urine ketones
Bicarbonate	Eosinophils	Urine bilirubin
Phosphate	Basophils	Urine glucose
Total bilirubin, direct bilirubin, indirect bilirubin	Neutrophils	
Alkaline phosphatase	Lymphocytes	
Aspartate transaminase	Monocytes	
Alanine transaminase	<b>Coagulation</b>	
Amylase	Activated partial thromboplastin time	
Lipase	Prothrombin time	
Gamma-glutamyl transferase	Prothrombin time International	
Protein	Normalized Ratio	
Albumin		
Creatine kinase		
Cholesterol		
Lactate dehydrogenase		

<sup>a</sup> If urinalysis results are positive for leukocyte esterase, nitrite, protein, or blood, microscopic examination of urine will be done, and results will be provided for leukocytes, erythrocytes, crystals, bacteria, and casts.

<sup>b</sup> If blood urea nitrogen cannot be collected, urea may be substituted.

<sup>c</sup> Hemoglobin A1c will be assessed per [Table 3-1](#) and [Table 3-2](#).

**Pregnancy ( $\beta$ -human chorionic gonadotropin) Tests:** All female subjects, regardless of childbearing potential, will complete the pregnancy tests outlined in [Table 3-1](#) and [Table 3-2](#). Serum pregnancy tests will be performed at the study site and analyzed at the central laboratory. Urine pregnancy tests will either be performed and analyzed at the site or, when there is no clinic visit scheduled, at home by using a home kit provided by the site. Results will be reported to the site by telephone. The urine pregnancy test on Day -28 must be negative before the first dose of study drug in the Run-in Period. The urine pregnancy test on Day 1 must be negative before the first dose of study drug in the Treatment Period. Additional pregnancy tests may be required according to local regulations and/or requirements.

**FSH:** Blood samples for FSH will be measured as needed for any postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be in the postmenopausal range as determined by the laboratory performing the test. Refer to [Section 11.6.7.1](#) for details regarding contraception guidelines.

**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 ([Section 8.1](#)). Subjects who have been enrolled and whose screening genotype does not confirm study eligibility must be discontinued from the study ([Section 9.9](#)).

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

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

### **11.6.3 Physical Examinations and Vital Signs**

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

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

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

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

### **11.6.4 Pulse Oximetry**

Pulse oximetry is a noninvasive measure of oxygen delivery to the tissues and has been correlated with clinical status and lung function. Arterial oxygen saturation by pulse oximetry will be assessed following at least a 5-minute rest. At visits when study drug is taken at the site, pulse oximetry will be collected before study drug dosing (Section 9.6.1).

### **11.6.5 Electrocardiograms**

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

- The subject will be instructed to rest for at least 5 minutes before having an ECG.
- The test should be performed in the supine position and before dosing (as applicable).

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 completion of study participation will be recorded as AEs.

To ensure safety of the subjects, a qualified individual at the study site will make comparisons to baseline measurements. If the QTcF is increased by >60 msec from the baseline or an absolute QTcF value is  $\geq 500$  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  $\geq 500$  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. If study sites cannot evaluate QTcF they should discuss alternatives with the medical monitor.

### **11.6.6 Ophthalmologic Examination**

Ophthalmologic examinations will be conducted only for subjects who are <18 years of age on the date of informed consent. The examination does not need to be completed if there is documentation of bilateral lens removal for the subject.

All examinations will be conducted by a licensed ophthalmologist or optometrist and will include:

- measurement of best-corrected distance visual acuity of each eye; and
- pharmacologically-dilated examination of the lens with a slit lamp.

The screening examination does not need to be conducted if there is documentation of an examination meeting the protocol requirements that was conducted within 3 months before the date of informed consent.

In addition to the screening ophthalmologic examination, subjects who are <18 years of age on the date of informed consent and who have completed at least 12 weeks of study drug treatment will have a single ophthalmologic examination within 4 weeks prior to completion of study participation (Section 9.1.7), except for those subjects who have withdrawn consent or assent (Table 3-2). This examination should be completed within 4 weeks before the Week 52 Visit, unless the subject prematurely discontinues study drug, in which case this examination should occur by the Safety Follow-up Visit (or ETT Visit for subjects who do not complete a Safety Follow-up Visit), as described in Section 9.1.5.

Any clinically significant abnormal findings will be reported as AEs.

### **11.6.7 Contraception and Pregnancy**

The effects of VX-121, ELX, TEZ, IVA, and D-IVA on conception, pregnancy, and lactation in humans are not known. VX-121, ELX, TEZ, IVA, and D-IVA did not show genotoxic potential in a standard battery of in vitro (Ames test, chromosomal aberration, or micronucleus in cultured mammalian cells) and in vivo (rodent micronucleus) studies. Reproductive toxicology studies of VX-121, ELX, TEZ, and IVA have not shown teratogenicity in rats and rabbits.

