Number of Subjects	Approximately 250 subjects will be enrolled in the study: • Approximately 40% of total subjects will be in the IVA comparator group (approximately 100 subjects) ○ In the IVA comparator group, up to 20% of subjects may be enrolled with an *R117H* mutation (approximately 20 subjects) • Up to 15% of total subjects may be enrolled with SwCl values <30 mmol/L at screening (approximately 40 subjects) Subjects will be randomized (1:1) to the VX-445/TEZ/IVA treatment arm or the control arm (IVA or TEZ/IVA).
Study Population	Male and female CF subjects 12 years of age or older with F/G and F/RF genotypes
Investigational Drug	During the Run-in Period, study drug refers to TEZ/IVA and IVA, as applicable. During the Treatment Period, study drug refers to VX-445/TEZ/IVA and matching placebo, TEZ/IVA and matching placebo, and IVA and matching placebo, as applicable. Active study drugs will be orally administered as fixed-dose combination (FDC) film-coated tablets of VX-445/TEZ/IVA or TEZ/IVA and film-coated IVA tablets. **Active substance:** VX-445/TEZ/IVA **Activity:** VX-445 is a CFTR corrector, TEZ is a CFTR corrector, and IVA is a CFTR potentiator (increased Cl^- secretion) **Strength:** 100 mg/50 mg/75 mg FDC tablet **Active substance:** TEZ/IVA **Activity:** CFTR corrector and CFTR potentiator (increased Cl^- secretion) **Strength:** 100 mg/150 mg FDC tablet **Active substance:** IVA **Activity:** CFTR potentiator (increased Cl^- secretion) **Strength:** 150 mg tablet
Study Duration	The total study duration is approximately 20 weeks (4 weeks for the Screening Period, 4 weeks for the Run-in Period, 8 weeks for the Treatment Period, and 4 weeks for the Safety Follow-up Period).
Study Design	This is a Phase 3, randomized, double-blind, active-controlled, parallel-group, multicenter study (Figure 2-1). In the Run-in Period, subjects will be assigned to the IVA or TEZ/IVA comparator group based on genotype. Subjects assigned to the IVA comparator group will receive IVA 150 mg every 12 hours (q12h) and subjects assigned to the TEZ/IVA comparator group will receive TEZ 100 mg once daily (qd)/IVA 150 mg q12h (Table 2-1). In the Treatment Period, subjects will be randomized (1:1) to the VX-445/TEZ/IVA treatment arm or control arm under a single randomization scheme. Subjects in the control arm who received IVA in the Run-in Period will receive IVA in the Treatment Period; subjects in the control arm who received TEZ/IVA in the Run-in Period will receive TEZ/IVA in the Treatment Period. Randomization will be stratified based on comparator group (IVA comparator versus TEZ/IVA comparator), $ppFEV_1$ as determined during the Run-in Period (Day -14 assessment; <70 versus ≥70), and SwCl as determined during the Run-in Period (Day -14 assessment; <30 mmol/L versus ≥30 mmol/L).

Table 3-1 Study VX18-445-104: Screening

Event/Assessment	Screening Period Day -56 Through Day -29	Comments
ICF and assent (when applicable)	X	
Inclusion and exclusion criteria review	X	Sections 8.1 and 8.2
Demographics	X	Section 11.1
Medical history	X	
CFTR genotype	X	Performed for all subjects (Section 11.6.2). In subjects with an *R117H* mutation, linkage to poly-T tract polymorphisms will also be determined from a second specimen. A subject's screening *CFTR* genotype **must** confirm eligibility before the subject enters the Run-in Period (Section 8.1).
FSH	X	Performed for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea (Section 11.6.2)
Serum pregnancy test (all females)	X	Section 11.6.2
Hematology	X	
Coagulation	X	
Serum chemistry	X	
Urinalysis	X	
Weight and height	X	Measured with shoes off (Section 11.1)
OE	X	Conducted only for subjects who are <18 years of age on the date of informed consent (Section 11.6.6)
Complete physical examination	X	Section 11.6.3
Vital signs	X	Performed after subject has been at rest for at least 5 minutes (Sections 11.6.3, 11.6.4, and 11.6.5)
Pulse oximetry	X	
Standard 12-lead ECG	X	
Spirometry	X	May be performed pre- or post-bronchodilator (Section 11.5.1)
Medications review	X	Section 9.5
Sweat chloride	X	Section 11.3
AEs and SAEs	Continuous from signing of the ICF through completion of study participation	Sections 9.1.7, 13.1.1.3, and 13.1.2.2

AE: adverse events; FSH: follicle-stimulating hormone; ICF: informed consent form; OE: ophthalmologic examination; SAE: serious adverse event

above (e.g., an allergic bronchospasm requiring intensive treatment in an emergency room or at home)

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

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

13.1.2.2 Reporting and Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent and assent (where applicable) through completion of study participation, regardless of causality, will be reported by the investigator to Vertex GPS **within 24 hours of identification**. In addition, all SAEs that occur after the 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 completion of study participation, the SAE Form will be completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (preferred choice)

Fax: [redacted]

For technical issues related to submitting the form, contact telephone: [redacted]

SAEs that occur after the Safety Follow-up Visit and are considered related to study drug(s) will be recorded on the Vertex 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.

for the VX-445/TEZ/IVA group. The primary null hypothesis to be tested is that the mean absolute change in $ppFEV_1$ from baseline through Week 8 is 0 for the VX-445/TEZ/IVA treatment group. The null hypothesis will be tested at a 2-sided significance level of 0.05.

