# 1 TITLE PAGE

*VERTEX PHARMACEUTICALS INCORPORATED*

# Clinical Study Protocol

**A Phase 2, Randomized, Double-blind Study to Evaluate the Efficacy and Safety of VX-561 in Subjects Aged 18 Years and Older With Cystic Fibrosis**

**Vertex Study Number: VX18-561-101**

[redacted]

**EudraCT Number: 2018-003970-28**

**Date of Protocol:** 03 October 2019 (Version 2.0)

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# 2 PROTOCOL SYNOPSIS

**Title** A Phase 2, Randomized, Double-blind Study to Evaluate the Efficacy and Safety of VX-561 in Subjects Aged 18 Years and Older With Cystic Fibrosis

**Brief Title** A Study to Evaluate Efficacy and Safety of VX-561 in Subjects Aged 18 Years and Older With Cystic Fibrosis

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

**Objectives**

**Primary Objective**

- To evaluate the efficacy of VX-561

**Secondary Objectives**

- To evaluate the pharmacodynamic (PD) effect of VX-561
- To evaluate the pharmacokinetics (PK) of VX-561, IVA, and relevant metabolites
- To evaluate the safety and tolerability of VX-561

**Endpoints**

**Primary Endpoint**

- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline at Week 12

**Secondary Endpoints**

- Absolute change in sweat chloride concentrations from baseline at Week 12
- PK parameters of VX-561, IVA, and relevant metabolites
- Safety and tolerability, based on the assessment of adverse events (AEs), laboratory test results, standard 12-lead ECGs, vital signs, and pulse oximetry

**Number of Subjects** Approximately 88 subjects were planned to enroll in 5 treatment arms (25 mg once daily [qd] VX-561, 50 mg qd VX-561, 150 mg qd VX-561, 250 mg qd VX-561, and IVA 150 mg every 12 hours [q12h]) in a ratio of 1:2:2:2:1 under the original protocol. The 25 mg qd VX-561 and 50 mg qd VX-561 treatment arms were discontinued; 44 subjects had been enrolled and randomized to the 5 treatment arms at this point. The remaining subjects planned to enroll will be randomized 2:2:1 to 3 treatment arms (250 mg qd VX-561, 150 mg qd VX-561, and IVA 150 mg q12h).

**Study Population** Male subjects and female subjects with CF who have a gating mutation and were previously taking a stable dose of IVA, ages 18 and older

**Investigational Drugs**

**Active substance**: VX-561

**Activity**: CFTR potentiator (increased $Cl^-$ secretion)

**Strength and route of administration**: 50-mg and 25-mg VX-561 tablets for oral administration

**Active substance**: IVA (VX-770)

**Activity**: CFTR potentiator (increased $Cl^-$ secretion)

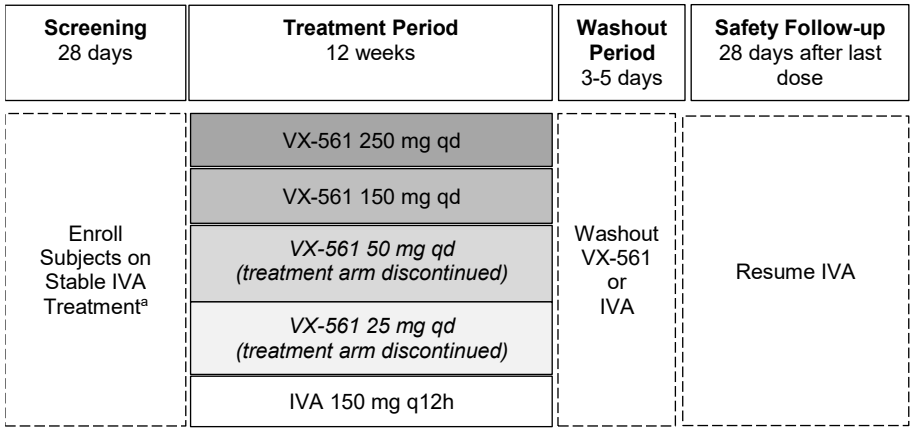
**Strength and route of administration**: 150-mg film-coated tablet for oral administration

**Study Duration** Including the Screening Period, each subject will participate in the study for approximately 20 weeks

**Study Design** This is a Phase 2 study of VX-561 monotherapy. A schematic of the study design is shown in Figure 2-1, which is randomized, double-blind, parallel-group, and active-controlled. The study will evaluate 4 dose levels of VX-561 in subjects with CF who have a gating mutation and were previously taking a stable dose of IVA. Randomization will be stratified by $ppFEV_1$ value at screening (<70 versus ≥70).

The original protocol included 25 mg qd VX-561 and 50 mg qd VX-561 treatment arms; both treatment arms were discontinued in the current protocol ([redacted]).

**Figure 2-1 VX18-561-101 Study Design**




[a] Approximately 88 subjects were planned to enroll in 5 treatment arms (25 mg qd VX-561, 50 mg qd VX-561, 150 mg qd VX-561, 250 mg qd VX-561, and IVA 150 mg q12h) in a ratio of 1:2:2:2:1 under the original protocol. The 25 mg qd VX-561 and 50 mg qd VX-561 treatment arms were discontinued; 44 subjects had been enrolled and randomized to the 5 treatment arms at this point. The remaining subjects planned to enroll will be randomized 2:2:1 to 3 treatment arms (250 mg qd VX-561, 150 mg qd VX-561, and IVA 150 mg q12h).