#### **11.6.7.1 Contraception**

Study participation requires compliance with the contraception guidelines outlined below:

**Contraception for the couple is waived for the following:**

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

investigator before the first dose of ELX/TEZ/IVA in the Run-in Period (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:
  - o Postmenopausal: Amenorrheic for at least 12 consecutive months and a serum FSH level within the laboratory's reference range for postmenopausal females
  - o Documented hysterectomy or bilateral oophorectomy/salpingo-oophorectomy

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

- Exclusive 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 effective contraception will be used as a couple. Acceptable methods of contraception must be in successful use from signing of consent, approximately 28 days before the first dose of ELX/TEZ/IVA in the Run-in Period (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**

Method	Male Subjects and Their Female (Non-study) Partners	Female Subjects and Their Male (Non-study) Partners
Vasectomy 6 months or more previously, with a documented negative postvasectomy semen analysis for sperm	Yes	Yes
Documented bilateral tubal ligation performed at least 6 months previously	Yes	Yes
Male or female condom with or without spermicide <sup>a</sup>	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.	Yes	Yes
Oral, patch, implanted, or injected hormonal contraceptives, if used consistently and correctly for at least 60 days before the first dose of study drug	Yes	Yes

Notes: At least 1 acceptable method of contraception must be used by couples not exempt from the contraception requirement. The first dose of study drug refers to the first dose of ELX/TEZ/IVA in the Run-in Period.

<sup>a</sup> A female condom cannot be used with a male condom due to risk of tearing.

**Additional notes:**

- Male and female subjects who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study if they become sexually active with a partner of the opposite sex.
- Male subjects must not donate sperm during the period starting from the first dose of ELX/TEZ/IVA in the Run-in Period until 90 days after the last dose of study drug.
- Female subjects of childbearing potential should not plan to become pregnant during the study or within 90 days after the last dose of study drug. For male subjects with a female partner of childbearing potential, the couple should not plan to become pregnant during the study or within 90 days after the last dose of study drug, with the exception of couples who plan to become pregnant by artificial insemination using sperm banked by the male subject before the first dose of ELX/TEZ/IVA in the Run-in Period or sperm from another source.
- Male subjects whose female partner becomes pregnant through well-documented in vitro fertilization (donated sperm) or banked sperm (collected before the subject received study drug), or is otherwise already pregnant before the male subject's first dose of ELX/TEZ/IVA in the Run-in Period, must be compliant with the contraception requirements. In this scenario, the male subject and his female partner must commit to using a male condom (to ensure there is no exposure of the fetus to study drug) from signing consent through 90 days after the last dose of study drug.
- Female subjects should not breast-feed a child from signing consent through 90 days following the last dose of study drug.
- Unique situations that may not fall within the above specifications may be discussed with the Vertex medical monitor or authorized designee on an individual basis.

**11.6.7.2 Pregnancy**

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

If a subject, or the female partner of a male subject, becomes pregnant while participating in the study, the study drug will be permanently discontinued immediately. The investigator will 1) notify the medical monitor and Vertex GPS within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy, and 2) send the Pregnancy Information Collection Form to Vertex GPS.

A subject (or their partner, if relevant) who becomes pregnant while on study will be followed until the end of the pregnancy, and the infant will be followed for 1 year after birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself is not an AE.

**12 STATISTICAL ANALYSIS****12.1 Sample Size and Power**

Approximately 400 subjects will be enrolled and randomized (1:1) to the VX-121/TEZ/D-IVA group or the ELX/TEZ/IVA group. Information regarding the powering of the primary and selected key secondary efficacy endpoint is presented below.

### Power for Primary Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the absolute change from baseline in ppFEV<sub>1</sub> through Week 24. The primary null hypothesis to be tested is that the mean absolute change in ppFEV<sub>1</sub> from baseline through Week 24 for VX-121/TEZ/D-IVA is inferior by >3 percentage points compared to ELX/TEZ/IVA.

The non-inferiority margin represents a clinically acceptable loss of effectiveness as outlined in regulatory guidances. Furthermore, a statistical approach using the Rothmann method recommends that the non-inferiority margin preserve at least 50% of the treatment effect of the active control (ELX/TEZ/IVA) compared to placebo, where the treatment effect is estimated by the lower bound of the 95% CI.<sup>21, 22</sup> In the overall population eligible for this study, the lower bound of the 95% CI of the treatment effect is approximately 12 percentage points for ppFEV<sub>1</sub>. The selected non-inferiority margin of 3 percentage points is consistent with this statistical method and the non-inferiority margin for ppFEV<sub>1</sub> used in clinical studies evaluating symptomatic CF treatments.<sup>23, 24</sup>

The null hypothesis will be tested at a 1-sided significance level of 0.025.