For the primary hypothesis, assuming a within-group SD of 7.0 percentage points and a 10% dropout rate at Week 8, a sample size of 125 subjects in the VX-445/TEZ/IVA arm will have >99% power to detect the within-group difference of 3.0 percentage points (1 sample *t*-test at a 2-sided significance level of 0.05).

The primary endpoint will be analyzed using a mixed-effects model for repeated measures (MMRM). The model will include the absolute change from baseline in $ppFEV_1$ at Day 15, Week 4, and Week 8 as the dependent variable; treatment group, visit, and treatment by visit as fixed effects; with continuous baseline $ppFEV_1$, continuous baseline SwCl, and comparator group (IVA comparator versus TEZ/IVA comparator) as covariates; and an unstructured covariance structure for the within-subject errors.

For the primary endpoint, the results obtained from the model will be the estimated within-treatment difference through Week 8 (average of Week 4 and Week 8) for the VX-445/TEZ/IVA group. The same model will be used to estimate between group differences (difference between VX-445/TEZ/IVA and the control group) through Week 8. The adjusted mean with a 2-sided 95% CI and a 2-sided *P* value will be provided for the primary endpoint and second key secondary endpoints.

The safety endpoints include AEs, clinical laboratory values, ECGs, vital signs, and pulse oximetry through completion of study participation. The safety analyses will be descriptive only.

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

IVA 150 mg every 12 hours (q12h) and subjects assigned to the TEZ/IVA comparator group will receive TEZ 100 mg once daily (qd)/IVA 150 mg q12h.

In the Treatment Period, subjects will be randomized (1:1) to the VX-445/TEZ/IVA treatment arm or control arm under a single randomization scheme. Subjects in the control arm who received IVA in the Run-in Period will receive IVA in the Treatment Period; subjects in the control arm who received TEZ/IVA in the Run-in Period will receive TEZ/IVA in the Treatment Period.

Randomization will be stratified; details are provided in Section 9.2.

The dosages for the Treatment Period are shown in Table 9-2.

Table 9-1 IVA and TEZ/IVA Comparator Group Mutations

IVA Comparator Group Mutations		
R117H	*G551D*	*G1244E*
G178R	*G551S*	*S1251N*
S549N	*G1069R*	*S1255P*
S549R	*R1070Q*	*G1349D*
TEZ/IVA Comparator Group Mutations		
711+3A>G	*R117C*	*S977F*
2789+5G>A	*E193K*	*F1052V*
3272-26A>G	*L206W*	*K1060T*
3849+10kbC>T	*R347H*	*A1067T*
E56K	*R352Q*	*R1070W*
P67L	*A455E*	*F1074L*
R74W	*D579G*	*D1152H*
D110E	*E831X*	*D1270N*
D110H	*S945L*	

IVA: ivacaftor; TEZ: tezacaftor

Note: This table represents all gating and residual function mutations that may qualify for enrollment in this study but is not intended to determine subject eligibility. Refer to Appendix A for a list of eligible mutations based on approved indications for treatment with IVA and/or TEZ/IVA.

Table 9-2 Treatment Groups and Dosages

Comparator Group	Treatment Arm	VX-445 Dosage	TEZ Dosage	IVA Dosage
IVA	VX-445/TEZ/IVA	200 mg qd	100 mg qd	150 mg q12h
	Control	0 mg	0 mg	150 mg q12h
TEZ/IVA	VX-445/TEZ/IVA	200 mg qd	100 mg qd	150 mg q12h
	Control	0 mg	100 mg qd	150 mg q12h

IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor

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

9.1.1 Screening

The Screening Period (Day -56 through Day -29) will occur within 28 days before the first dose of study drug in the Run-in Period.

Abbreviation	Definition
IDMC	independent data monitoring committee
IEC	independent ethics committee
IND	Investigational New Drug (application) (US)
IPD	important protocol deviation
IRB	institutional review board
IVA	ivacaftor
IWRS	interactive web response system
LUM	lumacaftor
M1-TEZ	metabolite of TEZ
max	maximum value
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal function
min	minimum value
MMRM	mixed-effects model for repeated measures
n	number of subjects
OATP1B1	organic anion transporting polypeptide 1B1
OE	ophthalmological examination
P	probability
PD	pharmacodynamic, pharmacodynamics
PEx	pulmonary exacerbation
P-gp	P-glycoprotein
PK	pharmacokinetic, pharmacokinetics
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
PR	PR interval, segment
PT	Preferred Term
q12h	every 12 hours
qd	once daily
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QTcF	QT interval corrected by Fridericia's formula
RD	respiratory domain
RF	residual function
RNA	ribonucleic acid
RR	interval from the onset of 1 QRS complex to the next
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SI	SI units (International System of Units)
SOC	System Organ Class
SUSAR	suspected, unexpected, serious adverse reaction
SwCl	sweat chloride
TC	triple combination
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TEZ	tezacaftor

- Inflammatory mediators
- Blood biomarkers

8 STUDY POPULATION

Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects receive study drug on Day -28.

