1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 3, Open-label Study Evaluating the Pharmacokinetics, Safety, and Tolerability of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 12 to Less Than 24 Months of Age

Vertex Study Number: VX22-445-122

IND Number: 132547

EU CT Number: 2023-503230-49-00

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Summary of Changes to the Protocol

The previous version of this protocol (Version 3.0, 15 December 2023) was amended to create the current version (Version 4.0, 16 January 2024). The protocol history is below.

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.1, 10 January 2023	Original version
Version 2.0, 17 August 2023	In Parts A and B, widened the Screening Visit 1 window and allowed for Screening Visit 1 and Screening Visit 2 to be conducted as a concurrent visit between Day -9 and Day -5 for subjects who have a historical *CFTR* genotype report and do NOT require central genotyping to be performed at Screening Visit 1; Clarified the timing of the fecal sample collection in Part B; Clarified that for subjects who participate in the LCI Substudy, the MBW assessment performed at screening must be acceptable, as defined in the study manual, in order to not perform the MBW assessment at Day 1; Updated inclusion criterion #2 to include subjects 12 to <24 months of age on Day 1 (rather than on date of informed consent) to avoid the possibility of a subject being ≥24 months of age at the time of the first dose on Day 1; Removed restriction for a parent or legal guardian of a subject who withdraws from the study to not be able to request withdrawal of the subject's information from the study data; Added a list of eligible minimal function (MF) *CFTR* mutations to clarify which mutations will be targeted for enrollment in at least 15 subjects in Part B; Updated the Risk and Benefit Assessment based on the current status of the ELX/TEZ/IVA development program
Version 3.0, 15 December 2023	Clarified the degree of burden and risk threshold and strategies used to minimize it, given the pediatric study population; Removed the option for the use of remote measures in extenuating circumstances, given the resolution of the global pandemic; Clarified that a retinal examination via fundoscopy is to be performed as part of the ophthalmologic examination; Added a brief description of the handling of a data security breach.
Version 4.0, 16 January 2024	Current version

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

Change and Rationale	**Affected Sections**
Added an expanded description of measures that will be implemented in the event of a data security breach.	Section 13.2.6

2 PROTOCOL SYNOPSIS

Title A Phase 3, Open-label Study Evaluating the Pharmacokinetics, Safety, and Tolerability of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 12 to Less Than 24 Months of Age

Brief Title Evaluation of ELX/TEZ/IVA in Cystic Fibrosis Subjects 12 to Less Than 24 Months of Age

Clinical Phase and Clinical Study Type Phase 3, pharmacokinetics (PK), safety, tolerability

Objectives

Part A

Primary Objectives

- To evaluate the PK of elexacaftor (ELX), tezacaftor (TEZ), ivacaftor (IVA), and relevant metabolites
- To evaluate the safety and tolerability of ELX/TEZ/IVA

Part B

Primary Objective

To evaluate the safety and tolerability of ELX/TEZ/IVA

Secondary Objectives

- To evaluate the PK of ELX, TEZ, IVA, and relevant metabolites
- To evaluate the pharmacodynamics (PD) of ELX/TEZ/IVA
- To evaluate the efficacy of ELX/TEZ/IVA

Endpoints

Part A

Primary Endpoints

- PK parameters of ELX, TEZ, IVA, and relevant metabolites
- Safety and tolerability assessments as determined by adverse events (AEs), clinical laboratory values, standard 12-lead ECGs, vital signs, and pulse oximetry

Part B

Primary Endpoint

Safety and tolerability assessments as determined by AEs, clinical laboratory values, standard 12-lead ECGs, vital signs, and pulse oximetry

Secondary Endpoints

- PK parameters of ELX, TEZ, IVA, and relevant metabolites
- Absolute change in sweat chloride (SwCl) from baseline through Week 24

Other Endpoints

- Number of pulmonary exacerbations (PEx) and cystic fibrosis (CF)-related hospitalizations through Week 24
- Absolute change in weight and weight-for-age z-score from baseline at Week 24
- Absolute change in length and length-for-age z-score from baseline at Week 24
- Absolute change in body mass index (BMI) and BMI-for-age z-score from baseline at Week 24

- Absolute change in weight-for-length z-score from baseline at Week 24
- Absolute change in fecal elastase-1 (FE-1) levels from baseline at Week 24
- Absolute change in serum levels of immunoreactive trypsinogen (IRT) from baseline at Week 24
- Absolute change in fecal calprotectin levels from baseline at Week 24
- Absolute change in lung clearance index $(LCI)_{2.5}$ from baseline through Week 24
- Acceptability and palatability of ELX/TEZ/IVA granules at Day 1 and at Week 24

Number of Subjects

Part A

Approximately 14 subjects are planned for enrollment. Subjects who participate in Part A may enroll in Part B if they meet eligibility criteria.

Part B

Approximately 50 subjects are planned for enrollment. At least 15 subjects with F/MF genotypes and at least 15 subjects with the F/F genotype are targeted for enrollment.

Study Population

Male and female CF subjects 12 to <24 months of age with at least one *F508del* mutation in the *CFTR* gene or another ELX/TEZ/IVA-responsive *CFTR* mutation. Subjects in Part A must weigh ≥7 kg at Screening Visit 2 (or the concurrent Screening Visit 1 and 2, as applicable).

Investigational Drug

Active substance: ELX (VX-445)/TEZ (VX-661)/IVA (VX-770)

Activity: CFTR correctors (ELX and TEZ) and potentiator (IVA)

Strength and route of administration:

Parts A and B: 40 mg ELX/20 mg TEZ/30 mg IVA fixed-dose combination (FDC) granules and 25 mg IVA granules for oral administration

Part B Only: 80 mg ELX/40 mg TEZ/60 mg IVA FDC granules and 59.5 mg IVA granules for oral administration; 60 mg ELX/30 mg TEZ/45 mg IVA FDC granules and 50 mg IVA granules for oral administration

Study Duration

Part A

Excluding the Screening Period, subjects will participate for up to approximately 6 weeks, including a Treatment Period of 15 days and a 4-week Safety Follow-up Period

Part B

Excluding the Screening Period, subjects will participate for up to approximately 28 weeks, including a Treatment Period of 24 weeks and a 4-week Safety Follow-up Period

Study Design

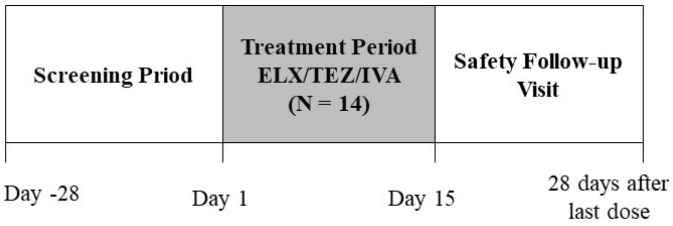
This is a Phase 3, open-label, 2-part (Parts A and B), multicenter study evaluating the PK, safety, tolerability, PD, and efficacy of ELX/TEZ/IVA in CF subjects 12 to <24 months of age.

Part A

Approximately 14 subjects will be enrolled in Part A (Figure 2-1). During the Treatment Period, subjects will be administered ELX/TEZ/IVA for approximately 15 days. Safety, tolerability, and available PK data will be reviewed by Vertex after Part A to confirm or revise the dosage levels chosen for Part B. Based on

emerging PK data, additional subjects may be enrolled as needed in Part A in order to provide sufficient information to confirm or revise the dosage levels for Part B.

Figure 2-1 VX22-445-122 Part A Study Design



ELX: elexacaftor; IVA: ivacaftor; N: total sample size; TEZ: tezacaftor
Note: ELX/TEZ/IVA will be administered from Day 1 through Day 15. The last dose of study drug will be the morning dose (ELX/TEZ/IVA) at the Day 15 Visit; the evening dose (IVA) will not be administered that day.

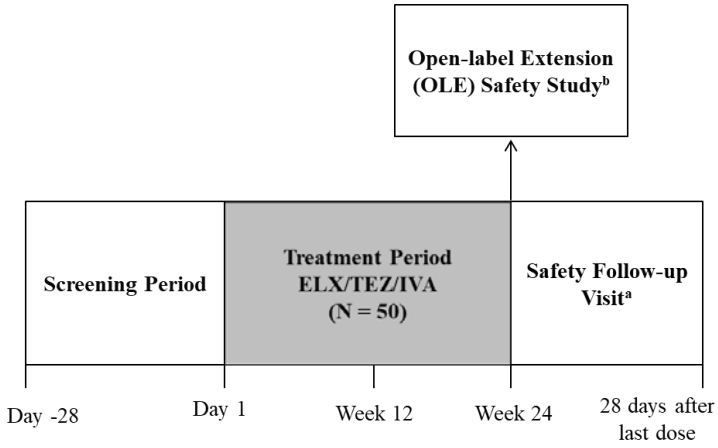
Part B

Part B will initiate after available data from Part A have been reviewed by Vertex and the Part B dosage levels have been confirmed or revised. Part B will enroll approximately 50 subjects, of whom at least 15 subjects will have F/MF genotypes and at least 15 subjects will have the F/F genotype (Figure 2-2). Subjects will be enrolled sequentially in Cohort B1 (18 to <24 months of age) followed by Cohort B2 (12 to <18 months of age). Initiation of Cohort B2 will be based on a review by Vertex of all Cohort B1 PK data through Week 4 and all safety data through Week 8. During the Treatment Period, subjects will be administered ELX/TEZ/IVA for approximately 24 weeks.

An optional LCI Substudy will be conducted.

Subjects from Cohorts B1 and B2 who are eligible will be offered the opportunity to enroll in an open-label extension (OLE) safety study.

Figure 2-2 VX22-445-122 Part B Study Design



ELX: elexacaftor; IVA: ivacaftor; N: total sample size; OLE: open-label extension; TEZ: tezacaftor
[a] The Safety Follow-up Visit is not required for subjects who enroll in an OLE safety study or continue on to a commercially available Vertex CFTR modulator within 28 days of the last dose of study drug. If a subject continues on to a commercially available Vertex CFTR modulator, the Early Termination of Treatment Visit will be completed before dosing with commercial drug begins.

[b] Subjects who are eligible will be offered the opportunity to enroll in an OLE safety study evaluating ELX/TEZ/IVA.

Planned doses for both study parts are summarized in Table 2-1. Doses are based on subject weight at Day 1. No dose adjustments will be made during the Part A Treatment Period. During the Part B Treatment Period, doses will be adjusted upward if the subject's weight is at or above the lower weight bound of the next higher dose at 2 consecutive in-clinic study visits. However, no dose adjustments will be made if a subject's weight decreases.

Table 2-1 VX22-445-122 Dose Regimens (Parts A and B)

Subject Weight at Day 1	ELX Dose	TEZ Dose	IVA Dose
Part A			
[redacted] kg only	40 mg qAM	20 mg qAM	30 mg qAM 25 mg qPM
Part B			
[redacted] kg	80 mg qAM	40 mg qAM	60 mg qAM 59.5 mg qPM
[redacted] kg	60 mg qAM	30 mg qAM	45 mg qAM 50 mg qPM
[redacted] kg	40 mg qAM	20 mg qAM	30 mg qAM 25 mg qPM

ELX: elexacaftor; IVA: ivacaftor; PK: pharmacokinetic; qAM: once every morning; qPM: once every evening; TEZ: tezacaftor

Assessments

PK Assessments (Parts A and B):

PK parameters of ELX, TEZ, IVA, and relevant metabolites

Safety Assessments (Parts A and B):

AEs, clinical laboratory assessments (serum chemistry, hematology, and coagulation), standard 12-lead ECGs, vital signs, pulse oximetry, ophthalmologic examinations, and physical examinations (PEs)

PD Assessment (Part B Only):

SwCl

Efficacy Assessments (Part B Only):

Weight, height, and other events related to outcome (e.g., PEx), multiple-breath washout (MBW; subjects in the optional LCI Substudy only)

Other Assessments (Part B Only):

Fecal samples; blood biomarker samples; and acceptability and palatability of ELX/TEZ/IVA granules

Statistical Analyses

Data from Parts A and B will be analyzed separately.

Part A

Approximately 14 subjects will be enrolled in Part A. Sample size calculations were determined based on ELX and M23-ELX estimates of clearance. Assuming that the variability in this age group is the same as the variability observed in adults, data from 14 subjects will allow at least 80% power to target a 95% CI within 60% and 140% of the geometric mean estimate of clearance for ELX and M23-ELX.

Part B

Approximately 50 subjects will be enrolled. With 40 subjects expected to complete Part B, there is a >95% chance of observing an AE in at least 1 subject if the true incidence rate is 10%.

For the primary endpoint, summary statistics will be provided for treatment-emergent AEs, clinical laboratory assessments, standard 12-lead ECGs, vital signs, and pulse oximetry.

IDMC Reviews An external independent data monitoring committee (IDMC) will conduct periodic safety review(s) of study data as outlined in the IDMC charter.

3 SCHEDULE OF ASSESSMENTS

Schedules of assessments are shown in Table 3-1 (Part A Screening Period), Table 3-2 (Part A Treatment Period and Safety Follow-up Visit), Table 3-3 (Part B Screening Period), and Table 3-4 (Part B Treatment Period and Safety Follow-up Visit).

Table 3-1 Study VX22-445-122: Part A Screening Period

Event/Assessment	Screening Visit 1 Day -28 to Day -5[a]	Screening Visit 2 Day -9 to Day -5[a]	Comments
Informed consent	X		
Demographics	X		Section 11.1
Medical history	X		Section 11.1
Ophthalmologic examination	X		Conducted by licensed practitioner qualified to perform all ophthalmologic examination procedures (Section 11.5.5). 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.
Full physical examination	X		Section 11.5.3
Weight and height (length)	X	X	Measured with the subject in a dry diaper or underclothes only (Section 11.5.3). If a child can stand unassisted and follow directions, stature should be measured as height; otherwise, stature will be measured as length. Only a single measurement of weight and height (length) is required if there is a concurrent Screening Visit 1 and 2.
Vital signs and pulse oximetry	X		Performed after the subject has been at rest for at least 5 minutes, if possible (Section 11.5.3).
Standard 12-lead ECG	X		Performed before any other procedures that may affect heart rate, such as blood draws, and in the supine position. If possible, performed after the subject has been at rest for at least 5 minutes (Section 11.5.4).
Serum chemistry		X	Screening hematology and chemistry results must be received and reviewed before the first dose of study drug is administered on Day 1 (Section 11.5.2).
Hematology		X	
Coagulation		X	Section 11.5.2
Medications review	X		Information regarding medications taken within 56 days before Screening Visit 1 (or the concurrent Screening Visit 1 and 2, as applicable) will be collected (Section 9.5).
Adverse events	**Continuous from signing of ICF through completion of study participation**		Section 13.1; completion of study participation is defined in Section 9.1.6.

CF: cystic fibrosis; ICF: informed consent form

[a] Screening Visit 1 and Screening Visit 2 may be conducted as a concurrent visit between Day -9 and Day -5 for subjects who have a historical *CFTR* genotype report and do NOT require central genotyping to be performed at Screening Visit 1. In the event that a concurrent screening visit is conducted, screening hematology and chemistry results must be received and reviewed before the first dose of study drug is administered on Day 1.