Assuming a within-group SD of 8 and 10% drop-out rate at Week 24 and a treatment difference of 0 between VX-121/TEZ/D-IVA and ELX/TEZ/IVA, a sample size of 200 subjects in each group for a total of 400 subjects will have more than 90% power to test the primary hypothesis for the primary endpoint, based on a 1-sided, 2-sample *t*-test at a significance level of 0.025.

### Power for Analysis of Selected Key Secondary Efficacy Endpoint

A key secondary efficacy endpoint is the absolute change in SwCl from baseline through Week 24. Assuming a within-group SD of 14 mmol/L and a 10% dropout rate at Week 24, a sample size of 200 subjects in each treatment group will have more than 90% power to detect a difference between the treatment groups of -5 mmol/L for the absolute change in SwCl from baseline through Week 24, based on a 2-sided, 2-sample *t*-test at a significance level of 0.05.

## 12.2 Analysis Sets

The following analysis sets are defined: All Subjects Set, Full Analysis Set (FAS), Safety Set, and Per-protocol Set (PPS).

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(s) and received at least 1 dose of study drug during the Treatment Period. The FAS will be used to summarize subject demographics and baseline characteristics, and for analyses of all efficacy endpoints in which subjects will be analyzed according to their randomized treatment group, unless otherwise specified.

The **Safety Set for the Run-in Period** will include all subjects who received at least 1 dose of study drug in the Run-in Period. This safety set will be used only for individual subject data listings, unless otherwise specified.

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

which subjects will be analyzed according to the treatment they actually received, unless otherwise specified.

The PPS will be a subset of FAS after excluding subjects with certain important protocol deviations and other situations; details will be provided in the statistical analysis plan (SAP).

### **12.3 Statistical Analysis**

This section presents a summary of the planned analyses for this protocol. Statistical analysis details will be provided in the SAP, which will be finalized before the clinical data lock for the study.

#### **12.3.1 General Considerations**

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

**Categorical variables** will be summarized using counts and percentages.

**Baseline** 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 SwCl, baseline will be defined as the average of the Day -14 and Day 1 values. If either the Day -14 or the Day 1 value are missing, the other will be used as the average.

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

The **Treatment-emergent (TE) Period for the Run-in Period** will be from the first dose date of study drug in the Run-in Period to (1) the first dose date of study drug in the Treatment Period for subjects who complete the Run-in Period and continue to the Treatment Period, or (2) 28 days after the last dose date of study drug in the Run-in Period or to the completion of study participation date (as defined in Section 9.1.7), whichever occurs first, for subjects who do not continue to the Treatment Period (e.g., subjects who do not meet the conditions to enter the Treatment Period).

The **TE Period for the Treatment Period** will include the time from the first dose date of study drug in the Treatment Period to 28 days after the last dose of the study drug or to the completion of study participation date, whichever occurs first.

#### **12.3.2 Background Characteristics**

Subject disposition, demographic and baseline characteristics, prior and concomitant medications, exposure, compliance, and important protocol deviations will be summarized. Details of the analysis will be provided in the SAP.

#### **12.3.3 Efficacy Analysis**

All efficacy analyses described in this section will be based on the FAS, unless otherwise specified. Only the principal features of the efficacy analysis will be presented in this section. Additional details will be included in the SAP.

##### **12.3.3.1 Analysis of Primary Endpoint**

The primary efficacy endpoint is the absolute change from baseline in ppFEV<sub>1</sub> through Week 24 (estimated by averaging Weeks 16 and 24). The primary analysis will be conducted with clinic spirometry data only and will be performed using a mixed-effects model for repeated measures

(MMRM) with absolute change from baseline in ppFEV<sub>1</sub> at Day 15, Week 4, Week 8, Week 16, and Week 24 as the dependent variable. The model will include treatment group, visit, and treatment-by-visit interaction as fixed effects, with continuous baseline ppFEV<sub>1</sub>, continuous baseline SwCl, and age at screening (<18 versus ≥18 years of age) as covariates. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the F test for fixed effects will be estimated using the Kenward-Roger approximation. An unstructured covariance structure will be used to model the within-subject errors. If the model estimation does not converge, a compound symmetry covariance structure will be used instead. Conditional on the observed data and covariates, missing data will be assumed to be missing at random; therefore, no imputation of missing data will be performed.