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

8.1 Inclusion Criteria

1. Subject (or his or her legally appointed and authorized representative) will sign and date an informed consent form (ICF), and, when appropriate, an assent form.
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Age 12 years or older, at the date of informed consent.
4. Confirmed diagnosis of CF as determined by the investigator.
5. Subject is heterozygous for *F508del* and either a gating or residual function mutation (F/G and F/RF genotypes) and is in a region where their genotype and age group are approved indications for treatment with IVA and/or TEZ/IVA (see Appendix A for qualifying mutations).
6. Forced expiratory volume in 1 second (FEV_1) value ≥40% and ≤90% of predicted mean for age, sex, race, and height (equations of the Global Lung Function Initiative [GLI])[11] at the Screening Visit. Spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria[12] for acceptability and repeatability.
7. Subjects must be able to produce a valid (quantity-sufficient) sweat sample at screening.
8. Stable CF disease as judged by the investigator.
9. Willing to remain on a stable CF treatment regimen (as defined in Section 9.5) through completion of study participation.

8.2 Exclusion Criteria

1. History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This includes, but is not limited to, the following:
   - Clinically significant cirrhosis with or without portal hypertension.
   - Solid organ or hematological transplantation.
   - Alcohol or drug abuse in the past year, including, but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator.
   - Cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (each being disease-free for the last 5 years).
2. Any of the following abnormal laboratory values at screening.

for F/F subjects, and open-label Study VX17-445-105 [Study 105] for both F/MF and F/F subjects).

9.3.3 Study Drug Dose

VX-445 Dosage

A VX-445 dose of 200 mg qd will be administered. This is the dosing regimen that was evaluated in the Phase 3 pivotal studies of VX-445/TEZ/IVA in CF subjects with F/MF and F/F genotypes.

TEZ and IVA Dosages

TEZ will be administered as 100 mg qd and IVA will be administered as 150 mg q12h. This is the approved dosing regimen for Symdeko, which is now approved in certain countries. IVA monotherapy will be administered as 150 mg q12h, which is the approved dosing regimen for Kalydeco.

Dosage for Subjects Aged 12 to 17 Years

Phase 3 studies with IVA and TEZ/IVA have demonstrated similar exposures between adults (≥18 years old) and adolescent subjects ≥12 to <18 years of age. In Studies 102 and 103, adolescent subjects in the F/MF and F/F genotype groups are being evaluated at the same dose as adult subjects because VX-445, TEZ, and IVA exposures are expected to be similar in adolescent subjects and adults. Therefore, in the current study, all subjects (both adolescents and adults) will receive the same dose of VX-445/TEZ/IVA.

9.3.4 Rationale for Study Assessments

The safety, pharmacokinetic (PK), 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 CF subjects. Additional exploratory assessments will be obtained to explore inflammatory mediators and other biomarkers.

9.4 Study Restrictions

9.4.1 Prohibited Medications

Table 9-3 lists prohibited medications. A non-exhaustive list of study prohibitions and cautions for medication will be provided in the Study Reference Manual. Guidance for concomitant medications is provided in Section 9.5.

Table 9-3 Prohibited Medications

Medication	Timing of Restriction: Start of Restriction	Timing of Restriction: End of Restriction	Rationale
Moderate and strong CYP3A inducers	None allowed after the first dose of study drug on Day -28	None allowed through completion of study participation	VX-445, 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 VX-445, TEZ, or IVA, will be prohibited.
Moderate and strong CYP3A inhibitors (except ciprofloxacin)[a]	None allowed after the first dose of study drug on Day -28	None allowed through completion of study participation	
Non-Vertex CFTR modulators (investigational or approved)	None allowed within 28 days or 5 terminal half-lives (whichever is longer) before screening	None allowed through completion of study participation	These agents may confound the results of this study.
Vertex CFTR modulators (investigational or approved), except for study drugs	None allowed from the first dose of study drug on Day -28	None allowed until after the last dose of study drug	These agents may confound the results of this study.

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).

9.5 Prior and Concomitant Medications

Information regarding prior and concomitant medications, including CF medications, other medications, and herbal and naturopathic remedies, will be collected from each subject's source documentation for medications taken within 56 days before the Screening Visit through completion of study participation, as defined in Section 9.1.7. Medications will be categorized as defined in Section 12.3.2.3.

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

- Subjects should remain on a stable treatment regimen for their CF from 28 days before the Day -28 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 -28 Visit. Subjects who are on Vertex CFTR modulators (investigational or approved) at the date of informed consent may remain on these during the Screening Period and should transition directly to study drug at the beginning of the Run-in Period on Day -28 without a washout (Table 9-3). Subjects should not initiate long-term treatment with new medication from 28 days before the Day -28 Visit through completion of study participation. Guidelines for stable treatment regimens for CF are as follows:

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

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

11.2.2 Processing and Handling of Pharmacokinetic Samples

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

11.2.3 Bioanalysis

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

11.3 Pharmacodynamics: Sweat Chloride

SwCl samples will be collected with an approved collection device. Each collection will occur before study drug dosing (Section 9.6.1). At each time point, 2 samples will be collected, 1 from each arm (left and right). Sweat samples will be sent to a central laboratory for testing and interpretation of results. Specific instructions for the collection, handling, processing, and shipping of SwCl samples to the central laboratory will be provided separately.