Table 3-2 Study VX22-445-122: Part A Treatment Period and Safety Follow-up Visit

Assessment[a]	Day 1	Day 2 and Day 4 (± 1 Day)	Day 8 (± 1 Day)	Day 15 (± 1 Day)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After Last Dose of Study Drug)	Comments
Clinic visit	X		X	X	X	X	
Telephone contact		X					Assess the subject's status, any AEs, concomitant medications, treatments, and procedures.
CF genotype (all subjects)	X						A previous *CFTR* genotype laboratory report may be used to establish eligibility, but the subject's genotype must be approved by the Vertex medical monitor (Section 8.1). Subjects who do not have a historical *CFTR* genotype report available will have genotyping performed at Screening Visit 1 instead of at Day 1, and the eligible *CFTR* mutation must be confirmed by central laboratory testing before the first dose of study drug. Refer to Appendix A for additional details.
Safety Assessments							
Full physical examination	X			X	X	X	Symptom-directed physical examinations will occur at any time during the study if deemed necessary by the investigator (Section 11.5.3).
Weight and height (length)	X			X	X	X	Measured with the subject in a dry diaper or underclothes only (Section 11.5.3). If a child can stand unassisted and follow directions, stature should be measured as height; otherwise, stature will be measured as length.
Vital signs and pulse oximetry	X		X	X	X	X	Performed after the subject has been at rest for at least 5 minutes, if possible (Section 11.5.3).
Standard 12-lead ECG	X		X	X	X	X	Performed before any other procedures that may affect heart rate, such as blood draws, and in the supine position. If possible, performed after the subject has been at rest for at least 5 minutes (Section 11.5.4).
Serum chemistry	X		X	X	X	X	Section 11.5.2
Hematology				X	X	X	Section 11.5.2
Observation 4 hours after the AM dose	X						Section 9.6.1
Medications review	**Continuous, from signing of ICF through completion of study participation**						Completion of study participation is defined in Section 9.1.6.
Non-pharmacological treatments and procedures review							
Adverse events	**Continuous, from signing of ICF through completion of study participation**						Section 13.1; completion of study participation is defined in Section 9.1.6.

[a] All assessments will be performed before study drug dosing unless noted otherwise.

Table 3-2 Study VX22-445-122: Part A Treatment Period and Safety Follow-up Visit

Assessment[a]	Day 1	Day 2 and Day 4 (± 1 Day)	Day 8 (± 1 Day)	Day 15 (± 1 Day)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After Last Dose of Study Drug)	Comments
PK Assessments							
PK sampling	X		X	X			**Day 1:** 2 hours (± 10 min) after the AM dose **Day 8**: before the AM dose (within 60 min), and at 1.5 hours (± 10 min) after the AM dose **Day 15:** before the AM dose (within 60 min), and at 3.5 and 6 hours (± 10 min) after the AM dose If study drug is not administered on the day of the visit (i.e., study drug interruption or permanent discontinuation of study drug), only 1 PK blood sample will be collected.
Study Drug Administration							
Study drug dosing	**ELX/TEZ/IVA (Day 1 through Day 15; AM dose only on Day 15)**						Administered within approximately 30 minutes of the start of a fat-containing meal or snack (e.g., standard "CF" meal or snack). On scheduled visits, the AM dose of study drug will be administered at the site after predose assessments have been completed (Section 9.6).
Study drug count			X	X	X		Section 10.4

AE: adverse event; CF: cystic fibrosis; ELX: elexacaftor; ETT: early termination of treatment; ICF: informed consent form; IVA: ivacaftor; PK: pharmacokinetic; TEZ: tezacaftor

Table 3-3 Study VX22-445-122: Part B Screening Period

Event/Assessment	Screening Visit 1 Day -28 to Day -5[a]	Screening Visit 2 Day -9 to Day -5[a]	Comments
Informed consent	X		
Demographics	X		Section 11.1
Medical history	X		Section 11.1
Ophthalmologic examination	X		Conducted by licensed practitioner qualified to perform all ophthalmologic examination procedures (Section 11.5.5). 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.
Full physical examination	X		Section 11.5.3
Weight and height (length)	X	X	Measured with the subject in a dry diaper or underclothes only (Section 11.5.3). If a child can stand unassisted and follow directions, stature should be measured as height; otherwise, stature will be measured as length. Only a single measurement of weight and height (length) is required if there is a concurrent Screening Visit 1 and 2.
Vital signs and pulse oximetry	X		Performed after the subject has been at rest for at least 5 minutes, if possible (Section 11.5.3).
Standard 12-lead ECG	X		Performed before any other procedures that may affect heart rate, such as blood draws, and in the supine position. If possible, performed after the subject has been at rest for at least 5 minutes (Section 11.5.4).
Multiple-breath washout	X		Performed (only for subjects with consent obtained for optional LCI Substudy) in multiple replicates pre-bronchodilator (Section 11.4.2).
Sweat chloride	X		Section 11.4.1
Fecal sample collection	X	X	Collected at the study site during the study visit; alternatively, for the Screening Visit 2 collection, samples may be collected at home by the subject's caregiver up to 24 hours before and brought to the study visit (Section 11.3.1). A sample does not need to be collected at Screening Visit 2 if it was collected at Screening Visit 1. Only a single fecal sample collection is required if there is a concurrent Screening Visit 1 and 2.
Blood biomarker sample (IRT)		X	Results not expected before the first dose; Section 11.3.1.
Serum chemistry		X	Screening hematology and chemistry results must be received and reviewed before the first dose of study drug is administered on Day 1 (Section 11.5.2).
Hematology		X	
Coagulation		X[b]	Section 11.5.2

[a] Screening Visit 1 and Screening Visit 2 may be conducted as a concurrent visit between Day -9 and Day -5 for subjects who have a historical *CFTR* genotype report and do NOT require central genotyping to be performed at Screening Visit 1. In the event that a concurrent screening visit is conducted, screening hematology and chemistry results must be received and reviewed before the first dose of study drug is administered on Day 1.

[b] If a subject weighs <6.8 kg at screening, the medical monitor should be contacted to discuss the timing of the coagulation assessment

Table 3-3 Study VX22-445-122: Part B Screening Period

Event/Assessment	Screening Visit 1 Day -28 to Day -5[a]	Screening Visit 2 Day -9 to Day -5[a]	Comments
Medications review	X		Information regarding medications taken within 56 days before Screening Visit 1 (or the concurrent Screening Visit 1 and 2, as applicable) will be collected (Section 9.5).
Adverse events	**Continuous, from signing of ICF through completion of study participation**		Section 13.1; completion of study participation is defined in Section 9.1.6.

CF: cystic fibrosis; ICF: informed consent form; IRT: immunoreactive trypsinogen; LCI: lung clearance index

Table 3-4 Study VX22-445-122: Part B Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug[b])	Comments
Clinic visit	X		X	X	X	X	X	X	X	X	X	
Telephone contact		X										Assess the subject's status, any AEs, concomitant medications, treatments, and procedures.
CF genotype (all subjects)	X[c]											A previous *CFTR* genotype laboratory report may be used to establish eligibility, but the subject's genotype must be approved by the Vertex medical monitor (Section 8.1). Subjects who do not have a historical *CFTR* genotype report available will have genotyping performed at Screening Visit 1 instead of at Day 1, and the eligible *CFTR* mutation must be confirmed by central laboratory testing

[a] All assessments will be performed before study drug dosing unless noted otherwise. For any assessments with multiple time points for an individual visit, only 1 set of assessments will be collected if study drug is not administered on the day of the visit (i.e., study drug interruption or permanent discontinuation of study drug).

[b] The Safety Follow-up Visit is not required for subjects who complete the Week 24 Visit and enroll in the OLE safety study or continue on to a commercially available Vertex CFTR modulator within 28 days after the last dose of study drug. If a subject continues on to a commercially available Vertex CFTR modulator, the ETT Visit (Section 9.1.4) will be completed before dosing with commercial drug begins.

[c] If a subject weighs <7.6 kg at Day 1, the medical monitor should be contacted to discuss the timing of the CF genotype assessment.

Table 3-4 Study VX22-445-122: Part B Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug[b])	Comments
												before the first dose of study drug. Refer to Appendix A for additional details.
Safety and Efficacy Assessments												
Ophthalmologic examination									X at or up to 4 weeks before	X		Section 11.5.5
Full physical examination	X					X			X	X		Symptom-directed physical examinations will occur at any time during the study if deemed necessary by the investigator (Section 11.5.3).
Weight and height (length)	X		X	X	X	X	X	X	X	X	X	Measured with the subject in a dry diaper or underclothes only (Section 11.5.3). If a child can stand unassisted and follow directions, stature should be measured as height; otherwise, stature will be measured as length.
Vital signs and pulse oximetry	X		X	X	X	X	X	X	X	X	X	Performed after the subject has been at rest for at least 5 minutes, if possible (Section 11.5.3).

Table 3-4 Study VX22-445-122: Part B Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug[b])	Comments
Standard 12-lead ECG	X		X			X			X	X	X	Performed before any other procedures that may affect heart rate, such as blood draws, and in the supine position. If possible, performed after the subject has been at rest for at least 5 minutes (Section 11.5.4).
Sweat chloride	X			X		X			X	X		Section 11.4.1
Multiple-breath washout	X[d]					X			X	X		Performed (only for subjects with consent obtained for optional LCI Substudy) in multiple replicates pre-bronchodilator (Section 11.4.2).
Serum chemistry	X		X	X	X	X	X	X	X	X	X	Section 11.5.2
Hematology			X	X[e]	X	X	X	X	X	X	X	
Coagulation								X				
Observation 4 hours after the AM dose	X											Section 9.6.1

[d] The Day 1 MBW assessment does not need to be performed if MBW was performed and acceptable, as defined in the study manual, at screening.

[e] If a subject weighs <6.7 kg at Week 4, the hematology assessment should be postponed to an unscheduled visit and the medical monitor should be contacted.

Table 3-4 Study VX22-445-122: Part B Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug[b])	Comments
Other events related to outcome	**Continuous, from signing of ICF through completion of study participation**											Includes PEx, administration of antibiotic therapy for sinopulmonary signs/symptoms, and hospitalizations for CF (Section 11.4.4). Completion of study participation is defined in Section 9.1.6.
Medications review	**Continuous, From Signing of ICF Through Completion of Study Participation**											Completion of study participation is defined in Section 9.1.6.
Non-pharmacological treatments and procedures review												
Adverse events	**Continuous, From Signing of ICF Through Completion of Study Participation**											Section 13.1; completion of study participation is defined in Section 9.1.6.

Table 3-4 Study VX22-445-122: Part B Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug[b])	Comments
Biomarker Assessments												
Fecal sample collection	X (predose)		X	X		X			X	X		Samples may be collected at home by the subject's caregiver up to 24 hours before the study visit and brought to the study visit (Section 11.3.1). Samples may be collected pre- or postdose (except for Day 1, which must be predose).
Blood biomarker sample (IRT)			X		X	X			X	X		Section 11.3.1
PK Assessments												
PK sampling			X	X		X	X			X		**Day 15:** before the AM dose (within 60 min) **Week 4**: before the AM dose (within 60 min), and at 2.5 and 5.5 hours (± 10 min) after the AM dose. **Weeks 12 and 16:** before the AM dose (within 60 min)

Table 3-4 Study VX22-445-122: Part B Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug[b])	Comments
Study Drug Administration												
Study drug dosing	**ELX/TEZ/IVA (Day 1 through evening before Week 24 Visit)**											Administered within approximately 30 minutes of the start of a fat-containing meal or snack (e.g., standard "CF" meal or snack). On scheduled visits, the AM dose of study drug will be administered at the site after predose assessments have been completed (Section 9.6).
Acceptability/ palatability assessment	X								X			For the Part B Week 24 visit, the relevant dose of study drug after which this assessment is to be completed is the first dose of study drug in the OLE study. If the subject does not enroll in the OLE, then the parent or legal guardian will answer only the retrospective questions of the facial hedonic scale questionnaire (Section 11.3.2).

Table 3-4 Study VX22-445-122: Part B Treatment Period and Safety Follow-up Visit

Event/ Assessment[a]	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug[b])	Comments
Study drug count			X	X	X	X	X	X	X	X		Section 10.4

AE: adverse event; CF: cystic fibrosis; ELX: elexacaftor; ETT: early termination of treatment; ICF: informed consent form; IRT: immunoreactive trypsinogen; IVA: ivacaftor; LCI: lung clearance index; MBW: multiple-breath washout; OLE: open-label extension; PEx: pulmonary exacerbation; PK: pharmacokinetic; TEZ: tezacaftor

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List of Abbreviations

Abbreviation	Definition
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
AM	morning
BMI	body mass index
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator gene
CFTR	cystic fibrosis transmembrane conductance regulator protein
CFR	Code of Federal Regulations
CI	confidence interval
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRO	contract research organization
CSIRT	Computer Security Incident Response Team
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTR	Clinical Trial Regulation
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
ELX	elexacaftor
ETT	Early Termination of Treatment
EU	European Union
F508del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FE-1	fecal elastase-1
FEV_1	forced expiratory volume in 1 second
F/F	homozygous for *F508del*
F/MF	heterozygous for *F508del* and a minimal function mutation
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GPS	Global Patient Safety
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors

Abbreviation	Definition
IDMC	independent data monitoring committee
IEC	independent ethics committee
IMP	investigational medicinal product
IND	Investigational New Drug (application) (US)
IRB	institutional review board
IRT	immunoreactive trypsinogen
IV	intravenous
IVA	ivacaftor
IWRS	interactive web response system
IXRS	interactive response system in which X represents voice or web, such as IWRS
LCI	lung clearance index
$LCI_{2.5}$	number of lung turnovers required to reduce the end tidal inert gas concentration to $1/40^{th}$ of its starting value
LFT	liver function test
LUM	lumacaftor
M23-ELX	M23 metabolite of elexacaftor
max	maximum value
MBW	multiple-breath washout
min	minimum value
MMRM	mixed-effects model for repeated measures
MSAP	modeling and simulation analysis plan
n	size of subsample
N	total sample size
OLE	open-label extension
PC	publication committee
PD	pharmacodynamic, pharmacodynamics
PE	physical examination
PEx	pulmonary exacerbation
P-gp	P-glycoprotein
PIP	pediatric investigation plan
PK	pharmacokinetic, pharmacokinetics
PR	PR interval, segment
q12h	every 12 hours
qAM	once every morning
qd	once daily
qPM	once every evening
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
RR	interval from the onset of 1 QRS complex to the next
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Definition
SD	standard deviation
SI	SI units (International System of Units)
SUSAR	suspected, unexpected, serious adverse reaction
SwCl	sweat chloride
TC	triple combination
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
ULN	upper limit of normal
US	United States

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[1] (approximately 32,000 in the US[2] and 52,000 in the EU[3]).

CF is caused by decreased quantity and/or function of the CFTR protein due to mutations in the *CFTR* gene.[4] 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.[5] 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.[6, 7] More effective treatments are needed for CF.