The primary result obtained from the model will be the estimated treatment difference through Week 24. The adjusted mean with a 2-sided 95% CI will be provided. The primary null hypothesis will be rejected and non-inferiority demonstrated if the lower bound of the 95% CI is ≥-3.0. The estimated within group change from baseline and the treatment difference at each post-baseline visit will also be provided, obtained from the model.

The primary null hypothesis of non-inferiority described above will be tested based on the FAS. If the lower bound of the 95% CI is greater than 0, then superiority for the primary endpoint is demonstrated and the 2-sided *P* value for superiority will be calculated.

Sensitivity analyses for handling missing data will be described in the SAP.

Supportive analyses and subgroup analyses (as appropriate) will also be described in the SAP.

### **12.3.3.2 Analysis of Secondary Endpoints**

#### **Analysis of Key Secondary Variables**

- Absolute change from baseline in SwCl through Week 24: The analysis of this variable will be based on an MMRM similar to the analysis of the primary endpoint above, with absolute change from baseline in SwCl at Day 15, Week 4, Week 16, and Week 24 as the dependent variable. The primary result obtained from the model will be the estimated treatment difference through Week 24. The LS mean estimate with a 2-sided 95% CI and a 2-sided *P* value will be provided. The estimated within group change from baseline and the treatment difference at each post-baseline visit, obtained from the model, will also be provided.
- Proportion of subjects with SwCl <60 mmol/L through Week 24 (pooled with data from Study VX20-121-103): The response corresponding to SwCl <60 mmol/L through Week 24 based on pooling data from FAS of this study and from Study VX20-121-103 (which has a similar study design and will evaluate CF subjects with other genotypes) will be analyzed. Details of this analysis will be described in the SAP.
- Proportion of subjects with SwCl <30 mmol/L through Week 24 (pooled with data from Study VX20-121-103): The response corresponding to SwCl <30 mmol/L through Week 24 based on data pooled from the FAS of this study and from Study VX20-121-103 will be analyzed. Details of this analysis will be specified in the SAP.

#### **Analysis of Other Secondary Variables**

The other secondary variables include: number of PEx through Week 52, absolute change from baseline in CFQ-R RD score through Week 24, absolute change from baseline in ppFEV<sub>1</sub>



through Week 52, absolute change from baseline in SwCl through Week 52, proportion of subjects with SwCl <60 mmol/L through Week 24, and proportion of subjects with SwCl <30 mmol/L through Week 24. The analysis details for these variables will be described in the SAP.

### **12.3.3.3 Multiplicity Adjustment**

A hierarchical testing procedure will be used to control the overall type I error at an alpha of 0.05. The key secondary endpoints will be formally tested at an alpha of 0.05 only if the primary analysis of absolute change from baseline in ppFEV<sub>1</sub> through Week 24 is statistically significant, i.e., null hypothesis of inferiority has been rejected. For a test at any step to be considered statistically significant within the testing hierarchy, it must be statistically significant, and all previous tests (if any) within the hierarchy must be statistically significant at the 0.05 level 2-sided (1-sided 0.025 level for the primary endpoint). Additional details will be provided in the SAP.

### **12.3.3.4 Analysis of Other Endpoints**

The analysis details of other endpoints will be described in the SAP.

## **12.3.4 Safety Analysis**

All safety analyses will be based on the data from the TE period for the Treatment Period for all subjects in the corresponding Safety Set for the Treatment Period, unless otherwise specified.

The overall safety profile of study drug will be assessed in terms of the following safety and tolerability assessments:

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (i.e., hematology, serum chemistry, coagulation, and urinalysis as applicable)
- Standard 12-lead ECGs
- Vital signs
- Pulse oximetry
- Ophthalmological examinations

Only descriptive analysis of safety will be performed and no statistical testing will be performed. The safety data during the Run-in Period will only be presented in listings, unless otherwise specified. Additional details will be provided in the SAP.

LFT elevations, creatine kinase elevations, rash, cataracts, hypoglycemia, and neuropsychiatric events will be designated as AEs of special interest.

## **12.4 Interim Analysis**

No interim analysis will be performed.

## **12.5 Data Monitoring Committee Analysis**

The DMC (Section 9.1.9) will conduct safety reviews of study data as outlined in the DMC Charter.

## **12.6 Clinical Pharmacology Analysis**

### **12.6.1 Pharmacokinetic Analysis**

The PK analysis of VX-121, TEZ, and D-IVA may be performed using nonlinear mixed-effects modeling and/or standard noncompartmental analysis, as data allow. Metabolites, including M1-TEZ, may be included in the analyses as supported by data. 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 clinical pharmacology analysis plan (CPAP).