See Section 10.7.1 for information about access to SwCl results.

11.4 Exploratory Assessments

These data will be used for exploratory purposes. Detailed procedures for the collection, processing, storage, and shipment of samples for exploratory assessments will be provided in a separate document.

11.4.1 Pharmacogenomics

An optional single blood sample (DNA sample) will be collected for potential exploratory evaluation of correlations between DNA markers with PK, PD, treatment response, AEs, and biomarkers related to health and disease, including CF, for subjects who choose to participate in this assessment.

11.4.2 Inflammatory Mediators

Blood samples (inflammatory mediator samples) will be collected at the time points noted in Table 3-2 and tested to assess markers related to inflammation. These markers may include, but are not limited to, C-reactive protein, immunoglobulin G, white blood cell (leukocyte) count, and interleukin-8.

11.4.3 Other Blood Biomarkers

Serum from an inflammatory mediator sample and an additional blood sample for plasma will be collected and banked for potential future exploratory evaluation of other blood biomarkers (e.g., proteins, peptides, lipids, metabolites, etc.) in relation to PK, PD, treatment response, AEs, and various disease manifestations of CF.

A blood sample for RNA isolation will be collected as indicated in Table 3-2 for potential exploratory evaluation of gene signatures associated with various disease manifestations of CF and/or treatment response.

11.4.4 Microbiology and Other Sputum Biomarkers

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

11.5 Efficacy

11.5.1 Spirometry

Spirometry will be performed according to the American Thoracic Society Guidelines/European Respiratory Society Guidelines[12] and according to the additional guidelines that follow.

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

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

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

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

All sites will be provided with spirometers to be used for all study assessments. Spirometry data will be transmitted to a centralized spirometry service for quality review. The investigator's

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

The safety laboratory test panels are shown in Table 11-1.

Table 11-1 Safety Laboratory Test Panels

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

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

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

Pregnancy (β-human Chorionic Gonadotropin) Tests for Female Subjects: All female subjects, regardless of childbearing potential status, must have a serum pregnancy test at screening. Serum pregnancy tests will be performed at the study site and analyzed at the central laboratory. Urine pregnancy tests will be performed and analyzed at the site. The urine pregnancy test on Day -28 and Day 1 must be negative before the first dose of study drug in each study period. Additional pregnancy tests may be required according to local regulations and/or requirements.

FSH (Screening Period Only): Blood samples for FSH will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be in the postmenopausal range as determined by the laboratory performing the test.

CFTR Genotype (Screening Period Only): *CFTR* genotyping will be performed for all subjects. A subject's screening *CFTR* genotype **must** confirm eligibility before the subject enters the Run-in Period. In subjects with an *R117H* mutation, linkage to poly-T tract polymorphisms will also be determined from a second specimen. Specific instructions will be provided in the Laboratory Manual.

discontinuation will be assumed to be missing at random; consequently, no imputation of missing data will be performed.

The primary results obtained from the model will be the estimated within-treatment difference through Week 8 (average of Week 4 and Week 8) for the VX-445/TEZ/IVA group. The adjusted mean with a 2-sided 95% CI and a 2-sided *P* value will be provided. Furthermore, the treatment difference at each post-baseline visit will also be provided, obtained from the model.

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

Supportive analyses and subgroup analyses by selected baseline characteristics will also be described in the SAP.

12.3.3.2 Analysis of Key Secondary Efficacy Endpoints

The key secondary endpoints are:

- **Absolute change in SwCl from baseline through Week 8 for the VX-445/TEZ/IVA group:** Analysis of this endpoint will be based on the same MMRM model as the analysis of the primary efficacy endpoint. Data obtained from the Day 15, Week 4, and Week 8 Visits will be included in the model.
- **Absolute change in ppFEV$_1$ from baseline through Week 8 for the VX-445/TEZ/IVA group compared to the control group:** Analysis of this endpoint will be based on the same MMRM model as the analysis of the primary efficacy endpoint. Data obtained from the Day 15, Week 4, and Week 8 Visits will be included in the model. However, the Day 15 Visit will not be included in the estimation of the average treatment effect through Week 8.
- **Absolute change in SwCl from baseline through Week 8 for the VX-445/TEZ/IVA group compared to the control group:** Analysis of this endpoint will be based on the same MMRM model as the analysis of the primary efficacy endpoint. Data obtained from the Day 15, Week 4, and Week 8 Visits will be included in the model.

Details will be provided in the SAP.