The most common disease-causing mutation is *F508del*: approximately 84.7% of people with CF in the US and 81.1% in Europe have at least one *F508del* allele.[6, 7]

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.[8, 9] The clinical testing and regulatory approval of CFTR modulators in certain countries for the treatment of people with CF caused by specific *CFTR* genotypes has 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.

The ELX/TEZ/IVA regimen is the first medicine to demonstrate clinical benefit in patients with a single *F508del* allele, regardless of the mutation of the second allele. A pivotal Phase 3 program in CF subjects 12 years of age or older demonstrated that ELX/TEZ/IVA provides substantial improvements in lung function, CFTR function, and nutritional status, and was generally safe and well tolerated with a low rate of treatment discontinuation.

5.2 Study Rationale

Given the progressive nature of CF, there is a strong rationale for preventing disease progression by treating patients earlier in life. Vertex evaluated ELX/TEZ/IVA TC therapy in Phase 3 studies in adult and pediatric (2 years of age and older) CF subjects with 1 or 2 copies of the *F508del* mutation, namely those with F/MF and F/F genotypes. Given the clinical benefit seen in a Phase 3 study of adults with CF with ELX/TEZ/IVA, the present study is designed to obtain pharmacokinetic (PK), safety, tolerability, pharmacodynamic (PD), and efficacy information to expand the evaluation of ELX/TEZ/IVA in the pediatric population 12 to <24 months of age who have at least one *F508del* mutation in the *CFTR* gene or another ELX/TEZ/IVA-responsive *CFTR* mutation. The study design for Parts A and B are in accordance with the approved pediatric investigation plan (PIP). In addition, all subjects who complete Part B and meet eligibility criteria will be offered enrollment into an open-label extension study to allow approximately 2 years of follow-up in accordance with the PIP.

6 STUDY OBJECTIVES

6.1 Primary Objectives

Part A

- To evaluate the PK of ELX, TEZ, IVA, and relevant metabolites
- To evaluate the safety and tolerability of ELX/TEZ/IVA

Part B

To evaluate the safety and tolerability of ELX/TEZ/IVA

6.2 Secondary Objectives

Part B

- To evaluate the PK of ELX, TEZ, IVA, and relevant metabolites
- To evaluate the pharmacodynamics (PD) of ELX/TEZ/IVA
- To evaluate the efficacy of ELX/TEZ/IVA

7 STUDY ENDPOINTS

7.1 Primary Endpoints

Part A

- PK parameters of ELX, TEZ, IVA, and relevant metabolites
- Safety and tolerability assessments as determined by adverse events (AEs), clinical laboratory values, standard 12-lead ECGs, vital signs, and pulse oximetry

Part B

Safety and tolerability assessments as determined by AEs, clinical laboratory values, standard 12-lead ECGs, vital signs, and pulse oximetry

7.2 Secondary Endpoints

Part B

- PK parameters of ELX, TEZ, IVA, and relevant metabolites
- Absolute change in sweat chloride (SwCl) from baseline through Week 24

7.3 Other Endpoints

Part B

- Number of pulmonary exacerbations (PEx) and CF-related hospitalizations through Week 24
- Absolute change in weight and weight-for-age z-score from baseline at Week 24
- Absolute change in length and length-for-age z-score from baseline at Week 24
- Absolute change in body mass index (BMI) and BMI-for-age z-score from baseline at Week 24

- Absolute change in weight-for-length z-score from baseline at Week 24
- Absolute change in fecal elastase-1 (FE-1) levels from baseline at Week 24
- Absolute change in serum levels of immunoreactive trypsinogen (IRT) from baseline at Week 24
- Absolute change in fecal calprotectin levels from baseline at Week 24
- Absolute change in lung clearance index $(LCI)_{2.5}$ from baseline through Week 24
- Acceptability and palatability of ELX/TEZ/IVA granules at Day 1 and at Week 24

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's legally appointed and authorized representative (e.g., parent or legal guardian) will sign and date an informed consent form (ICF).
2. Subjects (male and female) 12 to <24 months of age on Day 1.
3. In **Part A**, subjects must weigh ≥7 kg at Screening Visit 2 (or the concurrent Screening Visit 1 and 2, as applicable). There is no minimum weight in **Part B**.
4. Confirmed diagnosis of CF as determined by the investigator.
5. Subjects who have at least one *F508del* mutation in the *CFTR* gene or another ELX/TEZ/IVA-responsive *CFTR* mutation (Appendix A).
    - A previous *CFTR* genotype laboratory report may be used to establish eligibility, but the subject's genotype must be approved by the Vertex medical monitor.
    - All subjects will have a central laboratory genotype obtained on Day 1 (Parts A and B). Subjects with a historical *CFTR* genotype report may initiate study drug dosing before confirmation on central laboratory testing. Subjects who do not have a historical *CFTR* genotype report available will have genotyping performed at Screening Visit 1 instead of Day 1 in the respective Part, and the eligible *CFTR* mutation must be confirmed by central laboratory testing before the first dose of study drug. This assessment does not need to be repeated in the case of rescreening or for confirmed subjects in Part A who wish to screen for participation in Part B.
    - Subjects who have been enrolled based on a historical *CFTR* genotype laboratory report and whose central laboratory genotype does not confirm study eligibility must be discontinued from the study (Section 9.9).
6. Subjects with stable CF disease at the start of the Treatment Period as deemed by the investigator.

7. Subjects whose parent or legal guardian is willing to keep the subject on a stable CF medication regimen (other than *CFTR* modulators) through Day 15 (**Part A**), or through Week 24 (**Part B**) or, if applicable, through the Safety Follow-up Visit.

8. As judged by the investigator, the parent or legal guardian must be able to understand protocol requirements, restrictions, and instructions, and the parent or legal guardian should be able to ensure that the subject will comply with and is likely to complete the study as planned.

8.2 Exclusion Criteria

1. History of any illness or any clinical condition that, in the opinion of the investigator, might either 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:
    - Clinically significant cirrhosis with or without portal hypertension
    - Solid organ or hematological transplantation
    - Cancer
    - Any history of seizure
2. Any clinically significant laboratory abnormalities at the Screening Visits that would interfere with the study assessments or pose an undue risk for the subject (as deemed by the investigator).
3. Any of the following abnormal laboratory values at screening:
    - Hemoglobin <10 g/dL
    - Total bilirubin, aspartate transaminase (AST), or alanine transaminase (ALT) ≥2 × upper limit of normal (ULN)
    - Alkaline phosphatase (ALP) or gamma-glutamyl transferase (GGT) ≥3 × ULN
    - Abnormal renal function defined as glomerular filtration rate ≤45 mL/min/1.73 m^2 (calculated by the Bedside Schwartz equation)[10]
4. Any history of elevated serum ALT or AST ≥3 × ULN or total bilirubin ≥2 × ULN, unless occurring before 3 months of corrected gestational age and due to an identified proximate cause, such as reversible post-hepatic biliary obstruction, meconium ileus, infection, or neonatal hyperbilirubinemia, in the judgment of the investigator.
5. An acute upper or lower respiratory infection, PEx, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug).
6. Any history of respiratory tract culture positive for an organism associated with more rapid decline in pulmonary status (including, but not limited to, *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*).
7. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug (Day 1).

8. Ongoing or prior participation in an investigational drug study (including studies investigating ELX with or without coadministration with other study drugs) within 28 days of Screening Visit 1 (or the concurrent Screening Visit 1 and 2, as applicable).
    - o A washout period of 5 terminal half-lives of the previous investigational study drug, or **28** days, whichever is longer, must elapse before the Screening Visit.
    - o The duration of the elapsed time may be longer if required by local regulations.

      Note: Ongoing participation in a noninterventional study (including observational studies) is permitted.
9. Ongoing breastfeeding (or consumption of expressed breastmilk) by a subject whose mother is taking any CFTR modulator.
    - o If a mother chooses to stop their own CFTR modulator use, or to stop breastfeeding (and all other routes of feeding expressed breastmilk to the subject), so as to allow the subject to participate in this study, then a washout period of 28 days from last exposure must elapse before the Day 1 Visit.
10. Use of restricted medication within specified duration before the first dose of study drug as defined in Table 9-2.
11. 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.

9 STUDY IMPLEMENTATION

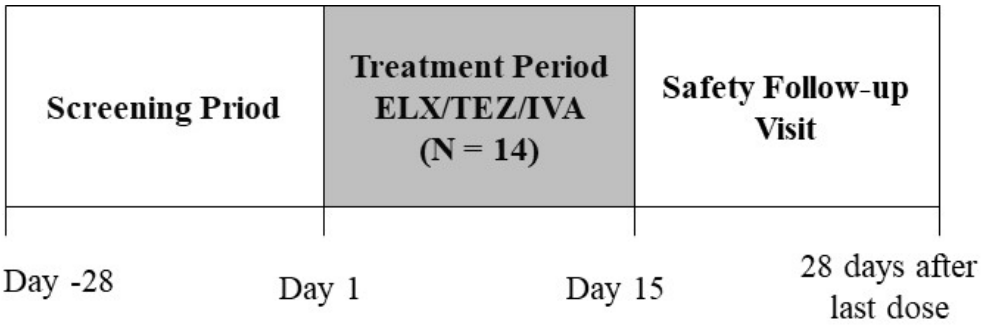
9.1 Study Design

This is a Phase 3, open-label, 2 part (Parts A and B), multicenter study evaluating the PK, safety, tolerability, PD, and efficacy of ELX/TEZ/IVA in CF subjects 12 to <24 months of age.

Part A

Approximately 14 subjects will be enrolled in Part A (Figure 9-1). During the Treatment Period, subjects will be administered ELX/TEZ/IVA for approximately 15 days. Safety, tolerability, and available PK data will be reviewed by Vertex after Part A to confirm or revise the dosage levels chosen for Part B. Based on emerging PK data, additional subjects may be enrolled as needed in Part A in order to provide sufficient information to select the dose(s) for Part B.

Figure 9-1 VX22-445-122 Part A Study Design



ELX: elexacaftor; IVA: ivacaftor; N: total sample size; TEZ: tezacaftor
Note: ELX/TEZ/IVA will be administered from Day 1 through Day 15. The last dose of study drug will be the morning dose (ELX/TEZ/IVA) at the Day 15 Visit; the evening dose (IVA) will not be administered that day.

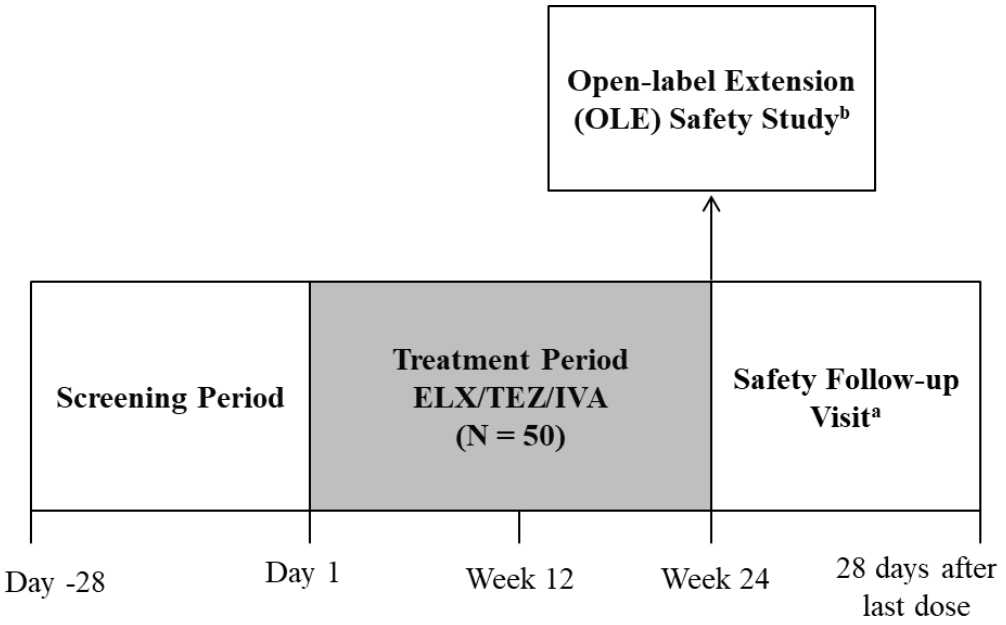
Part B

Part B will initiate after available data from Part A have been reviewed by Vertex and the Part B dose(s) has been confirmed or adjusted. Part B will enroll approximately 50 subjects, of whom at least 15 subjects will have F/MF genotypes (Appendix B) and at least 15 subjects will have the F/F genotype (Figure 9-2). Subjects will be enrolled sequentially in Cohort B1 (18 to <24 months of age) followed by Cohort B2 (12 to <18 months of age). Initiation of Cohort B2 will be based on a review by Vertex of all Cohort B1 PK data through Week 4 and all safety data through Week 8. During the Treatment Period, subjects will be administered ELX/TEZ/IVA for approximately 24 weeks.

An optional LCI Substudy will be conducted.

Subjects from Cohorts B1 and B2 who are eligible will be offered the opportunity to enroll in an open-label extension (OLE) safety study.

Figure 9-2 VX22-445-122 Part B Study Design



ELX: elexacaftor; IVA: ivacaftor; N: total sample size; OLE: open-label extension; TEZ: tezacaftor

[a] The Safety Follow-up Visit is not required for subjects who enroll in an OLE safety study within 28 days of the last scheduled visit in the Treatment Period.

[b] Subjects who are eligible will be offered the opportunity to enroll in an OLE safety study evaluating ELX/TEZ/IVA.

Planned doses for both study parts are summarized in Table 9-1. Doses are based on subject weight at Day 1. No dose adjustments will be made during the Part A Treatment Period. During the Part B Treatment Period, doses will be adjusted upward if the subject's weight is at or above the lower weight bound of the next higher dose at 2 consecutive in-clinic study visits. However, no dose adjustments will be made if a subject's weight decreases.

Table 9-1 VX22-445-122 Dose Regimens (Parts A and B)

Subject Weight at Day 1	ELX Dose	TEZ Dose	IVA Dose
Part A			
[redacted] kg only	40 mg qAM	20 mg qAM	30 mg qAM 25 mg qPM
Part B			
[redacted] kg	80 mg qAM	40 mg qAM	60 mg qAM 59.5 mg qPM
[redacted] kg to [redacted] kg	60 mg qAM	30 mg qAM	45 mg qAM 50 mg qPM

Table 9-1 VX22-445-122 Dose Regimens (Parts A and B)

Subject Weight at Day 1	ELX Dose	TEZ Dose	IVA Dose
[redacted] kg	40 mg qAM	20 mg qAM	30 mg qAM 25 mg qPM

ELX: elexacaftor; IVA: ivacaftor; PK: pharmacokinetic; qAM: once every morning; qPM: once every evening; TEZ: tezacaftor

9.1.1 Screening

Screening assessments are listed in Table 3-1 (Part A) and Table 3-3 (Part B).

Screening Visit 1 will occur at least 5 days and no more than 28 days before administration of study drug. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent from each subject's parent or legal guardian.

Screening Visit 2 will occur at least 5 days and no more than 9 days before administration of study drug. Screening hematology and chemistry results must be received and reviewed before the first dose of study drug is administered on Day 1.