### **12.6.2 Pharmacokinetic/Pharmacodynamic Analyses**

PD assessments to be included in PK/PD analyses may include SwCl, ppFEV<sub>1</sub>, as well as other endpoints such as CFQ-R RD score.

A sequential approach will be used to perform the population PK/PD analysis. The Bayesian estimates of individual PK parameters from the final population PK model will be used to simulate PK profiles for each subject. The simulated VX-121, TEZ, D-IVA, or metabolite plasma concentrations will be used in the potential pharmacological response models to describe changes in each endpoint from baseline. Fixed- and random-effect parameter estimates and the associated asymptotic SEs will be estimated.

## **13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS**

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

#### **13.1.1 Adverse Events**

##### **13.1.1.1 Definition of an Adverse Event**

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

An AE is considered serious if it meets the definition in Section [13.1.2.1](#).

##### **13.1.1.2 Clinically Significant Assessments**

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

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

- Concomitant signs or symptoms related to the abnormal study assessment

- Further diagnostic testing or medical/surgical intervention
- A change in the dose of study drug or discontinuation from the study

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

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

### 13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time the ICF is signed until the subject completes study participation, as defined in Section 9.1.7.

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

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

### 13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, Cancer Therapy Evaluation Program, [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm) (Accessed July 2021). When 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 in the CTCAE. The severity of an AE described by a term 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	Description
Grade 1 (Mild)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

**Table 13-1 Grading of AE Severity**

Classification	Description
<b>Grade 2 (Moderate)</b>	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL <sup>a</sup>
<b>Grade 3 (Severe)</b>	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL <sup>b</sup>
<b>Grade 4 (Life-threatening)</b>	Life-threatening consequences; urgent intervention indicated
<b>Grade 5 (Death)</b>	Death related to adverse event

Source: [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm) (Accessed July 2021)

ADL: activities of daily living; AE: adverse event

Note: A semi-colon indicates 'or' within the description of the grade.

<sup>a</sup> Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

<sup>b</sup> Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

### 13.1.1.5 Adverse Event Causality

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

**Table 13-2 Classifications for AE Causality**

Classification	Definition
<b>Related</b>	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.
<b>Possibly related</b>	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.
<b>Unlikely related</b>	The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.
<b>Not related</b>	The event is related to an etiology other than the investigational study drug (the alternative etiology will be documented in the subject's medical record).

AE: adverse event

### 13.1.1.6 Study Drug Action Taken

The investigator will classify the study drug action taken with regard to the AE. The action taken will be classified according to the categories in [Table 13-3](#).

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

Classification <sup>a</sup>	Definition
<b>Dose not changed</b>	Study drug dose not changed in response to an AE
<b>Dose reduced</b>	Study drug dose reduced in response to an AE
<b>Drug interrupted</b>	Study drug administration interrupted in response to an AE
<b>Drug withdrawn</b>	Study drug administration permanently discontinued in response to an AE

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

Classification <sup>a</sup>	Definition
<b>Not applicable</b>	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

<sup>a</sup> Refer to Sections 9.7 and 9.8 for directions regarding what drug actions are permitted per protocol.

### 13.1.1.7 Adverse Event Outcome

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

**Table 13-4 Classifications for Outcome of an AE**

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

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, surgery, or physical therapy. “No” indicates the absence of any kind of treatment for an AE.

## 13.1.2 Serious Adverse Events

### 13.1.2.1 Definition of a Serious Adverse Event

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

- Fatal (death, regardless of cause, that occurs during participation in the study or occurs after participation and is suspected of being a delayed toxicity due to administration of the study drug)
- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person’s ability to conduct normal life functions)

- Congenital anomaly or birth defect
- Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., an allergic bronchospasm requiring intensive treatment in an emergency room or at home)

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

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

#### **13.1.2.2 Reporting and Documentation of Serious Adverse Events**

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

For SAEs that occur after obtaining informed consent and assent (where applicable) through the completion of study participation, 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: [globalpatientsafety@vrtx.com](mailto:globalpatientsafety@vrtx.com) (preferred choice)

Fax: +1-617-341-6159

For technical issues related to submitting the form, contact telephone: +1-617-341-6677

SAEs that occur after the completion of study participation and are considered related to study drug(s) will be recorded on the Vertex Clinical Trial Safety Information Collection Form (hereafter referred to as the “SAE Form”) using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the investigator for relationship to the investigational study drug(s) and possible etiologies. On the SAE Form, relationship to study drug(s) will be assessed only as related (includes possibly related) or not related (includes unlikely related), and severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be

documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the event to resolution and report the outcome to Vertex using the SAE Form.