12.3.3.3 Analysis of Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints include:

- **Absolute change in CFQ-R RD score from baseline through Week 8 for the VX-445/TEZ/IVA group**: Analysis of this endpoint will be based on an MMRM model similar to the analysis of the primary efficacy endpoint. Data obtained from the Day 15, Week 4, and Week 8 Visits will be included in the model. However, the Day 15 Visit will not be included in the estimation of the average treatment effect through Week 8.
- **Absolute change in CFQ-R RD score from baseline through Week 8 for the VX-445/TEZ/IVA group compared to the control group**: Analysis of this endpoint will be based on an MMRM model similar to the analysis of the primary efficacy endpoint. Data obtained from the Day 15, Week 4, and Week 8 Visits will be included in the model. However, the Day 15 Visit will not be included in the estimation of the average treatment effect through Week 8.

Details will be provided in the SAP.

12.3.3.4 Multiplicity Adjustment

A hierarchical testing procedure will be used to control the overall type I error at an alpha of 0.05 for the primary endpoint and the key secondary endpoints tested. The key secondary endpoints will only be tested at an alpha of 0.05 if the primary endpoint of absolute change in $ppFEV_1$ from baseline through Week 8 for the VX-445/TEZ/IVA group is statistically significant. For a test at any step to be considered statistically significant within the testing hierarchy, it must be statistically significant, and all previous tests (if any) within the hierarchy must be statistically significant at the 0.05 level. The testing order of the key secondary endpoints is as follows:

1. First key secondary endpoint: Absolute change in SwCl from baseline through Week 8 for the VX-445/TEZ/IVA group
2. Second key secondary endpoint: Absolute change in $ppFEV_1$ from baseline through Week 8 for the VX-445/TEZ/IVA group compared to the control group
3. Third key secondary endpoint: Absolute change in SwCl from baseline through Week 8 for the VX-445/TEZ/IVA group compared to the control group

12.3.3.5 Analysis of Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include:

- **Absolute change in CFQ-R non-RD scores from baseline through Week 8**: Analysis of this endpoint will be based on an MMRM model similar to the analysis of the primary efficacy endpoint. Data obtained from the Day 15, Week 4, and Week 8 Visits will be included in the model. However, the Day 15 Visit will not be included in the estimation of the average treatment effect through Week 8.
- **Absolute change in BMI from baseline at Week 8**: Analysis of this endpoint will be based on an MMRM model similar to the analysis of the primary efficacy endpoint. Data obtained from the Day 15, Week 4, and Week 8 Visits will be included in the model.

Additional details will be specified in the SAP.

12.3.4 Safety Analysis

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

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

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

All safety data from the TE Period will be summarized by treatment group and overall.

All safety data will be presented in individual subject data listings, including safety data from the Run-in Period.

12.3.4.1 Adverse Events

For analysis purposes, AEs will be classified as pretreatment AEs, TEAEs during the Run-in Period, TEAEs during the Treatment Period, or post-treatment AEs, defined as follows:

- **Pretreatment AE**: any AE that started before the first dose of study drug (TEZ/IVA or IVA) during the Run-in Period
- **TEAE during the Run-in Period**: any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose date of study drug (TEZ/IVA or IVA) through the end of the TE Period for the Run-in Period
- **TEAE during the Treatment Period**: any AE that worsened (either in severity or seriousness) or that was newly developed at or after the first dose of study drug (TC or placebo + TEZ/IVA or placebo + IVA) through the end of the TE Period for the Treatment Period
- **Post-treatment AE**: any AE that worsened (either in severity or seriousness) or that was newly developed after:
    - the TE Period for the Run-in Period if the subject did not receive treatment in the Treatment Period
    - the TE Period for the Treatment Period if the subject received treatment in the Treatment Period

For AEs with missing or partial start dates, if there is no clear evidence that the AEs started before or after study drug treatment, then the AEs will be classified as TEAEs corresponding to the Treatment Period. Unless otherwise specified, TEAE refers to TEAE during the Treatment Period.

AE summary tables will be presented for TEAEs, overall and by treatment group, 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
- Grade 3 and Grade 4 TEAEs
- Serious TEAEs
- TEAEs leading to death
- Frequently reported TEAEs

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

severity summaries, and the strongest relationship level will be presented in the relationship summaries. In addition, a listing containing individual subject level AE data for all deaths and other serious and significant AEs will be provided separately. All AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings.

12.3.4.2 Clinical Laboratory Assessments

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

The number and percentage of subjects with at least 1 threshold analysis event during the TE Period will be summarized overall and by treatment group. 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.

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

12.3.4.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided overall and by treatment group, at each scheduled visit and time point, as applicable, for the following standard 12-lead ECG interval measurements (in msec): RR, PR, QT, and QT corrected for HR (QTcF), QRS duration, and HR (beats per minute [bpm]).

The number and percentage of subjects with at least 1 threshold analysis event during the TE Period will be summarized overall and by treatment group. The threshold analysis criteria will be provided in the SAP.

Additional ECG analyses may be described in the SAP.

12.3.4.4 Vital Signs

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

The number and percentage of subjects with at least 1 threshold analysis event during the TE Period will be summarized overall and by treatment group. The threshold analysis criteria will be provided in the SAP.

Additional vital signs analyses may be described in the SAP.

12.3.4.5 Pulse Oximetry

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

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

12.3.4.6 Physical Examination

Physical examination findings will be presented in an individual subject data listing only.