Screening Visit 1 and Screening Visit 2 may be conducted as a concurrent visit between Day -9 and Day -5 for subjects who have a historical *CFTR* genotype report and do NOT require central genotyping to be performed at Screening Visit 1. In the event that a concurrent screening visit is conducted, screening hematology and chemistry results must be received and reviewed before the first dose of study drug is administered on Day 1.

To prepare for study participation, the subject's parent or legal guardian will be instructed on the study restrictions (Section 9.4).

Subjects who participate in Part A may enroll in Part B, provided they meet eligibility criteria.

9.1.1.1 Repetition of Screening Assessments

Parts A and B

Screening assessments may be repeated once to establish study eligibility, except for liver function test (LFT) assessment(s). If any LFT values at the initial Screening Visit 2 (or the concurrent Screening Visit 1 and 2, as applicable) are elevated (total bilirubin, AST, or ALT ≥2 × ULN; ALP or GGT ≥3 × ULN), then the LFT assessment(s) may not be repeated; however, if there is clear evidence of a laboratory error or equipment malfunction, then collection of a repeat sample for the appropriate laboratory test may be performed.

If the repeat values of the individual assessment(s) satisfy the eligibility criteria and have been completed within the screening window or extended screening window (Section 9.1.1.3), then the results can be considered qualifying for the study.

9.1.1.2 Rescreening

Subjects may be rescreened once. If a subject is rescreened, the subject's parent or legal guardian will provide informed consent, and all screening assessments will be repeated, except for:

- *CFTR* genotyping
- Ophthalmologic examination (if performed within 3 months before the date of informed consent)
- SwCl testing
- MBW (subjects in the optional LCI Substudy only)

If a subject is rescreened, a new (up to 28-day) screening window will begin when the first rescreening assessment has been initiated.

Rescreening is not allowed if the LFT values obtained at the original Screening Visit 2 (or the concurrent Screening Visit 1 and 2, as applicable) and retesting (if applicable) were exclusionary (i.e., total bilirubin, AST, or ALT ≥2 × ULN; or ALP or GGT ≥3 × ULN). However, if the subject is rescreening for a reason unrelated to LFT values, and any LFT values during rescreening are exclusionary and there is clear evidence of a laboratory error or equipment malfunction, then collection of a repeat sample may be performed as described in Section 9.1.1.1.

9.1.1.3 Extension of Screening Period Window

A subject may have the overall (up to 28-day) screening 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 (Section 11.5.5)

9.1.2 Treatment Period

Treatment Period assessments are listed in Table 3-2 (Part A) and Table 3-4 (Part B).

The Treatment Period will last approximately 15 days in Part A and 24 weeks in Part B. Study drug administration details are provided in Section 9.6.

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 and complete assessments for all study visits, as described in Section 9.1.4.

9.1.3 Follow-up

The Safety Follow-up Visit is scheduled to occur 28 (± 7) days after the last dose of study drug. The Safety Follow-up Visit is not required for Part B subjects who complete the Week 24 Visit and enroll in the open-label extension (OLE) safety study or continue on to a commercially available Vertex CFTR modulator within 28 days after the last dose of study drug. If a subject continues on to a commercially available Vertex CFTR modulator, the Early Termination of Treatment (ETT) Visit (Section 9.1.4) will be completed before dosing with commercial drug begins.

Safety Follow-up Visit assessments are listed in Table 3-2 (Part A) and Table 3-4 (Part B).

9.1.4 Early Termination of Treatment

If a subject prematurely discontinues study drug treatment, an 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 (Table 3-2 for Part A and Table 3-4 for Part B), if applicable (Section 9.1.3).

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.

Subjects who prematurely discontinue study drug treatment will continue to complete all scheduled study visits for assessments following completion of the ETT Visit, as detailed in Table 3-2 (Part A) and Table 3-4 (Part B).

If a subject withdraws from the study and the subject's parent or legal guardian also withdraws consent, no further assessments will be performed. Vertex may retain and continue to use any data and samples collected before such withdrawal of consent (Section 9.9).

9.1.5 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 the subject's parent or legal guardian is subsequently unable to be contacted by telephone (3 documented attempts by telephone within 2 weeks following the second missed visit)
- The subject's parent or legal guardian does not respond within 2 weeks to a registered letter sent after the 3 attempted telephone contacts.

9.1.6 Completion of Study Participation

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

Part A

- For subjects who complete the Treatment Period: the Safety Follow-up Visit
- For subjects who prematurely discontinue study drug treatment but whose parent or legal guardian does not withdraw consent: the latest of the Day 15 Visit, ETT Visit, or Safety Follow-up Visit
- For subjects whose parent or legal guardian withdraws consent: date of withdrawal of consent (Section 9.9)

Part B

- For subjects who complete the Treatment Period and enter an OLE safety study or continue on to a commercially available CFTR modulator within 28 days of the Week 24 Visit: the Week 24 Visit
- For subjects who complete the Treatment Period and do not enter an OLE safety study, and do not continue on to a commercially available CFTR modulator within 28 days of the Week 24 Visit: the Safety Follow-up Visit

- For subjects who prematurely discontinue study drug treatment but do not withdraw consent: the latest of the Week 24 Visit, ETT Visit, or Safety Follow-up Visit (if required)
- For subjects who withdraw consent: date of withdrawal of consent (Section 9.9)

If subjects are lost to follow-up (Section 9.1.5), 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 13.2.10.

9.1.7 Independent Data Monitoring Committee

Safety and tolerability data will be reviewed by an independent data monitoring committee (IDMC) to ensure the safety of the subjects (Section 12.5). Procedural details of the IDMC's structure and function, frequency of meetings, and data planned for review will be in the IDMC charter. The IDMC charter will be finalized before the first subject is screened.

9.2 Method of Assigning Subjects to Treatment Groups

This is an open-label study.

9.3 Rationale for Study Elements

9.3.1 Study Design

This open-label study is designed to evaluate the PK and safety of ELX/TEZ/IVA in this pediatric CF population and confirm the doses and appropriate weight cut-offs. The design is consistent with ICH guidelines for the study of human subjects, especially children, and balances safety concerns with potential benefits for the individual.

9.3.2 Study Population

This study will enroll CF subjects 12 to <24 months of age who have at least one *F508del* mutation in the *CFTR* gene or another ELX/TEZ/IVA-responsive *CFTR* mutation as listed in Appendix A. ELX/TEZ/IVA is expected to provide clinical benefit to these patients based on the results of Phase 3 studies (Studies VX17-445-102 and VX17-445-103), which demonstrated the efficacy and safety of ELX/TEZ/IVA in CF subjects ≥12 years of age who have F/F and F/MF genotypes. A pivotal study of ELX/TEZ/IVA in CF subjects 6 through 11 years of age (inclusive; VX18-445-106) demonstrated efficacy and safety similar to results seen in CF subjects ≥12 years of age. A pivotal study of ELX/TEZ/IVA in CF subjects 2 through 5 years of age (inclusive; VX20-445-111) demonstrated efficacy and safety similar to results seen in CF subjects ≥6 years of age.

Given the progressive nature of CF, there is a strong rationale for treating patients earlier in life. Experience with other CFTR modulators in pediatric subjects 12 to <24 months of age, including LUM/IVA and IVA, suggests that the safety profile of ELX/TEZ/IVA will be similar in children and adults, which supports evaluation of ELX/TEZ/IVA in pediatric subjects in the present study.

9.3.3 Study Drug Dose and Duration

An ELX dose of 200 mg once daily (qd) in TC with TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h) was evaluated in pivotal Phase 3 studies of adult and adolescent (≥12 years of age) CF subjects with F/F and F/MF genotypes. These studies demonstrated that treatment with this

ELX/TEZ/IVA regimen resulted in rapid, robust, clinically meaningful, and statistically significant improvements in all primary and key secondary efficacy and PD endpoints.

TC regimens of ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h and ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h were evaluated in a Phase 3 study of CF subjects 6 to <12 years of age with F/F and F/MF genotypes, and TC regimens of ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h and ELX 80 mg qd/TEZ 40 mg qd/IVA 60 mg once every morning (qAM) and 59.5 mg once every evening (qPM) were evaluated in a Phase 3 study of CF subjects 2 to <6 years of age, which enrolled subjects with F/F and F/MF genotypes, for which eligibility included subjects with at least one *F508del* mutation or another ELX/TEZ/IVA-responsive mutation. These studies demonstrated safety and efficacy similar to results seen in CF subjects ≥12 years of age.

Part A

The TC regimen of ELX 40 mg qAM/TEZ 20 mg qAM/IVA 30 mg qAM and 25 mg qPM selected for evaluation in Part A was based on population PK modeling. This modeling used TC data from CF subjects ≥2 years of age and simulated exposures for body weights typical of the 12- to <24-month-old population. The simulations indicated that the proposed dosing regimen for Part A is predicted to provide ELX, TEZ, and IVA exposures within the range of prior clinical experience.

Part B

For Part B, subjects will be administered either ELX 80 mg qAM/TEZ 40 mg qAM/IVA 60 mg qAM and 59.5 mg qPM, ELX 60 mg qAM/TEZ 30 mg qAM/IVA 45 mg qAM and 50 mg qPM, or ELX 40 mg qAM/TEZ 20 mg qAM/IVA 30 mg qAM and 25 mg qPM. The appropriate weight cutoffs for the switch between these regimens will be confirmed or adjusted based on population PK modeling updated to include PK data from Part A and additional PK data from TC studies conducted in CF subjects ≥2 years of age.

Duration of Dosing

The 15-day duration of dosing in Part A provides an adequate assessment PK, safety, and tolerability of ELX/TEZ/IVA before exposing subjects to a longer treatment duration of 24 weeks in Part B.

9.3.4 Rationale for Study Assessments

The PK, safety, efficacy, and PD assessments are standard parameters for clinical studies in drug development and are generally recognized as reliable, accurate, and relevant to the study of subjects with CF. A number of these assessments are part of routine clinical care for pediatric CF patients; however, they may be performed more frequently as part of this study than they would as routine care. Baseline and follow-up ophthalmologic examinations are recommended for monitoring of pediatric patients treated with IVA-containing drug regimens and have been added to the standard safety assessments as appropriate.

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 in Part B.

LCI is a measure of ventilation inhomogeneity assessed by multiple-breath washout (MBW) that is based on tidal breathing techniques that have been evaluated in patients as young as infants.[11,

[12] Studies have shown that LCI correlates with forced expiratory volume in 1 second (FEV_1) in its ability to measure airway disease and can detect lung disease at an earlier stage than spirometry.[13, 14] Furthermore, data from Study VX10-770-106 in CF patients with an FEV_1 >90% showed LCI to be a more sensitive outcome measure than FEV_1. This study will explore the value of LCI in the detection of early changes in lung function in infants with CF. Because performing MBW assessments in young children can be difficult[15], only subjects for whom consent was obtained for the optional LCI Substudy will undergo the MBW assessments.

To assess the acceptability/palatability of the formulation, all Part B subjects will have their acceptance of the dose administered recorded. The reaction of the subject will be assessed by the investigator or authorized designee as described in Section 11.3.2.

9.4 Study Restrictions

Table 9-2 summarizes 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

	Timing of Restriction		
Medication	**Start of Restriction**	**End of Restriction**	**Rationale**
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through completion of study participation	ELX, TEZ, and 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 ELX, TEZ, or IVA, are prohibited.
Moderate and strong CYP3A inhibitors (except ciprofloxacin)[a]	None allowed within 14 days before the first dose of the study drug on Day 1	None allowed through completion of study participation	
CFTR modulators (investigational or approved), except for study drugs[b]	None allowed within 28 days before the first dose of the study drug on Day 1	None allowed until after the last dose of study drug	These agents may confound the results of this study.

CYP: cytochrome P450; ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor

[a] Ciprofloxacin is not a moderate CYP3A inhibitor on the basis of results of a drug-drug interaction study conducted with IVA, a sensitive CYP3A substrate (Kalydeco [ivacaftor] US Package Insert).

[b] This prohibition also refers to ingestion via breastmilk (Section 8.2).

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 Screening Visit 1 (or the concurrent Screening Visit 1 and 2, as applicable) through completion of study participation, as defined in Section 9.1.6.

For subjects who are screened but are not subsequently enrolled, details of prior medication will be documented only in the subject's source documents.

- Subjects should remain on a stable treatment regimen for their CF from 28 days before the Day 1 Visit 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 Day 1 Visit. Subjects should not initiate long-term treatment with new medication from 28 days before the Day 1 Visit through completion of study participation. Guidelines for stable treatment regimens for CF are as follows:
    - Subjects who are treated chronically with inhaled tobramycin or other inhaled antibiotics should remain on that regimen throughout the study.
    - Subjects who cycle onto and off of an inhaled antibiotic should continue on their prior schedule. The timing of the first dose of study drug on the Day 1 Visit should be synchronized as closely as possible (e.g., not more than ± 3 days) to the first day in the cycle onto the inhaled antibiotic.
    - Subjects who alternate between 2 different inhaled antibiotics should remain on the same cycling schedule during the study. The timing of the first dose of study drug on the Day 1 Visit should be synchronized as closely as possible (e.g., not more than ± 3 days) to the first day in the cycle onto 1 of the inhaled antibiotics.
- Subjects may receive doses of prednisone or prednisolone of up to 2 mg/kg daily for up to 5 days.
- ELX may inhibit OATP1B1 and OATP1B3, which may increase the exposure of medicinal products that are substrates for these transporters. Substrates such as statins, glyburide, nateglinide, and repaglinide should be used with caution.
- IVA is a weak inhibitor of P-glycoprotein (P-gp). Administration of 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 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.
- Information about bronchodilator use during the study will be collected and documented. Subjects who are using a bronchodilator should have their MBW assessments (subjects in the optional LCI Substudy only) performed according to the guidelines provided in Section 11.4.2.

9.6 Administration

9.6.1 Dosing

Study drug will be orally administered with the approved foods and liquids listed in the Study Manual (e.g., apple sauce). The doses to be administered are shown in Table 9-1.

Study drug should be administered within approximately 30 minutes of the start of a fat-containing meal or snack, such as a standard "CF" meal or snack or a standard meal according to the following guidelines:

1. On days of scheduled visits (regardless of time of day), the morning study drug dose (ELX/TEZ/IVA) will be administered at the site after predose assessments have been completed. On days of scheduled visits that occur in the afternoon, more than 6 hours from the usually scheduled morning study drug dose (ELX/TEZ/IVA), the subject should not take the evening study drug dose (IVA), and the next scheduled morning study drug dose (ELX/TEZ/IVA) should be taken at the usual time.
2. All doses of study drug (morning and evening, as applicable) should be administered at approximately every 12 hours (± 1 hour for **Part A** and ± 2 hours for **Part B**) on each dosing occasion. For example, if the morning study drug dose (ELX/TEZ/IVA) is administered at 08:00 hour on Day 1, all subsequent morning doses should be administered between 07:00 hour and 09:00 hour for **Part A**, and between 06:00 hour and 10:00 hour for **Part B**.
3. At the Day 1 Visit, all subjects will be observed for 4 hours after the morning study drug dose (ELX/TEZ/IVA).
4. The date, amount taken, and time of study drug administration including whether food was taken with each dose, will be recorded in the source document for 2 days before PK sample collection and on the days of PK sample collection.
5. For visits after the Day 1 Visit, the subject's parent or legal guardian will be instructed to bring all used and unused study drug to the site; study drug will be dispensed at each visit, as appropriate.
6. **Part A:** The last dose of study drug will be the morning dose (ELX/TEZ/IVA) at the Day 15 Visit; the evening dose (IVA) will not be administered that day.