### **13.1.2.3 Expedited Reporting and Investigator Safety Letters**

Vertex, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities, IEC, and participating investigators in accordance with current ICH E2A Guidelines and/or local regulatory requirements, as applicable. In addition, Vertex, or authorized designee, will be responsible for the submission of safety letters to central IECs.

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

## **13.2 Administrative Requirements**

### **13.2.1 Product Complaints**

A product complaint is defined as any verbal or written communication addressed to Vertex, or designee, of inquiry or dissatisfaction with the identity, strength, quality, or purity of a released drug product, IMP, or medical device. In addition, suspected counterfeit/falsified product is considered a product complaint.

Product complaints are to be reported to Vertex.

### **13.2.2 Ethical Considerations**

The study will be conducted in accordance with the current ICH E6 GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and in accordance with local applicable laws and regulations. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, sample ICF, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or Vertex, as allowable by local applicable laws and regulations.

### **13.2.3 Subject Information and Informed Consent**

After the study has been fully explained, written informed consent will be obtained from the subject or legal representative or guardian (if applicable), and assent will be obtained from the subject (if applicable) before study participation. The method of obtaining and documenting the informed consent and assent (if applicable) and the contents of the consent will comply with current ICH E6 GCP Guidelines and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

### **13.2.4 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.

### **13.2.5 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.

### **13.2.6 Subject Privacy**

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

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

### **13.2.7 Record Retention**

The investigator will maintain all study records according to current ICH E6 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.

### **13.2.8 Study Termination**

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



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

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

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

### **13.2.9 End of Study**

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

### **13.3 Data Quality Assurance**

Vertex or its designated representative will conduct a study site visit to verify the qualifications of each investigator, inspect clinical study site facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct study documentation per current ICH E6 GCP Guidelines.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each subject. Data collected during the study, including results from screening, will be recorded in a data capture system for each enrolled subject. Each subject's set of captured data records, once complete, will be signed and dated by the investigator.

### **13.4 Monitoring**

The study will be monitored by Vertex or its designee in accordance with written procedures. Monitoring and auditing procedures developed or approved by Vertex for these activities comply with GCP regulatory requirements and guidelines.

The monitoring strategy may include onsite, remote, and central monitoring activities, in accordance with local regulations. The study site monitor will ensure that the study 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 electronic data capture (EDC) application sufficient to permit study site personnel to enter or correct information in the CRFs on the subjects for which they are responsible.

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

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

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

Vertex will retain the CRF data and corresponding audit trails. A copy of the final archival CRF will be placed in the investigator's study file.

### **13.6 Confidentiality and Disclosure**

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.

### **13.7 Publications and Clinical Study Report**

#### **13.7.1 Publication of Study Results**

Vertex is committed to reporting the design and results of all clinical studies in a complete, accurate, balanced, transparent, and timely manner, consistent with Good Publication Practices (GPP3).<sup>25</sup>

**Publication Planning:** Vertex staff along with the lead PIs, the steering committee, and/or the publication committee will work together to develop a publication plan.

**Authorship:** Authorship of publications will be determined based on the Recommendations for Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states that authorship should be based on the following 4 criteria<sup>26</sup>:

1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
2. Drafting of the article or revising it critically for important intellectual content;
3. Final approval of the version to be published; and
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet conditions 1, 2, 3, and 4. All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Contributions such as medical writing, enrollment of subjects, acquisition of funding, collection of data, or general supervision of the research group, alone, do not justify authorship.

**Contributors:** Contributors who meet fewer than all 4 of International Committee of Medical Journal Editors (ICMJE) criteria for authorship will not be listed as authors, but their contribution will be acknowledged and specified either as a group (e.g., “study investigators”) or individually (e.g., “served as scientific advisor”).

**Publication Review:** As required by a separate clinical study agreement, Vertex must have the opportunity to review all publications, including any manuscripts, abstracts, oral/slide presentations, and book chapters regarding this study before submission to congresses or journals for consideration.