12.3.4.7 Other Safety Analysis

Not applicable

12.3.5 Exploratory Endpoints

12.3.5.1 Analysis of Exploratory Endpoints

Details of other analyses, including inflammatory mediators and blood biomarkers analyses, will be provided in a separate document.

12.3.6 Interim and Independent Data Monitoring Committee Analyses

12.3.6.1 Interim Analysis

Not applicable

12.3.6.2 Independent Data Monitoring Committee Analysis

The IDMC (Section 9.1.8) will conduct safety reviews of study data. Details will be described in the IDMC charter.

12.4 Clinical Pharmacology Analysis

12.4.1 Pharmacokinetic Analysis

PK analysis of VX-445, TEZ, M1-TEZ, and IVA may be performed using nonlinear mixed-effects modeling, as data allow. Descriptive statistics will be used to summarize predose plasma concentrations for all analytes.

A detailed description of the planned PK analysis will be presented in the clinical pharmacology analysis plan.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

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

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

13.1.1.2 Clinically Significant Assessments

Study assessments including laboratory tests, ECGs, physical examinations, and vital signs will be assessed and those deemed to have clinically significant worsening from baseline will be documented as an AE. When possible, a clinical diagnosis for the study assessment will be

provided, rather than the abnormal test result alone (e.g., urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself will be listed as the AE (e.g., bacteria in urine or decreased hemoglobin).

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

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

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

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

13.1.1.3 Documentation of Adverse Events

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

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

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

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed July 2018). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." 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	Definition
Mild (Grade 1)	Mild level of discomfort and does not interfere with regular activities
Moderate (Grade 2)	Moderate level of discomfort and significantly interferes with regular activities
Severe (Grade 3)	Significant level of discomfort and prevents regular activities
Life-threatening (Grade 4)	Any adverse drug event that places the subject, in the view of the investigator, at immediate risk of death

AE: adverse event

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	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.

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

Classification	Definition

AE: adverse event

13.1.1.7 Adverse Event Outcome

An AE will be followed until the investigator has determined and provided the final outcome. The outcome will be classified according to the categories 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 followup)

AE: adverse event

13.1.1.8 Treatment Given

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

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

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

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

13.1.2.3 Expedited Reporting and Investigator Safety Letters

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

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

13.2 Administrative Requirements

13.2.1 Ethical Considerations

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

13.2.2 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject or legal representative or guardian (if applicable), and assent will be obtained from the subject (if applicable), before study participation. The method of obtaining and documenting the informed consent and assent (if applicable) and the contents of the consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by Vertex or its designee. When determining the age of the subject, other study eligibility criteria, and timing of collection applicable assessments, the informed consent will be used as the reference (e.g., age at time of informed consent, date of informed consent, timing of AE collection).

13.2.3 Investigator Compliance

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

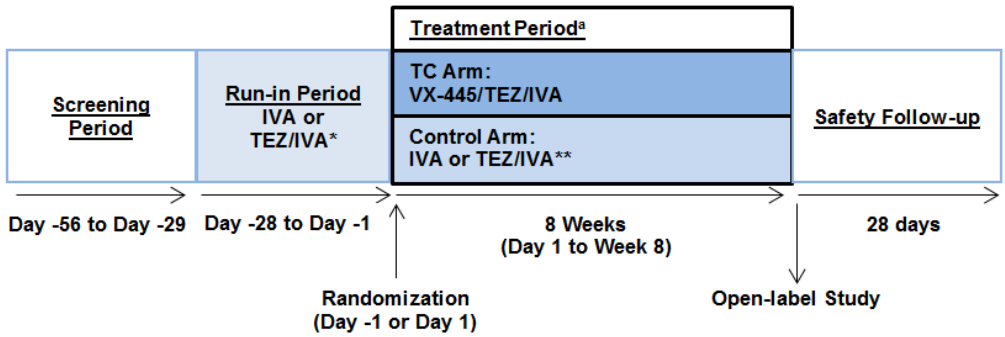
When circumstances require an immediate departure from procedures set forth in the protocol, the investigator will contact Vertex to discuss the planned course of action. If possible, contact will be made before the implementation of any changes. Any departures from the protocol will be fully documented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

Table 2-1 Treatment Groups and Dosages

Comparator Group	Treatment Arm	VX-445 Dosage	TEZ Dosage	IVA Dosage
IVA	VX-445/TEZ/IVA	200 mg qd	100 mg qd	150 mg q12h
	Control	0 mg	0 mg	150 mg q12h
TEZ/IVA	VX-445/TEZ/IVA	200 mg qd	100 mg qd	150 mg q12h
	Control	0 mg	100 mg qd	150 mg q12h

IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor

Figure 2-1 VX18-445-104 Study Design



IVA: ivacaftor; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TC: triple combination; TEZ: tezacaftor

Note: The Safety Follow-up Visit is not required for subjects who complete the Week 8 Visit and enroll in an open-label study within 28 days after the last dose of study drug.

[a] Subjects will be randomized 1:1 to the TC arm or the control arm. Randomization will be stratified based on comparator group (IVA comparator versus TEZ/IVA comparator), $ppFEV_1$ as determined during the Run-in Period (Day -14 assessment; <70 versus ≥70), and SwCl as determined during the Run-in Period (Day -14 assessment; <30 mmol/L versus ≥30 mmol/L).