   Part B: At the Week 24 Visit, the morning study drug dose (ELX/TEZ/IVA) will NOT be administered. The last dose of study drug will be the evening dose (IVA) administered the day before the Week 24 Visit.

9.6.2 Missed Doses

If 6 hours or less have passed since the missed morning (ELX/TEZ/IVA) or evening (IVA) 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 study drug dose (ELX/TEZ/IVA) as soon as possible and should not take the evening study drug dose (IVA).

Evening dose: If more than 6 hours have passed since the missed **evening** dose, the subject should not take the missed study drug dose (IVA). The next scheduled morning study drug dose (ELX/TEZ/IVA) 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. If any unacceptable toxicity arises, individual subjects will discontinue dosing (Section 9.1.4).

9.8 Study Drug Interruption and Stopping Rules

In subjects who have interrupted study drug for >72 hours for any reason, the investigator should resume study drug only after a thorough investigation of the cause for interruption. The investigator will evaluate the subject's clinical stability and should consider resumption of study drug only after the subject is clinically stable and there is no comorbidity or condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject.

The medical monitor should be notified of an interruption of study drug that lasts >72 hours for any reason and of the resumption of study drug after such interruption. In subjects for whom study drug was previously interrupted, the medical monitor should be notified of any plan to discontinue study drug, before the discontinuation has occurred, if possible.

9.8.1 Liver Function Tests

The central laboratory will notify the medical monitor of ALT or AST >3 × ULN and total bilirubin >2 × ULN that are derived from centrally submitted samples.

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

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

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

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

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

Study drug administration **must be discontinued** if the following criteria are 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) 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 ≤2 × ULN, whichever is higher. Regardless of the duration of interruption, the medical monitor should be notified prior to resumption of study drug. Upon resumption of study drug, transaminases and bilirubin should be assessed weekly 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 (Section 13.1.1.4), 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 with differential, liver function tests), photographs of the rash, and dermatology consultation. The investigator may consider resumption of study drug if considered clinically appropriate.

9.9 Removal of Subjects

A subject's parent or legal guardian may withdraw the subject 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 (study drug dosing or study procedures), or administrative reasons. A subject who withdraws from study drug treatment will continue to be followed unless the subject withdraws consent.

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

- Has a *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).

Subjects who discontinue study treatment early should continue to return for study assessments, as noted in Section 9.1.4.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject's parent or legal guardian. 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's parent or legal guardian return all unused investigational product(s), request that the subject return for a Safety Follow-up Visit, if applicable (see Section 9.1.4), and follow up with the subject's parent or legal guardian regarding any unresolved adverse events (AEs).

If a subject withdraws consent for the study, no further assessments will be performed. Vertex may retain and continue using the study data and samples after the study ends and may use the samples and information in the development of the study compound, for other drugs and

diagnostics, in publications and presentations, and for education purposes. If a subject withdraws from the study, the study data and samples collected will remain part of the study. A subject's parent or legal guardian may request destruction of the samples collected from the subject during the study as long as those samples can be identified as the subject's samples.

9.10 Replacement of Subjects

Part A

Subjects who withdraw or are withdrawn for nonsafety reasons during the study drug Treatment Period may be replaced at Vertex's discretion as needed in Part A, based on emerging PK data, to confirm the dose(s) for Part B.

Part B

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

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. An interactive web response system (IWRS) will be used to dispense dosage based on subject weight.

10.2 Packaging and Labeling

Study drug granules will be supplied by Vertex. Study drug labeling will be in compliance with applicable local and national regulations. Additional details about packaging, labeling, and dispensing study drug will be in the Pharmacy Manual.

10.3 Study Drug Supply, Storage, and Handling

Table 10-1 provides the study drug information. 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 as described in Section 10.4 or via the drug accountability forms as instructed by Vertex.

Detailed instructions regarding the storage, handling, and dispensation of the study drug will be provided in the Pharmacy Manual.

Table 10-1 Study Drug

Drug Name	Formulation[a]/Route	Formulation Strength
ELX/TEZ/IVA	FDC Granules/Oral	40-mg ELX/20-mg TEZ/30-mg IVA
ELX/TEZ/IVA	FDC Granules/Oral	60-mg ELX/30-mg TEZ/45-mg IVA
ELX/TEZ/IVA	FDC Granules/Oral	80-mg ELX/40-mg TEZ/60-mg IVA
IVA	Granules/Oral	25-mg IVA
IVA	Granules/Oral	50-mg IVA
IVA	Granules/Oral	59.5-mg IVA

ELX: elexacaftor; FDC: fixed-dose combination; IVA: ivacaftor; qAM: once every morning; qPM: once every evening; TEZ: tezacaftor

[a] Granules will be supplied in individual sachets. For each dose level, 1 morning study drug dose (ELX/TEZ/IVA) will be contained per sachet, and 1 evening study drug dose (IVA) will be contained per a separate sachet; thus, dosage and how supplied are equivalent for each given dose.

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. The subject's parent or legal guardian 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. 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 and 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's parent or legal guardian of study drug dosing requirements. Compliance will also be assessed by ongoing study drug count.

If a subject's parent or legal guardian 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 an open-label study; however, subjects and their parent or legal guardian should not be informed of their study-related LCI, SwCl, FE-1, calprotectin, and IRT results during the Treatment Period (Part B only), regardless of whether the subject permanently discontinues treatment.

11 ASSESSMENTS

The schedule of assessments is shown in Table 3-1, Table 3-2, Table 3-3, and Table 3-4.

11.1 Subject and Disease Characteristics

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

Medical history will be elicited from each subject's parent or legal guardian 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.

11.2 Pharmacokinetics

11.2.1 Blood Sampling

Blood samples will be collected to determine plasma concentrations of ELX, TEZ, 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 or affected by any study drugs. To reduce subject burden and minimize discomfort of blood draws, local anesthetic may be used at the discretion of the investigator and the investigator may elect to enlist dedicated staff (e.g., a child life specialist) to support the subject during blood draws.

Actual sampling times may change upon agreement between the clinical pharmacologist and investigator, but the number of samples will remain the same. 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 (before morning dose [ELX/TEZ/IVA])	within 60 minutes before dosing
≥1.5 to ≤6 hours after morning dose (ELX/TEZ/IVA)	± 10 minutes

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 in the source document.

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 Laboratory Manual.

11.2.3 Bioanalysis

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

11.3 Other Assessments (Part B Only)

These data will be used for internal exploratory purposes and may or may not be included in the clinical study report (CSR). Detailed procedures for the collection of blood and fecal samples and additional procedures for processing and handling samples will be provided in a separate document. To reduce subject burden and minimize discomfort of blood draws, local anesthetic may be used at the discretion of the investigator and the investigator may elect to enlist dedicated staff (e.g., a child life specialist) to support the subject during blood draws.

11.3.1 FE-1, Calprotectin, and IRT

FE-1 and IRT will be measured to assess exocrine pancreatic function. Biomarkers including (but not limited to) calprotectin will be measured to assess gastrointestinal inflammation.

Fecal samples for assessment of FE-1 and calprotectin will be collected at the study site during the study visit; alternatively, samples may be collected at home by the subject's caregiver up to 24 hours before the study visit and brought to the study visit (except for Screening Visit 1, where a sample may not be collected prior to informed consent). The sample may be collected pre- or postdose (except for Day 1, which must be predose). Only a single fecal sample collection is required if there is a concurrent Screening Visit 1 and 2.

Instructions for the collection, processing, storage, and shipment of fecal samples (for FE-1 and calprotectin measurement) and blood samples for IRT measurement will be provided in a separate Laboratory Manual.

11.3.2 Acceptability/Palatability Assessment

The acceptability/palatability of study drug will be assessed by the investigator or authorized designee. All subjects will be observed for their facial expressions, and the reaction will be scored using a visual analog scale that incorporates a 5-point facial hedonic scale[16]; any spontaneous comments in regard to likes or dislikes will also be noted. Assessments will be done by the investigator or authorized designee in consultation with the parent/legal guardian. The parent/legal guardian will be familiarized with the visual analog scale using hypothetical situations before taste testing is conducted.

For the Part B Week 24 visit, the relevant dose of study drug after which the acceptability/ palatability assessment is to be completed is the first dose of study drug in the OLE study. If the subject does not enroll in the OLE, then the parent or legal guardian will answer only the retrospective questions of the modified facial hedonic scale questionnaire.

11.4 PD and Efficacy Assessments (Part B Only)

11.4.1 Sweat Chloride

The SwCl test is a standard diagnostic tool for CF, serving as a biomarker of CFTR activity. Sweat samples will be sent to a central laboratory for testing and interpretation of results. Individual SwCl test results will not be disclosed to the study sites. Specific instructions for collection, handling, processing, and shipping of SwCl samples to the central laboratory will be provided separately. The SwCl test must be conducted predose relative to the morning study drug dose (ELX/TEZ/IVA) during the Treatment Period. At each time point, 2 samples will be collected, 1 sample from each arm (left and right).

11.4.2 Multiple-breath Washout (Optional LCI Substudy Only)

MBW will be performed only for subjects whose parent or legal guardian has provided additional or separate informed consent for the procedure and only at sites that are adequately trained and qualified. To facilitate the regular, tidal breathing required for an acceptable MBW measurement, the investigator will provide mild sedation for the subject and the subject will be monitored during the assessment by continuous pulse oximetry.

For subjects participating in the optional LCI Substudy, the procedure will be performed in multiple replicates at screening (Table 3-3) and at additional time points as noted in Table 3-4; the final LCI value will be calculated from the technically acceptable washout replicates by a central reader. The final LCI value at each visit will be the value provided by the LCI vendor based on the replicates.

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

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

The MBW test should be performed pre-bronchodilator. During the Treatment Period, MBW testing 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), MBW testing should be performed according to the following:

- If a subject's screening or Day 1 MBW test is pre-bronchodilator, but, on a subsequent visit, the subject's parent/legal guardian forgets to withhold the subject's bronchodilator use, a post-bronchodilator MBW test will be obtained for that visit only, and the visit will not be rescheduled.
- If, during screening or on Day 1, the subject's parent/legal guardian forgets to withhold the subject's dose of bronchodilator, the MBW test should be performed post-bronchodilator, and all subsequent MBW tests (according to the schedule of assessments) should be performed post-bronchodilator.

Parents/legal guardians will not be informed of study-related LCI results.

Detailed MBW procedures will be supplied separately in a Study Manual.

11.4.3 Height (Length) and Weight

Refer to Section 11.5.3.

11.4.4 Other Events Related to Outcome

11.4.4.1 Pulmonary Exacerbations

Given the absence of a consensus definition for PEx in clinical trials in this population, the definition appearing below will be applied to the signs and symptoms shown below for the analysis of PEx.

Definition: New or changed treatment with oral, inhaled, or intravenous (IV) antibiotics **AND** fulfillment of 1 criterion from List A or 2 criteria from List B, within the period 3 days before antibiotic start date through antibiotic stop date.[17]

The occurrence of any new or changed antibiotic therapy (IV, inhaled, oral) and the presence of the following signs and symptoms will be recorded in the source documents:

List A:

- Oxygen saturation <90% on room air *or* ≥5% decrease from baseline
- New lobar infiltrate(s) or atelectasis on chest x-ray
- Hemoptysis (more than streaks on more than 1 occasion in past week)

List B:

- Increased work of breathing or respiratory rate (duration ≥3 days)
- New or increased adventitial sounds on lung examination (duration ≥3 days)
- Weight loss ≥5% decrease from highest value or decrease across 1 major percentile for age in past 6 months
- Increased cough (duration ≥3 days)
- Worked harder to breathe during physical activity (duration ≥3 days)
- Increased chest congestion or change in sputum (duration ≥3 days)

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

The following information will be determined for protocol-defined PEx:

- Number of PEx
- Number of days with PEx
- Time-to-first PEx
- Number of PEx requiring hospitalizations
- Number of days hospitalized for PEx
- Time-to-first hospitalization for PEx

- Number of PEx requiring IV antibiotic therapy
- Number of days on IV antibiotic therapy for PEx
- Time-to-first IV antibiotic therapy for PEx

11.4.4.2 Hospitalization for CF

Each subject's parent or legal guardian will be queried about planned and unplanned subject hospitalizations lasting ≥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 Safety

Safety evaluations will include AEs; clinical laboratory assessments; and clinical evaluation of vital signs, pulse oximetry, standard 12-lead ECGs, PEs, and ophthalmologic examinations. Safety will be monitored continuously from the signing of the ICF through completion of study participation (defined in Section 9.1.6) according to the schedule of assessments (Table 3-1 through Table 3-4).

Medical history and PE information will be collected during the course of the study and will be captured in the source documentation. PEs post-baseline will not be captured for inclusion into the study database. However, any untoward findings identified on PEs conducted after the administration of the first dose of study drug will be captured as an AE if those findings meet the definition of an AE. Demographic data collected at Screening Visit 1 (or the concurrent Screening Visit 1 and 2, as applicable) will be included in the study database.

11.5.1 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.

11.5.2 Clinical Laboratory Assessments

Blood samples will be analyzed at a central laboratory. Screening Visit 2 (or the concurrent Screening Visit 1 and 2, as applicable) hematology and chemistry results must be received and reviewed before the first dose of study drug is administered on Day 1. All blood samples will be collected while subjects are in a seated or supine position. To reduce subject burden and minimize discomfort of blood draws, local anesthetic may be used at the discretion of the investigator and the investigator may elect to enlist dedicated staff (e.g., a child life specialist) to support the subject during blood draws.

Specific instructions for the collection, processing, and shipment for centrally drawn 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
Glucose	Hemoglobin
Blood urea nitrogen[a]	Erythrocytes
Creatinine	Mean corpuscular volume
Sodium	Platelets
Potassium	Reticulocytes
Calcium	Leukocytes
Chloride	Differential (absolute and percent):
Magnesium	Eosinophils
Bicarbonate	Basophils
Phosphate	Neutrophils
Total bilirubin	Lymphocytes
Direct bilirubin	Monocytes
Indirect bilirubin (calculated)	**Coagulation**
Alkaline phosphatase	Activated partial thromboplastin time
Aspartate transaminase	Prothrombin time
Alanine transaminase	Prothrombin time International Normalized Ratio
Amylase	
Lipase	
Gamma-glutamyl transferase	
Protein	
Albumin	
Creatine kinase	
Cholesterol	

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

CF genotype: CF genotyping will be performed on all subjects. A previous *CFTR* genotype laboratory report may be used to establish eligibility, but the subject's genotype must be approved by the Vertex medical monitor (Section 8.1). Subjects who have been enrolled based on a historical *CFTR* genotype laboratory report and whose central laboratory genotype does not confirm study eligibility must be discontinued from the study (Section 9.9). This assessment does not need to be repeated in the case of rescreening or for confirmed subjects in Part A who wish to screen for participation in Part B.