### **13.7.2 Clinical Study Report**

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

## 14 REFERENCES

- 1 Cystic Fibrosis Foundation. 2019 Patient Registry Annual Data Report. Bethesda, MD: 2020.
- 2 European Cystic Fibrosis Society. 2018 ECFS Patient Registry Annual Data Report. Karup, Denmark: 2020.
- 3 Ruseckaite R, Ahern S, Ranger T, Dean J, Gardam M, Bell S, et al. The Australian Cystic Fibrosis Data Registry Annual Report, 2017. Monash University: Department of Epidemiology and Preventative Medicine; March 2019, Report #20.
- 4 Cystic Fibrosis Canada. The Canadian Cystic Fibrosis Registry 2019 Annual Data Report. Toronto, Ontario: Cystic Fibrosis Canada; 2020.
- 5 Rommens JM, Iannuzzi MC, Kerem B, Drumm ML, Melmer G, Dean M, et al. Identification of the cystic fibrosis gene: Chromosome walking and jumping. *Science*. 1989;245(4922):1059-65.
- 6 Kreindler JL. Cystic fibrosis: Exploiting its genetic basis in the hunt for new therapies. *Pharmacol Ther*. 2010;125(2):219-29.
- 7 Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *Lancet Respir Med*. 2017;5(2):107-18.
- 8 Sawicki GS, McKone E, Pasta DJ, Wagener J, Johnson C, Konstan MW. The effect of ivacaftor on the rate of lung function decline in CF patients with a G551D-CFTR mutation. *J Cyst Fibros*. 2014;13:S6.
- 9 Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324-43.
- 10 Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med*. 2019;200(8):e70-e88.
- 11 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130(6):461-70.
- 12 Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006;145(4):247-54.
- 13 Counahan R, Chantler C, Ghazali S, Kirkwood B, Rose F, Barratt TM. Estimation of glomerular filtration rate from plasma creatinine concentration in children. *Arch Dis Child*. 1976;51(11):875-78.
- 14 Regnault A, Balp M-M, Kulich K, Viala-Danten M. Validation of the Treatment Satisfaction Questionnaire for Medication in patients with cystic fibrosis. *J Cyst Fibros*. 2012;11(6):494-501.
- 15 Goss CH, Quittner AL. Patient-reported outcomes in cystic fibrosis. *Proc Am Thorac Soc*. 2007;4(4):378-86.

- 16 Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of the Cystic Fibrosis Questionnaire in the United States. *Chest*. 2005;128(4):2347-54.
- 17 Henry B, Aussage P, Grosskopf C, Goehrs JM. Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. *Qual Life Res*. 2003;12(1):63-76.
- 18 Wenninger K, Aussage P, Wahn U, Staab D, German Cystic Fibrosis Questionnaire study group. The revised German Cystic Fibrosis Questionnaire: validation of a disease-specific health-related quality of life instrument. *Qual Life Res*. 2003;12(1):77-85.
- 19 Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *N Engl J Med*. 1994;331(10):637-42.
- 20 Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med*. 2011;365(18):1663-72.
- 21 VanDevanter DR, Heltshe, S.L., Spahr, J., Beckett, V.V., Daines, C.L., Dasenbrook, E.C., Gibson, R.L., Jain, R., Sanders, D.B., Goss, C.H., Flume, P.A.,. Rationalizing endpoints for prospective studies of pulmonary exacerbation treatment response in cystic fibrosis. *J Cyst Fibros*. 2017;16(5):607-15.
- 22 Schumi J, Wittes, J.T. Through the looking glas: understanding non-inferiority. *Trials*. 2011;12(106):1-12.
- 23 Konstan MW, Flume PA, Kappler M, Chiron R, Higgins M, Brockhaus F, et al. Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial. *J Cyst Fibros*. 2011;10(1):54-61.
- 24 Mayer-Hamblett N, Nichols, D.P., Odem-Davis, K., Riekert, K.A., Sawicki, G.S., et al. Evaluating the impact of stopping chronic therapies after modulator drug therapy in cystic fibrosis: the SIMPLIFY clinical trial study design. *Ann Am Thorac Soc*. 2021;18(8):1397-405.
- 25 Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good publication practice for communicating company-sponsored medical research: GPP3. *Ann Intern Med*. 2015;163(6):461-4.
- 26 International Committee of Medical Journal Editors (ICMJE). December 2017. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. Available at: <http://www.icmje.org/recommendations/>. Accessed 18 August 2021.

## APPENDIX A: EXAMPLES OF ELIGIBLE MF MUTATIONS

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

- (1) biological plausibility of no translated protein (genetic sequence predicts the complete absence of CFTR protein), or
- (2) in vitro testing that supports lack of responsiveness to TEZ, IVA, or TEZ/IVA