Assessments

Efficacy: Spirometry and CFQ-R

PD: SwCl

Safety: AEs, clinical laboratory assessments, ECGs, vital signs, pulse oximetry, physical examinations, and ophthalmologic exams (for subjects <18 years of age)

Pharmacokinetics (PK): VX-445, TEZ, M1-TEZ, and IVA plasma concentrations

Exploratory: DNA sample (optional), inflammatory mediators, blood biomarker samples, and sputum samples

Statistical Analyses

Approximately 250 subjects will be enrolled and randomized (1:1) to the VX-445/TEZ/IVA treatment arm or control arm (IVA or TEZ/IVA).

The primary efficacy endpoint is the absolute change in $ppFEV_1$ from baseline through Week 8

Table 3-2 VX18-445-104: Run-in Period, Treatment Period, and Safety Follow-up Visit

Event/Assessment[a]	Run-in Period (4 Weeks)		Treatment Period (8 Weeks)				ETT Visit[b]	Safety Follow-up Visit 28 (± 7) Days After the Last Dose of Study Drug (If Applicable)[c]	Comments
	Day -28 ± 1 Day	Day -14 ± 2 Days	Day 1[d]	Day 15 ± 3 Days	Week 4 ± 5 Days	Week 8 ± 5 Days			
Clinic visit	X	X	X	X	X	X	X	X	
Inclusion and exclusion criteria confirmation	X								Section 8
CFQ-R	X		X	X	X	X	X	X	Must be completed before any other assessments at relevant clinic visits (Section 11.5.2).
Weight and height	X		X	X	X	X	X	X	Measured with shoes off. Height will only be collected for subjects ≤21 years of age on the date of informed consent (Section 11.1).
OE								X	For subjects <18 years of age on the date of informed consent, an OE is required during Safety Follow-up only if the subject completed study drug dosing through Week 8 of the Treatment Period (Section 11.6.6)
Physical examination	Abbrev		Complete			Complete	Complete		Section 11.6.3
Pregnancy testing	Urine		Urine		Urine	Urine	Serum	Serum	All female subjects (Section 11.6.2)
Standard 12-lead ECG	X		X	X	X	X	X	X	After subject has rested for at least 5 minutes and before dosing, as applicable (Section 11.6.5)

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

[b] If the 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 during the Treatment Period will continue to complete all scheduled study visits for assessments following completion of the ETT Visit (Section 9.1.5).

[c] The Safety Follow-Up Visit is required for all subjects, unless the subject completes the Week 8 Visit and has enrolled in an open-label study within 28 days after the last dose of study drug (Section 9.1.4). If an 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 (Section 9.1.5).

[d] To enter the Treatment Period, conditions for entry (Section 9.1.3) must be satisfied.

3 SCHEDULE OF ASSESSMENTS

Schedules of assessments are in Table 3-1 and Table 3-2.

All visits will be scheduled relative to the Day 1 Visit (first dose of randomized study drug in the Treatment Period). For example, the Week 8 (± 5 days) Visit would occur after 8 weeks of study drug administration in the Treatment Period has been completed.

The Cystic Fibrosis Questionnaire-Revised (CFQ-R) must be completed before any other assessment (except signing of the informed consent form [ICF]) at relevant clinic visits. Remaining assessments may be performed in any order when more than 1 assessment is required at a particular time point. All assessments will be performed before study drug dosing (Section 9.6.1), unless noted otherwise.

Screening assessments will be used to confirm that subjects meet the eligibility criteria (Table 3-1). The investigator (or an appropriate authorized designee) will obtain informed consent and assent, if applicable, from each subject before any study procedure takes place.

9.1.1.1 Repetition of Screening Assessment(s)

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

9.1.1.2 Rescreening

Subjects who have not entered the Run-in Period may be rescreened once. If a subject is rescreened, all screening assessments will be repeated, except for the following assessments, which are not required to be repeated:

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

If a subject is rescreened, a new screening window will begin when the first rescreening assessment has been initiated.

9.1.1.3 Extension of Screening Period Window

A subject may have the Screening Period window extended by 2 weeks for the following reasons:

- Repetition of the Screening Period assessments (Section 9.1.1.1)
- Unexpected operational or logistic delays, or to meet the eligibility criteria
- Scheduling of OE (for subjects <18 years of age on the date of informed consent, Section 11.6.6)

9.1.2 Run-in Period

The Run-in Period has a 4-week duration and is designed to establish a reliable on-treatment (IVA for the IVA comparator group and TEZ/IVA for the TEZ/IVA comparator group) baseline for the Treatment Period. The first dose of open-label IVA or TEZ/IVA (as applicable) will be administered at the Day -28 Visit. The last dose of open-label IVA will be administered in the evening on Day -1 (1 day before the Day 1 Visit).

A subject's screening *CFTR* genotype **must** confirm eligibility before the subject enters the Run-in Period (Section 11.6.2).