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

For purposes of study conduct and unless noted otherwise, 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.

11.5.3 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 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. Any clinically significant abnormal findings in PEs will be reported as AEs, as applicable.

Height (or length, as appropriate) and weight will be measured with the subject in a dry diaper or underclothes only, as applicable. If a child can stand unassisted and follow directions, stature should be measured as height; otherwise, stature will be measured as length. Height should be measured with shoes off. Length should be measured while the subject is supine by measuring from the crown of the head to the bottom of the feet, with the hips and legs straightened. Only a single measurement of weight and height (length) is required if there is a concurrent Screening Visit 1 and 2.

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

Arterial oxygen saturation by pulse oximetry will be assessed following at least a 5-minute rest, if possible, and before study drug dosing.

11.5.4 Electrocardiograms

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

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

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

To ensure safety of the subjects, the investigator will make comparisons of the ECG findings to baseline measurements. Repeat ECGs will be performed as deemed appropriate. Subject eligibility to continue in the study will be evaluated.

11.5.5 Ophthalmologic Examination

All examinations will be conducted by a licensed practitioner qualified to perform all ophthalmologic examination procedures and will include a pharmacologically dilated examination of the lens with a slit lamp and a retinal examination via fundoscopy.

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.

Any clinically significant abnormal findings will be reported as AEs.

Part B Only

In addition to the screening ophthalmologic examination, all subjects who have completed at least 12 weeks of study drug treatment will have a single follow-up ophthalmologic examination. This examination should be completed at or up to 4 weeks before the Week 24 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 Table 3-4.

11.5.6 Contraception and Pregnancy

Not applicable.

12 STATISTICAL ANALYSIS

12.1 Sample Size and Power

Part A

Approximately 14 subjects will be enrolled in Part A. Sample size calculations were determined based on ELX and M23-ELX estimates of clearance. Assuming that the variability in this age group is the same as the variability observed in adults, data from 14 subjects will allow at least 80% power to target a 95% CI within 60% and 140% of the geometric mean estimate of clearance for ELX and M23-ELX.

Part B

No formal power calculation was performed. The number of subjects in Part B is deemed adequate to meet the primary safety objective. Approximately 50 subjects will be enrolled. The incidence of AEs is a safety endpoint. With 40 subjects expected to complete Part B, there is a >95% chance of observing an AE in at least 1 subject if the true incidence rate is 10%. Table 12-1 presents estimated probabilities for observing at least 1 subject with an AE for the given incidence rate (θ) and number of subjects completing Part B. The probabilities were calculated by assuming a binomial distribution for the number of AEs using SAS®.

Table 12-1 Probability of Observing At Least 1 Subject With an AE in the Study if the AE Incidence (θ) is 5% and 10%

Number of Subjects Completing Part B	θ = 5%	θ = 10%
40	87.1%	98.5%
45	90.1%	99.1%

θ: incidence; AE: adverse event

12.2 Analysis Sets

Assignment of subjects to analysis sets will be done before the clinical data lock for the study. The following analysis sets will be defined separately for Part A and Part B.

All Subjects Set

The All Subjects Set will include all subjects who are enrolled (defined as subjects having data in the clinical database) 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.

Full Analysis Set (FAS)

The FAS will include all subjects who are enrolled (defined as subjects having data in the clinical database) and carry the intended *CFTR* allele mutation and received at least 1 dose of study drug. The FAS will be used to summarize subject demographics and baseline characteristics, and for analyses of all efficacy and PD endpoints, unless otherwise specified.

Safety Set

The Safety Set will include all subjects who received at least 1 dose of study drug. The Safety Set will be used for all safety analyses, unless otherwise specified.

12.3 Statistical Analysis

Methodological and related details will be in the statistical analysis plan (SAP). Updates and/or modifications to the SAP will be summarized in the CSR.

12.3.1 General Considerations

Data from Part A and Part B will be analyzed separately. All individual subject data will be presented in individual subject data listings.

Continuous variables will be summarized using the following descriptive summary statistics: number of subjects (n), mean, standard deviation (SD), median, minimum value (min), and maximum value (max). The precision of the measurement for each continuous variable will be specified in the SAP.

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

Treatment-emergent (TE) Period for Parts A and B will include the time from the first dose of study drug in the respective Part to 28 days after the last dose of study drug, or to the completion of study participation date (as defined in Section 9.1.6), whichever occurs first.

Baseline value, unless specified otherwise, will be defined for Parts A and B as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the respective Part. Details will be provided in the SAP.

Change (absolute change) from baseline will be calculated as post-baseline value − baseline value.

12.3.2 Background Characteristics

Subject disposition, demographic and baseline characteristics, prior and concomitant medications, study drug exposure, compliance (Part B only), and other background characteristics will be summarized for Part A and Part B separately.

12.3.3 Pharmacodynamic and Efficacy Analysis (Part B only)

Two of the secondary objectives for Part B are to evaluate the PD and efficacy of ELX/TEZ/IVA. Principal features of the PD and efficacy analyses are presented in this section. Further details will be provided in the SAP.

12.3.3.1 Analysis of Primary PD and Efficacy Endpoints

Not applicable as PD/efficacy is not a primary endpoint.

12.3.3.2 Analysis of Secondary PD and Efficacy Endpoints

Absolute change in SwCl from baseline through Week 24 is a secondary endpoint and used to assess PD; observed values and change from baseline will be summarized based on the FAS in Part B. Absolute change from baseline in SwCl will be analyzed using a mixed-effects model for repeated measures (MMRM) approach. The model will include absolute change from baseline in SwCl as the dependent variable, with visit, baseline SwCl value, and genotype group as covariates. Data obtained from the Week 4, Week 12, and Week 24 visits will be included in the model. An unstructured covariance structure will be used to model the within-subject variations.

The primary result obtained from the model will be the average treatment effect through Week 24. The estimated mean change from baseline in SwCl through Week 24, along with the corresponding 95% CI and 2-sided *P* value will be provided. The treatment effect at each post-baseline visit, obtained from the model, will be provided as well.

Summary statistics for observed values and change from baseline in SwCl through Week 24 and at each visit will also be provided.

12.3.3.3 Multiplicity Adjustment

No multiplicity adjustment is planned.

12.3.3.4 Analysis of Other Efficacy Endpoints

Efficacy assessments, along with other assessments, are considered other endpoints in this study. Descriptive statistics will be provided based on the FAS in Part B. Additional analyses may be provided in the SAP.

- **Number of PEx and CF-related hospitalizations through Week 24** will be summarized.

For the following endpoints, observed values and absolute change from baseline at Week 24 will be summarized:

- **Weight and weight-for-age z-score**

- **Length and length-for-age z-score**
- **BMI and BMI-for-age z-score**
- **Weight-for-length z-score**
- **FE-1 levels**
- **Serum levels of IRT**
- **Fecal calprotectin levels**

For **acceptability and palatability of ELX/TEZ/IVA granules at Day 1 and at Week 24,** the 5-point modified facial hedonic scale for drug acceptability assessment will be summarized.

The **absolute change in $LCI_{2.5}$ from baseline through Week 24** will be summarized for the LCI Substudy only, when sufficient data are available.

12.3.4 Safety Analysis

Safety is a secondary objective of Part A and the primary objective of Part B. All safety analyses will be conducted for the Safety Set in Part A and Part B separately. The safety profile of study drug will be assessed based on the following safety and tolerability endpoints:

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

12.3.4.1 Adverse Events

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

- **Pretreatment AE:** any AE that occurred before the first dose of study drug in a study Part
- **TEAE:** any AE that worsened (either in severity or seriousness) or newly developed on or after the first dose of study drug through the end of the TE Period for each corresponding study Part
- **Post-treatment AE:** any AE that worsened (either in severity or seriousness) or newly developed after the TE Period for each corresponding study Part

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

AE summary tables will be presented for TEAEs only and will include the following:

- All TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity

- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- Serious TEAEs
- Serious TEAEs related to study drug
- TEAEs leading to death
- Grades 3, 4, and 5 TEAEs (Section 13.1.1.4)

Summaries will be presented using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will only be counted once. Only the maximum severity level will be presented in severity summaries and the strongest relationship level in the relationship summaries.

An AE overview table will be provided. In addition, a listing containing individual subject level AE data for all deaths and other serious and significant AEs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in an individual subject data listing.

12.3.4.2 Clinical Laboratory Assessments

For TE laboratory measurements, the observed values and change from baseline values of the continuous hematology and serum chemistry results will be summarized in SI units at each scheduled visit.

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

12.3.4.3 Electrocardiogram

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

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

12.3.4.4 Vital Signs

For treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized at each scheduled visit. The following vital signs parameters will be summarized: systolic and diastolic blood pressure (mm Hg), body temperature (ºC), pulse rate (heart rate, beats per minute), and respiration rate (breaths per minute).

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

12.3.4.5 Pulse Oximetry

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

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

12.3.4.6 Ophthalmologic Examinations

The ophthalmologic examination results will be presented in individual subject data listings.

12.4 Interim Analysis

Not applicable.

12.5 Independent Data Monitoring Committee Analysis

The IDMC (Section 9.1.7) will conduct periodic planned safety review(s) of study data. Details of the safety and efficacy review(s) will be described in the IDMC Charter.

12.6 Clinical Pharmacology Analysis

12.6.1 Pharmacokinetic Analysis

The PK analysis of ELX, TEZ, IVA, and relevant metabolites may be performed using nonlinear mixed effects modeling and/or standard noncompartmental analysis, as data allow. Metabolites may be included in the analyses as supported by data. Descriptive statistics will be used to summarize PK parameter values and observed trough concentrations 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

PK/PD analyses may be performed on selected PD assessments, which include SwCl and $LCI_{2.5}$, as well as other endpoints such as BMI or BMI z-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 ELX, TEZ, IVA, or metabolite plasma concentrations will be used in the potential pharmacological response models to describe changes in each endpoint. Fixed- and random-effect parameter estimates and their uncertainty 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 in source documents from the time the ICF is signed until the following times:

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

- For enrolled subjects who do not have a Safety Follow-up Visit, the earliest of
    - 28 days after the last dose of study drug, or
    - the ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (see Section 9.1.4)

All subjects' parents or legal guardians 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 source documents. 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 (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
Grade 2 (Moderate)	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4 (Life-threatening)	Life-threatening consequences; urgent intervention indicated

Table 13-1 Grading of AE Severity

Classification	Description
Grade 5 (Death)	Death related to adverse event

Source: 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.
[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] 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
Related	There is an association between the event and the administration of investigational study drug, a plausible mechanism for the event to be related to the investigational study drug and causes other than the investigational study drug have been ruled out, and/or the event reappeared on re-exposure to the investigational study drug.
Possibly related	There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
Unlikely related	The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.
Not related	The event is related to an etiology other than the investigational study drug (the alternative etiology will be documented in the subject's medical record).

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

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

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's parent or legal guardian signed the ICF, and the hospitalization or procedure was planned before ICF signing, the hospitalization or procedure will not be

considered to indicate an SAE, unless an AE caused the hospitalization or procedure to be rescheduled sooner or to be prolonged relative to what was planned. In addition, hospitalizations clearly not associated with an AE (e.g., social hospitalization for purposes of respite care) will not be considered to indicate an SAE.

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

13.1.2.2 Reporting and Documentation of Serious Adverse Events

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

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

Please send completed SAE Forms to Vertex GPS via:

Email: 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 Safety Follow-up Visit 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 (e.g., the Eudravigilance database, in accordance with the current EU

Clinical Trial Regulation [CTR]), 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. See the Pharmacy Manual for additional information.

13.2.2 Ethical Considerations

The study will be conducted in accordance with the protocol and the following:

- the current ICH E6 GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and
- local applicable laws and regulations (including the EU CTR [No 536/2014])

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' parents or legal guardians (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, informed consent will be obtained from the legal representative or guardian of the subject before study participation. The method of obtaining and documenting the informed consent 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 and Data Protection

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all data, 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 case report forms (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's parent or legal representative 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.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure, dissemination, or access.

Vertex shall handle data security breaches, including personal data breaches, in accordance with internal procedures and applicable laws and regulations. Vertex has an internal incident response plan that is executed by Vertex's Computer Security Incident Response Team (CSIRT). The CSIRT is led by Vertex's head of cyber-threat operations and the Chief Information Security Officer. Any data security breach that results in a personal data breach will also involve Vertex's Chief Privacy Officer.

Vertex is aligned with the National Institute of Standards and Technology's Cybersecurity Framework of identify, protect, detect, respond, and recover. Vertex also adheres to its Information Security Policy. The purpose of this policy is to identify the information security risks and establish the standards necessary to ensure the appropriate control and protection of Vertex's electronic information as it is stored, managed, transported, and handled as per applicable laws, regulations, and internal policies.

The CSIRT incident response plan is comprised of 6 phases:

1. Preparation – predefined playbook (scenarios), monitoring and alerting, roles and responsibilities, established retainers with specialized incident response vendors, and key stakeholders.
2. Detection, analysis, and escalation – responding to alerts/notifications of an event, analysis and triage, and escalation channels once a valid security incident is identified. The core team will use subject matter experts from other teams to assist, as needed.
3. Investigation and containment – identification of the scope/impact, creation of incident documentation, and the collection of evidence. The tasks in this phase continue for the remainder of the incident.
4. Eradication/mitigation – depending upon the type of incident, containment actions could happen very quickly. The extended team works to remove the threat and allow the restoration and recovery processes to begin.
5. Recovery – systems, data, and services are recovered to normal business operations.
6. Post-incident – incident report is produced detailing the nature, timeline, scope, and incident response activities. In addition, lessons learned are documented, which will feed into Vertex portfolio plans and strategic roadmaps to prevent the incident from happening again.

Continuous communication occurs with senior leaders, corporate communications, internal and external legal counsel, insurance, and, depending on the nature of the data security breach, other parties such as study sites and vendors. Vertex will adhere to the relevant legal and regulatory requirements for data security breach reporting.

The process defined above may be modified for compliance with applicable laws, regulations, and internal policies.

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 Start of Study

The start of study is defined as the date that the first study site is activated.

13.2.9 Study Termination

At any time, Vertex may terminate this study in its entirety, any study part, or 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.

13.2.10 End of Study

For the purpose of reporting summary results, the end of study is defined as the last scheduled visit (or scheduled contact) of the last subject (based on all sites globally, as applicable) to ensure that all data from the enrolled subject population are captured in the database and included in the final analyses (completion of study participation is defined in Section 9.1.6).

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. Study data for each enrolled subject will be entered into a CRF by study site personnel using a secure, validated, web-based electronic data capture (EDC) application. The investigator will affirm the completeness and accuracy of the data by signing each casebook before data lock. If applicable, periodic investigator signatures may also be required.

Instances of missing, discrepant, or uninterpretable data will be queried with the investigator for resolution.

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 Data Capture

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

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

the study and will document the dates and details of study procedures, AEs, other observations, and subject status.

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

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

Vertex will retain the CRF data and corresponding audit trails. A copy of the final archival CRF 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).[18]

Publication Planning: Vertex staff along with the lead principal investigators, 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:

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.