### Inclusion of MF Mutations Based on In Vitro Testing

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

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

### Eligible MF Mutations

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

#### Examples of Eligible MF Mutations for VX20-121-102

MF Mutation Category	Mutation					
Nonsense mutations	Q2X	L218X	Q525X	R792X	E1104X	
	S4X	Q220X	G542X	E822X	W1145X	
	W19X	Y275X	G550X	W882X	R1158X	
	G27X	C276X	Q552X	W846X	R1162X	
	Q39X	Q290X	R553X	Y849X	S1196X	
	W57X	G330X	E585X	R851X	W1204X	
	E60X	W401X	G673X	Q890X	L1254X	
	R75X	Q414X	Q685X	S912X	S1255X	
	L88X	S434X	R709X	Y913X	W1282X	
	E92X	S466X	K710X	Q1042X	Q1313X	
	Q98X	S489X	Q715X	W1089X	Q1330X	
	Y122X	Q493X	L732X	Y1092X	E1371X	
	E193X	W496X	R764X	W1098X	Q1382X	
	W216X	C524X	R785X	R1102X	Q1411X	
	Canonical splice mutations	185+1G→T	711+5G→A	1717-8G→A	2622+1G→A	3121-1G→A
		296+1G→A	712-1G→T	1717-1G→A	2790-1G→C	3500-2A→G
296+1G→T		1248+1G→A	1811+1G→C	3040G→C	3600+2insT	
405+1G→A		1249-1G→A	1811+1.6kbA→G	(G970R)	3850-1G→A	
405+3A→C		1341+1G→A	1811+1643G→T	3120G→A	4005+1G→A	
406-1G→A		1525-2A→G	1812-1G→A	3120+1G→A	4374+1G→T	
621+1G→T		1525-1G→A	1898+1G→A	3121-2A→G		
711+1G→T			1898+1G→C			

### Examples of Eligible MF Mutations for VX20-121-102

MF Mutation Category	Mutation				
Small ( $\leq 3$ nucleotide) insertion/deletion (ins/del) frameshift mutations	182delT	1078delT	1677delTA	2711delT	3737delA
	306insA	1119delA	1782delA	2732insA	3791delC
	306delTAGA	1138insG	1824delA	2869insG	3821delT
	365-366insT	1154insTC	1833delT	2896insAG	3876delA
	394delTT	1161delC	2043delG	2942insT	3878delG
	442delA	1213delT	2143delT	2957delT	3905insT
	444delA	1259insA	2183AA→G <sup>a</sup>	3007delG	4016insT
	457TAT→G	1288insTA	2184delA	3028delA	4021dupT
	541delC	1343delG	2184insA	3171delC	4022insT
	574delA	1471delA	2307insA	3171insC	4040delA
	663delT	1497delGG	2347delG	3271delGG	4279insA
	849delG	1548delG	2585delT	3349insT	4326delTC
	935delA	1609del CA	2594delGT	3659delC	
	Non-small ( $> 3$ nucleotide) insertion/deletion (ins/del) frameshift mutations	CFTRdele1	CFTRdele16-17b		1461ins4
CFTRdele2		CFTRdele17a,17b		1924del7	
CFTRdele2,3		CFTRdele17a-18		2055del9→A	
CFTRdele2-4		CFTRdele19		2105-2117del13insAGAAA	
CFTRdele3-10,14b-16		CFTRdele19-21		2372del8	
CFTRdele4-7		CFTRdele21		2721del11	
CFTRdele4-11		CFTRdele22-24		2991del32	
CFTR50kdel		CFTRdele22,23		3121-977_3499+248del2515	
CFTRdup6b-10		124del23bp		3667ins4	
CFTRdele11		602del14		4010del4	
CFTRdele13,14a		852del22		4209TGTT→AA	
CFTRdele14b-17b	991del5				
Missense mutations that • Are non-responsive in vitro to TEZ, IVA, or TEZ/IVA	A46D	V520F	Y569D	N1303K	
	G85E	A559T	L1065P		
	R347P	R560T	R1066C		
	L467P	R560S	L1077P		
	I507del	A561E	M1101K		

IVA: ivacaftor; MF: minimal function; SwCl: sweat chloride; TEZ: tezacaftor

Source: CFTR2.org [Internet]. Baltimore (MD): Clinical and functional translation of CFTR. The Clinical and Functional Translation of CFTR (CFTR2), US Cystic Fibrosis Foundation, Johns Hopkins University, the Hospital for Sick Children. Available at: <http://www.cftr2.org/>. Accessed 15 February 2016.

<sup>a</sup> Also known as 2183delAA→G.

**15                    PROTOCOL SIGNATURE PAGES**

**15.1                  Sponsor Signature Page**

Protocol #:	VX20-121-102	Version #:	3.0	Version Date:	19 August 2021
Study Title: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-121 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for <i>F508del</i> and a Minimal Function Mutation (F/MF)					

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

Printed Name	Title
Signature	Date



**15.2 Investigator Signature Page**

Protocol #:	VX20-121-102	Version #:	3.0	Version Date:	19 August 2021
Study Title: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-121 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for <i>F508del</i> and a Minimal Function Mutation (F/MF)					

I have read Protocol VX20-121-102, Version 3.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-121, ELX, TEZ, D-IVA, IVA, and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

\_\_\_\_\_  
Printed Name

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date