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

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

Abbreviation	Definition
t-test	statistical test used when the independent variable is binary and the dependent variable is continuous
ULN	upper limit of normal
US	United States
WHO-DD	World Health Organization Drug-Dictionary

- Hemoglobin <10 g/dL
- Total bilirubin ≥2 × upper limit of normal (ULN)
- Aspartate transaminase (AST), alanine transaminase (ALT), or gamma-glutamyl transferase (GGT) ≥3 × ULN
- Abnormal renal function defined as estimated glomerular filtration rate ≤50 mL/min/1.73 m^2 (calculated by the Modification of Diet in Renal Disease Study Equation)[13,14] for subjects ≥18 years of age, or ≤45 mL/min/1.73 m^2 (calculated by the Counahan-Barratt equation)[15] for subjects 12 to 17 years of age (inclusive)

3. An acute upper or lower respiratory infection, pulmonary exacerbation (PEx), or change in therapy (including antibiotics) for sinopulmonary disease within 28 days before the first dose of study drug in the Run-in Period (Day -28).
4. Lung infection with a microbial pathogen that is associated with a more rapid decline in pulmonary status (including, but not limited to, *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*). For subjects who have had a history of a positive culture, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
   - The subject has not had respiratory tract culture positive for these organisms within the 12 months before the date of informed consent.
   - The subject has had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent one within the 6 months before the date of informed consent.
5. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug in the Run-in Period (Day -28).
6. Ongoing or prior participation in a study of an investigational treatment other than a Vertex CFTR modulator within 28 days or 5 terminal half-lives (whichever is longer) before screening. The duration of the elapsed time may be longer if required by local regulations.
7. Use of prohibited medications as defined in Table 9-3 within the specified window before the first dose of study drug in the Run-in Period (Day -28).
8. Pregnant or breast-feeding females. All female subjects, regardless of childbearing potential status, must have negative pregnancy tests at the Screening Visit (Day -56) and at the Day -28 Visit, before the first dose of study drug in the Run-in Period.
9. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site. However, an adult (aged 18 years or older) who is a relative of a study staff member may be enrolled in the study provided that
   - the adult lives independently of and does not reside with the study staff member, and
   - the adult participates in the study at a site other than the site at which the family member is employed.

- Subjects who are taking inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.
- Subjects who cycle onto and off of an inhaled antibiotic should continue on their prior schedule. The timing of the first dose of study drug on the Day 1 Visit should be synchronized as closely as possible (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 10 mg/day chronically, or up to 60 mg daily for up to 5 days.
- VX-445 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 must have their spirometry assessments performed according to the guidelines provided in Section 11.5.1.

9.6 Administration

9.6.1 Dosing

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

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

1. It is recommended that the dose be taken within 30 minutes of the start of the meal or snack.
2. In the IVA comparator group, study drug in the Run-in Period will be administered as 1 IVA tablet in the morning and 1 IVA tablet in the evening. Study drug in the Treatment Period will be administered as 2 fixed-dose combination (FDC) TC tablets or matching placebo tablets and 1 IVA tablet or matching placebo tablet in the morning, and 1 IVA tablet in the

assessment of the spirometry results will be used for the screening assessment and determination of eligibility.

See Section 10.7.1 for information about access to spirometry results.

The measured spirometric values listed below will be converted to percent predicted values using the standard equations of GLI.[11]

- Forced expiratory volume in 1 second (FEV_1) (L)
- Forced vital capacity (FVC) (L)
- FEV_1/FVC (ratio)
- Forced expiratory flow, midexpiratory phase ($FEF_{25\%-75\%}$) (L/s)

11.5.2 Cystic Fibrosis Questionnaire-Revised

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

Subjects will be asked to complete the CFQ-R in their native language, if validated translations are available.[16, 17] If there is no validated translation available in the subject's native language, the subject will not complete the questionnaire. Copies of the CFQ-R used will be provided in the Study Reference Manual. Validated translations of the CFQ-R, if available, will be provided for participating centers in non-English-speaking countries.[18, 19]

The CFQ-R will be completed before any other assessments are performed at that visit.

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

11.6 Safety

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

For subjects <18 years of age on the date of informed consent, OEs will also be performed at screening (if not done within the preceding 3 months).

11.6.1 Adverse Events

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

11.6.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory, with the exception of the urine pregnancy tests. On Day -28 and Day 1, blood samples will be collected before the first dose of study drug in each study period.

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

For the 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.

11.6.3 Physical Examinations and Vital Signs

A physical examination of all body systems and vital signs assessment will be performed at screening and select study visits (see Table 3-1 and Table 3-2). At other visits, symptom-directed physical examinations and symptom-directed vital signs assessments can be performed at the discretion of the investigator or healthcare provider.

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

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

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

11.6.4 Pulse Oximetry

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

11.6.5 Electrocardiograms

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

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

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

To ensure the safety of the subjects, a qualified individual at the study site will make comparisons to baseline measurements. If the QTcF is increased by >60 msec from the baseline or an absolute QTcF value is ≥500 msec for any scheduled ECG, 2 additional ECGs will be

13.2.4 Access to Records

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

13.2.5 Subject Privacy

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

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

13.2.6 Record Retention

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

13.2.7 Study Termination

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

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

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