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APPENDIX A Eligible ELX/TEZ/IVA-Responsive CFTR Mutations

As described in Section 8.1, subjects with at least one *F508del* mutation in the *CFTR* gene, or with another mutation in the *CFTR* gene that is responsive to ELX/TEZ/IVA based on in vitro data, qualify to be screened for the study. The list of qualifying ELX/TEZ/IVA-responsive *CFTR* mutations is presented below.

CFTR Mutations Responsive to ELX/TEZ/IVA Based on In Vitro Data

3141del9[a]	G126D	R334L	S549R	H939R	W1098C
546insCTA	H139R	R334Q	G551D	S945L	F1099L
P5L	I148T	I336K	G551S	M952I	M1101K
S13F	M152V	T338I	R553Q	M952T	I1139V
L15P	Y161D	S341P	A554E	L967S	D1152H
G27R	Y161S	L346P	V562I	G970D	V1153E
R31L	L165S	R347H	Y563N	S977F	S1159F
A46D	R170H	R347L	P574H	D979V	S1159P
E56K	I175V	R347P	F575Y	I980K	R1162L
E60K	G178E	A349V	G576A	L997F	V1240G
P67L	G178R	R352Q	G576A;R668C[†]	A1006E	G1244E
R74Q	F191V	R352W	D579G	Y1014C	G1249R
R74W	D192G	Q359R	E588V	F1016S	S1251N
R74W;V201M[†]	E193K	W361R	S589N	I1027T	S1255P
R74W;V201M;D1270N[†]	G194R	S364P	I601F	Y1032C	I1269N
R74W;D1270N[†]	G194V	E403D	D614G	T1036N	D1270N
R75Q	H199Y	D443Y;G576A;R668C[†]	I618T	F1052V	W1282R
G85E	V201M	D443Y	G622D	T1053I	R1283M
E92K	P205S	L453S	G628R	H1054D	R1283S
Q98R	L206W	A455E	R668C	K1060T	Q1291R
Y109N	V232D	V456A	S737F	G1061R	V1293G
D110E	A234D	V456F	R751L	R1066H	L1324P
D110H	Q237E	G463V	V754M	A1067T	L1335P
E116K	Q237H	E474K	R792G	G1069R	G1349D
R117C	R258G	G480C	I807M	R1070Q	I1366N
R117G	M265R	S492F	E822K	R1070W	H1375P
R117H	F311del	I502T	D836Y	F1074L	L1480P
R117L	F311L	F508C	S912L	L1077P	
R117P	G314E	F508C;S1251N[†]	D924N	H1085P	
A120T	L320V	S549N	R933G	H1085R	

[a] If a subject has the *3141del9* genotype (per medical record), the investigator should contact Vertex as soon as possible to allow for timely confirmation of genotype by the central laboratory per specialized assays.

[†] Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

APPENDIX B Eligible MF *CFTR* Mutations

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

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

(2) in vitro testing that supports lack of responsiveness to IVA and 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 IVA and TEZ/IVA in the assay

Eligible MF Mutations

The mutations below are detectable by an FDA-cleared genotyping assay or other method (e.g., sequencing).

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.

Non-exhaustive List of Minimal Function *CFTR* Mutations Eligible for VX22-445-122

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

185+1G>T	711+5G>A	1717-8G>A	2622+1G>A	3121-1G>A
296+1G>A	712-1G>T	1717-1G>A	2790-1G>C	3500-2A>G
296+1G>T	1248+1G>A	1811+1G>C	3040G>C (G970R)	3600+2insT
405+1G>A	1249-1G>A	1811+1.6kbA>G		3850-1G>A
405+3A>C	1341+1G>A	1811+1643G>T	3120G>A	4005+1G>A
406-1G>A	1525-2A>G	1812-1G>A	3120+1G>A	4374+1G>T
621+1G>T	1525-1G>A	1898+1G>A	3121-2A>G	
711+1G>T		1898+1G>C		

182delT	1119delA	1782delA	2732insA	3791delC
306insA	1138insG	1824delA	2869insG	3821delT
365-366insT	1154insTC	1833delT	2896insAG	3876delA
394delTT	1161delC	2043delG	2942insT	3878delG
442delA	1213delT	2143delT	2957delT	3905insT
444delA	1259insA	2183AA>G [a]	3007delG	4016insT
457TAT>G	1288insTA	2184delA	3028delA	4021dupT
541delC	1343delG	2184insA	3171delC	4022insT
574delA	1471delA	2307insA	3171insC	4040delA
663delT	1497delGG	2347delG	3271delGG	4279insA
849delG	1548delG	2585delT	3349insT	4326delTC
935delA	1609del CA	2594delGT	3659delC	
1078delT	1677delTA	2711delT	3737delA	

Non-exhaustive List of Minimal Function *CFTR* Mutations Eligible for VX22-445-122

CFTRdele1	CFTRdele16-17b	991del5
CFTRdele2	CFTRdele17a,17b	1461ins4
CFTRdele2,3	CFTRdele17a-18	1924del7
CFTRdele2-4	CFTRdele19	2055del9>A
CFTRdele3-10,14b-16	CFTRdele19-21	2105-2117del13insAGAAA
CFTRdele4-7	CFTRdele21	2372del8
CFTRdele4-11	CFTRdele22-24	2721del11
CFTR50kbdel	CFTRdele22,23	2991del32
CFTRdup6b-10	124del23bp	3121-977_3499+248del2515
CFTRdele11	306delTAGA	3667ins4
CFTRdele13,14a	602del14	4010del4
CFTRdele14b-17b	852del22	4209TGTT>AA

A46D	V520F	Y569D	N1303K
G85E	A559T	L1065P	
R347P	R560T	R1066C	
L467P	R560S	L1077P	
I507del	A561E	M1101K	

CFTR: cystic fibrosis transmembrane conductance regulator gene

Source: CFTR2.org. 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.

[a] Also known as 2183delAA>G.

APPENDIX C Risk and Benefit Assessment

Cystic fibrosis (CF) is an autosomal recessive disease caused by decreased quantity and/or function of the CFTR protein due to mutations in the *CFTR* gene.[4] CFTR is an ion channel that regulates the flow of chloride and other ions across epithelia in various tissues, including the lungs, pancreas and other gastrointestinal organs, and sweat glands.[5] Decreased CFTR quantity or function results in the failure to regulate chloride transport in these tissues leading to the multisystem pathology associated with CF.[19] Progressive loss of lung function is the leading cause of mortality.[20] The clinical manifestations are those of progressive airway obstruction and bronchiectasis, with periods of worsening pulmonary symptoms associated with a decline in pulmonary function and increased bacterial density in airway secretions (pulmonary exacerbations [PEx]). Obstruction of airways with thick mucus, establishment of chronic bacterial infection in the airways, and damaging inflammatory responses are all thought to play a role in causing irreversible structural changes in the lungs, leading to respiratory failure. In addition, poor growth and nutritional status have historically been common in patients with CF owing to a number of factors, including pancreatic insufficiency-related fat malabsorption, increased energy expenditure attributable to progressive lung disease, appetite suppression attributable to chronic infection, and CF-related diabetes.[21]

Severity of CF is determined by the extent of the loss of CFTR-mediated chloride transport caused by the 2 *CFTR* mutant alleles. The most common disease-causing mutation is *F508del*: approximately 85.5% of individuals in the US and 80.3% of individuals in Europe have at least one *F508del* allele.[2, 22] The *F508del* mutation causes severe defects in processing and trafficking that result in little-to-no F508del-CFTR protein at the epithelial cell surface. The small amount of F508del-CFTR protein that does reach the cell surface has defective channel gating activity. These decreases in both the quantity and function of the F508del-CFTR protein at the cell surface result in the complete or near complete loss of CFTR-mediated chloride transport.

There is currently no cure for CF. The majority of CF therapies currently available, including nutritional supplements, antibiotics, and mucolytics, target the downstream consequences and symptoms of the disease. CFTR modulators (i.e., correctors and potentiators) represent a major advance in the treatment of CF because they are systemic therapies that target the underlying cause of the disease and have been shown to modify the course of CF disease by improving survival. CFTR modulators have also been shown to reduce the rate of decline in lung function, although the decline is not halted with currently available modulators.[8, 9] The therapeutic activity of CFTR modulators has been established with products developed by Vertex and approved for the treatment of CF in patients with specific *CFTR* genotypes. These treatments include ivacaftor (IVA) monotherapy (Kalydeco™), lumacaftor (LUM)/IVA (Orkambi™), tezacaftor (TEZ)/IVA (Symdeko™, Symkevi™), and more recently, the triple combination (TC) of elexacaftor (ELX)/TEZ/IVA (Trikafta™, Kaftrio™).

ELX/TEZ/IVA is the only CFTR modulator therapy to demonstrate substantial clinical benefit derived from a single *F508del* allele, and thus can provide benefit to all CF patients who have at least one *F508del* mutation, or another responsive mutation, regardless of the mutation on the second allele.

Development of the ELX/TEZ/IVA Triple Combination Regimen

ELX is a next-generation CFTR corrector that has both a different chemical structure and a different mechanism of action from first-generation CFTR correctors (e.g., TEZ) and CFTR potentiators (e.g., IVA). ELX and TEZ bind directly to CFTR at different sites to facilitate, in an additive fashion, the processing and trafficking of F508del-CFTR. The F508del-CFTR delivered to the cell surface by ELX and TEZ has defective channel gating activity that can be potentiated by IVA. In vitro, the TC of ELX/TEZ/IVA provides the greatest increase in the amount and function of CFTR compared to the individual CFTR modulators alone (ELX, TEZ, or IVA) or the dual combinations thereof (ELX/IVA, ELX/TEZ, or TEZ/IVA).

The pivotal program consisted of 2 Phase 3 studies: Study 102 (in CF patients heterozygous for *F508del* and a minimal function mutation [F/MF genotypes]) and Study 103 (in CF patients homozygous for *F508del* [F/F genotype]). These studies were conducted to demonstrate that ELX/TEZ/IVA can provide clinical benefit in CF subjects with at least one *F508del* allele (Study 102) and demonstrate added benefit of ELX/TEZ/IVA in comparison to TEZ/IVA alone in F/F subjects (Study 103). Specifically,

- Study 102 was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study in F/MF subjects 12 years of age and older that evaluated the efficacy and safety of ELX/TEZ/IVA compared to placebo for up to 24 weeks.
- Study 103 was a randomized, double-blind, active-controlled, parallel-group, multicenter study in F/F subjects 12 years of age and older that evaluated the efficacy and safety of ELX/TEZ/IVA compared to TEZ/IVA for 4 weeks; a 4-week TEZ/IVA Run-in Period was included to establish an on-treatment (TEZ/IVA) baseline.

Subjects who completed either Studies 102 or 103 had the opportunity to enroll in Study 105, a Phase 3, open-label, multicenter study that evaluated the long-term safety and efficacy of ELX/TEZ/IVA treatment.

After completion of Studies 102 and 103, an additional study (Study 104) designed to assess the efficacy of ELX/TEZ/IVA in CF subjects ≥12 years of age heterozygous for *F508del* and a gating (G) or residual function (RF) mutation (F/G and F/RF genotypes) was completed. Study 104 demonstrated superiority of ELX/TEZ/IVA compared to approved therapies for subjects with F/G and F/RF genotypes. Study 110 was an open-label, rollover study that enrolled subjects from Study 104.

Study 106 assessed the safety and efficacy of ELX/TEZ/IVA in CF subjects 6 through 11 years of age (inclusive) with F/F or F/MF genotypes. Study 107 is an ongoing, open-label, rollover study that enrolled subjects from Study 106.

Study 111 assessed the safety and efficacy of ELX/TEZ/IVA in CF subjects 2 through 5 years of age (inclusive). Regulatory applications to extend the existing approved indications for ELX/TEZ/IVA are ongoing or planned in most regions. Study 112 is an ongoing, open-label, rollover study that enrolled subjects from Study 111.

In the development program (as of the data lock point [DLP] of 10 January 2023), a total of 3,295 subjects have been exposed to ELX, either as monotherapy or combination therapy in clinical studies, representing a total exposure of approximately 4,706.78 patient-years. Across

the Phase 3 program in subjects 2 years of age and older (Studies 102, 103, 104, 105, 106, 110 , and 111), 904 subjects received at least 1 dose of ELX/TEZ/IVA.

ELX/TEZ/IVA is approved in the US, European Economic Area, Great Britain, Switzerland, Australia, Canada, New Zealand, Brazil, Israel, Uruguay, and Russia for the treatment of CF (approved ages and genotypes vary by region – see local label).

Benefits

Substantial and unprecedented clinical benefit was demonstrated with ELX/TEZ/IVA in the pivotal Phase 3 program that enrolled CF subjects ≥12 years of age with at least one *F508del* mutation. Study 102 evaluated ELX/TEZ/IVA compared with placebo in F/MF subjects during a 24-week Treatment Period. Study 103 evaluated ELX/TEZ/IVA compared with TEZ/IVA in F/F subjects during a 4-week Treatment Period (after a 4-week TEZ/IVA Run-in Period to establish an on-treatment [TEZ/IVA] baseline).

Rapid, robust, clinically meaningful, and statistically significant improvements were observed for all primary and key secondary endpoints. The therapeutic effects of ELX/TEZ/IVA in F/MF subjects, including those who have an MF mutation that produces no protein, indicates that a single *F508del* is sufficient to derive clinical benefit and that all patients with at least one *F508del* mutation can benefit from ELX/TEZ/IVA regardless of the mutation on the second allele. TEZ/IVA is a standard-of-care treatment that provides clinically meaningful benefit for CF patients with specific genotypes, and the Phase 3 results in F/F subjects demonstrate the substantial benefit and superiority of ELX/TEZ/IVA compared to TEZ/IVA.

- As a clinically accepted measure of disease progression in CF, lung function (as measured by forced expiratory volume in 1 second [FEV_1]) declines with age and is a significant predictor of mortality.[23] In Study 102, ELX/TEZ/IVA resulted in a percent predicted FEV_1 (**$ppFEV_1$**) improvement of 13.8 percentage points compared to placebo at Week 4; this improvement was sustained through Week 24 (14.3 percentage points). In Study 103, ELX/TEZ/IVA resulted in a $ppFEV_1$ improvement of 10.0 percentage points compared to TEZ/IVA at Week 4. Consistent treatment effects were observed across all subgroups analyzed (e.g., age, gender, region, and baseline $ppFEV_1$).
- PEx is a clinical event that recurs throughout the life of a CF patient; frequent recurrence of PEx is associated with a more rapid rate of decline in lung function.[24, 25] ELX/TEZ/IVA resulted in a 63% reduction in the annualized **PEx** rate compared to placebo in Study 102. Robust reductions in the rate of PEx requiring hospitalization or use of intravenous antibiotics were also observed.
- Sweat chloride (SwCl) is a sensitive pharmacodynamic measure of CFTR function. Substantial improvements in CFTR function as measured by **SwCl** were demonstrated in both studies, with treatment differences of -41.8 mmol/L over placebo in Study 102 and -45.1 mmol/L over TEZ/IVA in Study 103.
- Cystic Fibrosis Questionnaire- Revised (CFQ-R) is an instrument that measures the health-related quality of life for CF patients. Improvements in **CFQ-R respiratory domain (RD)** score, which measures the impact of respiratory symptoms on quality of life, were markedly greater than the minimum clinically important difference (4 points)[26], with treatment differences of 20.2 points over placebo in Study 102 and 17.4 points over TEZ/IVA in Study 103.

- Malnourishment is an independent predictor of mortality in CF patients.[27] Modulation of CFTR function in the gastrointestinal tract may lead to improvements in digestion and, consequently, weight gain. In Study 102, ELX/TEZ/IVA resulted in improvements in body mass index (**BMI)** (1.04 kg/m^2) and **body weight** (2.9 kg) compared to placebo. In Study 103, following a 4-week TEZ/IVA run-in, ELX/TEZ/IVA resulted in improvements in BMI (0.60 kg/m^2) and body weight (1.6 kg) compared to TEZ/IVA.

Persistence of efficacy was demonstrated in the placebo-controlled Study 102; the rapid, robust, clinically meaningful, and statistically significant improvements in ppFEV$_1$, SwCl, and CFQ-R RD seen after 4 weeks of ELX/TEZ/IVA treatment were maintained through 24 weeks. The open-label extension study for subjects in Studies 102 and 103 (Study 105) confirmed durability of effect, through 192 weeks.

In Study 104, following a 4-week IVA or TEZ/IVA run-in period, treatment with ELX/TEZ/IVA resulted in a statistically significant improvement in ppFEV$_1$ from IVA or TEZ/IVA baseline through Week 8 (3.7 percentage points). Mean improvement in ppFEV$_1$ was observed at the first assessment on Day 15. Improvements in ppFEV$_1$ were observed regardless of age, baseline ppFEV$_1$, sex, geographic region, and genotype groups (F/G or F/RF). Improvements observed in Study 104 were sustained through 96 weeks of treatment with ELX/TEZ/IVA in Study 110 Part A.

In Study 106 Part B, efficacy was a secondary objective. Treatment with ELX/TEZ/IVA resulted in within-group improvements through or at Week 24 in ppFEV$_1$, SwCl, CFQ-R RD score, BMI z-score, and number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value (LCI$_{2.5}$). Rapid improvements in these endpoints were detected and sustained through Week 24. Improvements observed in Study 106 were sustained through an interim analysis of 96 weeks of treatment with ELX/TEZ/IVA in Study 107 Part A.

In Study 111 Part B, efficacy was a secondary objective. Treatment with ELX/TEZ/IVA resulted in rapid, robust, and clinically impactful improvements over 24 weeks in SwCl and LCI$_{2.5}$.

By substantially improving lung function, PEx rate, and non-pulmonary outcomes, ELX/TEZ/IVA treatment is expected to modify the long-term course of CF disease, reducing the rate of decline in lung function and improving survival. Long-term benefits consistent with disease modification are anticipated given that ELX/TEZ/IVA, like other CFTR modulators[8, 9], treats the underlying cause of disease.

In summary, the ELX/TEZ/IVA pivotal Phase 3 program demonstrated efficacy in subjects who have at least one *F508del* mutation. However, more than 160 additional *CFTR* mutations have been shown to be responsive to ELX/TEZ/IVA in vitro. In many regions, CF patients with these mutations currently do not have an indicated CFTR modulator treatment, nonetheless they are expected to derive clinical benefit from ELX/TEZ/IVA based on (1) current understanding of the biology of the *CFTR* mutations (2) the known mechanism by which CFTR modulators act on defective CFTR proteins that contain these mutations (3) in vitro evidence indicating responsiveness of these proteins to ELX/TEZ/IVA and (4) the established relationship between in vitro responsiveness and clinical benefit. Thus, ELX/TEZ/IVA is expected to provide substantial clinical benefit to all patients who have at least one *F508del* allele, or another responsive mutation, regardless of the mutation on the second allele.

Risks

Nonclinical Data

The nonclinical safety program supports the chronic administration of the TC regimen of ELX/TEZ/IVA in humans at the intended clinical doses. Nonclinical data for ELX, TEZ, or IVA revealed no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential, and repeated dose toxicity.

Dose range finding juvenile toxicity studies in rats exposed during postnatal day 7 to 35 (PND 7 to 35) showed mortality and moribundity, even at low doses. Findings were dose related and generally more severe when dosing with TEZ was initiated earlier in the postnatal period (PND 7, which would be approximately equivalent to a human neonate). Findings of convulsions and death were observed in juvenile rats that received a TEZ dose level of 100 mg/kg/day (approximately equivalent to 1.9 times the maximum recommended human dose [MRHD] based on summed AUCs of TEZ and its metabolite, M1-TEZ). A no effect dose level was identified at 30 mg/kg/day (approximately equivalent to 0.8 times the MRHD based on summed AUCs of TEZ and its metabolite, M1-TEZ). In the pivotal juvenile toxicity study, exposure in rats from PND 21 to 49 did not show toxicity at the highest dose which was approximately 2 times the intended human exposure. TEZ and its metabolite, M1-TEZ, are substrates for P-glycoprotein (P-gp). Lower brain levels of P-gp activity in younger rats resulted in higher brain levels of TEZ and M1-TEZ. These findings are not relevant for the pediatric population 1 year of age and older, for whom levels of P-gp activity are equivalent to levels observed in adults.

The nonclinical safety data for ELX, TEZ, IVA, and the TC regimen of ELX/TEZ/IVA are further discussed in the Investigator's Brochure.

Clinical Data

In the ELX/TEZ/IVA development program, 3,295 subjects have received at least 1 dose of ELX as monotherapy or as part of a TC regimen. The recommended dose of ELX/TEZ/IVA for patients ≥12 years of age and patients 6 to <12 years of age weighing ≥30 kg (ELX 200 mg once daily [qd]/TEZ 100 mg qd/IVA 150 mg every 12 hours [q12h]) was evaluated in 4 completed Phase 3 studies, 2 completed open-label extension studies, and 1 ongoing open-label extension. The recommended dose of ELX/TEZ/IVA for patients 2 to <6 years of age weighing ≥14 kg (ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h) or ≥10 kg and <14 kg (ELX 80 mg qd/TEZ 40 mg qd/IVA 60 mg once every morning and 59.5 mg once every evening) was evaluated in 1 completed Phase 3 study and 1 ongoing open-label extension study.

The safety profile of ELX/TEZ/IVA is derived primarily from the placebo-controlled Study 102 in F/MF subjects, which provides the context for evaluating safety in other studies and settings. Overall, the adverse events (AEs) were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects ≥12 years of age. Adverse drug reactions were generally mild or moderate in severity and can be readily recognized, monitored, and managed. The safety profile is generally similar across subgroups of patients, including age, sex, $ppFEV_1$, geographic regions, and genotypes. There was a low rate of AEs leading to treatment discontinuation.

The incidence of elevated transaminase AEs was higher in the ELX/TEZ/IVA group than in the placebo group; most of the AEs in the ELX/TEZ/IVA group were mild to moderate in severity and associated with transaminase elevations <5 × upper limit of normal (ULN), and there were

few treatment interruptions or discontinuations. The incidence of alanine transaminase (ALT) and aspartate transaminase (AST) laboratory elevations >3 × ULN was slightly higher in the ELX/TEZ/IVA group than in the placebo group, while the incidences of ALT and AST laboratory elevations >5 × ULN and >8 × ULN were generally comparable between treatment groups.

The incidence of rash events was higher in the ELX/TEZ/IVA group than in the placebo group. The rash events were exanthematous, mostly mild to moderate in severity and nonserious, with few treatment interruptions or discontinuations. In both the ELX/TEZ/IVA and placebo groups, the incidence of rash was higher in females than in males. There was also an increase in the incidence of rash in female subjects taking hormonal therapy compared with those not taking hormonal therapy; the increase was larger in the ELX/TEZ/IVA group than in the placebo group.

There was a higher incidence of creatine kinase (CK) laboratory elevations in the ELX/TEZ/IVA group than in the placebo group. The majority of subjects with CK elevation events had asymptomatic laboratory elevations, many of which were preceded by exercise.

Increases from baseline in mean blood pressure (BP) parameters were observed in the ELX/TEZ/IVA group; these increases ranged from 2.0 to 3.5 mm Hg for mean systolic BP and 1.1 to 1.9 mm Hg for mean diastolic BP, without a trend of continued increase during the study. The incidence of subjects in the hypertensive range was similar between treatment groups, and there were few AEs of BP increase.

Overall, the safety results from Studies 102 (F/MF; placebo-controlled), 103 (F/F; active-controlled), and 104 (F/G and F/RF; active-controlled) were consistent. Safety data from the open-label extension Studies 105 and 110 were also consistent with the safety data in Studies 102, 103, and 104; no new safety concerns were identified with extended ELX/TEZ/IVA treatment.

An additional study, Study 106, evaluated the safety of ELX/TEZ/IVA dosed for 15 days (Part A) and 24 weeks (Part B) in pediatric subjects 6 through 11 years of age with F/MF and F/F genotypes. The safety results were consistent with the known safety profile of ELX/TEZ/IVA. AEs were generally consistent with manifestations or complications of underlying CF disease, and no clinically significant trends were reported in any laboratory assessments, vital signs, pulse oximetry, or ECGs. Safety data from an interim analysis of the open-label extension Study 107 Part A were also consistent with the safety data in Study 106; no new safety concerns were identified with extended ELX/TEZ/IVA treatment.

Study 111 evaluated the safety of ELX/TEZ/IVA in CF subjects 2 through 5 years of age. Part A included a 15-day Treatment Period in pediatric subjects with F/MF and F/F genotypes and Part B included a 24-week Treatment Period in pediatric subjects with at least one *F508del* mutation in the *CFTR* gene or an ELX/TEZ/IVA-responsive *CFTR* mutation. Overall, ELX/TEZ/IVA was generally safe and well tolerated with low rates of treatment discontinuation in subjects 2 through 5 years of age. The data were consistent with the established safety profile of ELX/TEZ/IVA; no new safety concerns were identified.

ELX/TEZ/IVA has low potential for causing clinically significant drug interactions. Caution and appropriate monitoring are recommended for co-administration with P-gp substrates and CYP2C9 substrates with a narrow therapeutic index (e.g., digoxin and warfarin) due to inhibition of P-gp and CYP2C9 by IVA. ELX may inhibit OATP1B1 and OATP1B3 based on in vitro data;

as such, caution and appropriate monitoring is recommended for co-administration with medicinal products that are substrates of OATP1B1/1B3, such as statins. As ELX, TEZ, and IVA are CYP3A substrates (IVA is a sensitive substrate), use of strong CYP3A inducers is not recommended and dose adjustments are recommended for ELX/TEZ/IVA with concomitant moderate and strong CYP3A inhibitors.

The effects of ELX/TEZ/IVA on conception, pregnancy, and lactation in humans are unknown. Nonclinical studies suggest that ELX, TEZ, and IVA are not teratogenic. ELX, TEZ, and IVA are excreted into the milk of lactating female rats; therefore, excretion into human milk is probable.

Safety profiles of the TC components IVA and TEZ/IVA, which are approved for the treatment of CF in patients of certain ages and with certain mutations, have been well characterized in previous clinical studies and postmarketing data.

Cataracts have been reported in pediatric patients receiving IVA or IVA-containing regimens. Overall, cumulative ophthalmological data do not support an association between IVA treatment and cataracts, although a contributing role cannot be completely excluded. Data from ELX/TEZ/IVA Phase 3 studies are consistent with previous experience with IVA and IVA-containing regimens.

As of the DLP of 10 January 2023, it is estimated that 60,341 patients (representing 88,771 person-years) have been exposed to ELX/TEZ/IVA through worldwide commercial use since the international birth date of ELX/TEZ/IVA. The postmarketing data has been generally consistent with the data from clinical studies. The ELX/TEZ/IVA Investigator's Brochure and global product labels have been updated to describe postmarketing cases of hepatic injury and a case of liver transplant in a patient with advanced liver disease.

In summary, the safety profile of ELX/TEZ/IVA has been adequately characterized, with risks that are readily identified clinically or with routine laboratory monitoring and can be managed within the clinical study protocol.

Benefit-Risk Conclusions

ELX/TEZ/IVA was evaluated in a comprehensive clinical development program, with a Phase 3 program that included 904 CF subjects 2 years of age and older (Studies 102, 103, 104, 105, 106, 110, and 111).

The pivotal Phase 3 program demonstrated that ELX/TEZ/IVA provides unprecedented clinical benefit in CF patients with at least one *F508del* allele. Both pivotal Phase 3 studies in subjects ≥12 years of age met the primary and all key secondary endpoints, which included $ppFEV_1$, PEx, CFQ-R RD scores, BMI, and SwCl levels. These results demonstrated that in CF patients, the effect of ELX/TEZ/IVA on a single *F508del* allele is sufficient to derive unprecedented clinical benefit, regardless of the mutation on the second allele. The substantial improvements in lung function (a significant predictor of mortality[23]) and reductions in PEx (a major contributor to lung damage and FEV_1 decline[24, 25]) are expected to translate to long-term disease modification, similar to other CFTR modulators.[8, 9] Non-pulmonary aspects of CF also significantly affect the course of disease and patient outcomes. Normal BMI is associated with better lung function[2], and weight is an independent predictor of mortality.[23, 27]

The safety profile of ELX/TEZ/IVA has been well characterized within the development program and postmarketing experience. ELX/TEZ/IVA is generally safe and well tolerated in

patients ≥2 years of age, with a low rate of treatment discontinuation. Risks are readily recognized, monitored, and managed within the clinical study protocol.

Given the progressive nature of CF, there is a strong rationale for treating patients earlier in life. Experience with CFTR modulators (including TEZ/IVA) in pediatric subjects suggests that the safety profile of ELX/TEZ/IVA will be similar in children and adults, which supports evaluation of ELX/TEZ/IVA in pediatric subjects.

The overall risk to subjects participating in ELX/TEZ/IVA clinical studies will be minimized as much as possible. Key safety eligibility criteria, close safety monitoring of subjects, prudent stopping rules, and guidance for use of concomitant medications are included in the study protocol.

Based on the data from nonclinical and clinical studies with ELX/TEZ/IVA, and the potential for CF patients to directly benefit from development of this treatment, the overall benefit-risk for ELX/TEZ/IVA is considered acceptable.

15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX22-445-122	Version #: 4.0	Version Date: 16 January 2024
Study Title: A Phase 3, Open-label Study Evaluating the Pharmacokinetics, Safety, and Tolerability of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 12 to Less Than 24 Months of Age		

This clinical study protocol has been reviewed and approved by the sponsor's authorized representative.

Printed Name	Title and Function
Signature	Date
Vertex Pharmaceuticals Incorporated	50 Northern Avenue Boston, MA 02210-1862, USA
Sponsor Name	Sponsor Address

15.2 Investigator Signature Page

Protocol #: VX22-445-122	Version #: 4.0	Version Date: 16 January 2024
Study Title: A Phase 3, Open-label Study Evaluating the Pharmacokinetics, Safety, and Tolerability of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects 12 to Less Than 24 Months of Age		

I have read Protocol VX22-445-122, Version 4.0, and agree to conduct the study according to its terms. I understand that all information concerning ELX (VX-445)/TEZ (VX-661)/IVA (VX-770) and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date