**Study Rationale** This study is being conducted to evaluate the efficacy and PD effect (i.e., change in sweat chloride) for a range of VX-561 doses to support VX-561 dose selection for future studies, including studies of VX-561 in triple combination (TC) with CFTR correctors, such as VX-121 and TEZ.

Subjects will be on stable IVA treatment at baseline and will be randomized to study drug treatment groups on Day 1 (VX-561 or IVA). Change in $ppFEV_1$ from IVA baseline is the primary endpoint. However, dose selection of VX-561 for future studies may consider the totality of data, including exposure-response analyses for efficacy ($ppFEV_1$) and PD (sweat chloride) endpoints.

**Assessments** **Safety:** AEs, clinical laboratory assessments, clinical evaluation of vital signs, ECGs, physical examinations, and pulse oximetry

**Efficacy:** Spirometry

**PD:** Sweat chloride

**PK:** VX-561, IVA, and relevant metabolites

**Statistical Analyses**

The following efficacy analyses will be conducted for $ppFEV_1$ and sweat chloride:

The analysis of the absolute change in $ppFEV_1$ from baseline at Week 12 will be based on a mixed-effects model for repeated measures (including 250 mg qd VX-561, 150 mg qd VX-561, and IVA 150 mg q12h treatment arms only). The primary results will be the within-group comparison for each VX-561 arm. The adjusted mean with a 2-sided 95% CI will be provided. Between-group estimates of each VX-561 arm and IVA arm will also be provided.

The analysis of the absolute change from baseline in sweat chloride at Week 12 will be conducted similarly to $ppFEV_1$ (including 250 mg qd VX-561, 150 mg qd VX-561, and IVA 150 mg q12h treatment arms only).

A sequential approach will be used to perform the population PK/PD analyses for VX-561. Bayesian estimates of individual PK parameters from the final population PK model will be used to simulate PK profiles for each subject, which will be used in exposure-response models to describe changes in sweat chloride and ppFEV1 from baseline.

Safety analyses for all treatment arms (including the 25 mg qd VX-561 and 50 mg qd VX-561 treatment arms that were discontinued) will be conducted to support the dose selection. Descriptive analyses will be provided for the safety data comprising AEs, clinical laboratory assessments, ECGs, vital signs, and pulse oximetry; no statistical hypothesis testing will be performed. The PK results for VX-561, IVA, and relevant metabolites will be reported with descriptive statistics.

Sample size

Based on the initial study design that included 4 dose groups of VX-561 and an IVA 150 mg q12h dose group, assuming a within-group SD of 7 percentage points and a 10% dropout rate at Week 12: a sample size of 22 subjects in the 50, 150, and 250 mg qd VX-561 arms will provide a 95% CI of ± 3.4 percentage points around the observed mean absolute change in $ppFEV_1$ from baseline at Week 12, based on 2-sided, 1-sample t statistics; a sample size of 11 subjects in the other arms will provide a 95% CI of ± 5.4 percentage points around the observed mean.

Following discontinuation of the 25 mg qd VX-561 and 50 mg qd VX-561 treatment arms, the remaining subjects planned to enroll will be randomized in a 2:2:1 ratio to the 3 current treatment arms with a sample size of approximately 28 subjects for the 250 mg qd VX-561 treatment arm, approximately 28 subjects for the 150 mg qd VX-561 treatment arm, and approximately 14 subjects for the IVA 150 mg q12h treatment arm. The total study sample size including discontinued arms and current arms is approximately maintained as planned (N = 88). Under the same assumption as the original design (within-group SD of 7 percentage points and 10% dropout rate at Week 12): a sample size of 28 subjects in the 250 mg qd VX-561 and 150 mg qd VX-561 arms will provide a 95% CI of ± 2.9 percentage points around the observed mean absolute change in $ppFEV_1$ from baseline at Week 12, based on 2-sided, 1-sample t statistics; a sample size of 14 subjects in the IVA 150 mg q12h arm will provide a 95% CI of ± 4.4 percentage points around the observed mean.

**IDMC Reviews**

An independent data monitoring committee (IDMC) will conduct safety reviews of study data as outlined in the IDMC charter. The planned IDMC reviews (with reference to number of subjects and duration of study) will be specified in the IDMC charter.

# 3 SCHEDULE OF ASSESSMENTS

The schedule of assessments is provided in Table 3-1.

**Table 3-1 Study VX18-561-101: Screening Visit, Treatment Period, Washout Visit, and Safety Follow-up Visit**

| Event/Assessment[a] | Screening Visit[b] | Treatment Period | | | | | Washout Visit | ETT Visit[c] | Safety Follow-up 28 (± 7) Days After Last Dose of Study Drug |
|---|---|---|---|---|---|---|---|---|---|
| | Day -28 to Day -1 | Day 1 | Day 15 (± 3 day) | Week 4 (± 5 days) | Week 8 (± 5 days) | Week 12 (± 5 days) | 4 (± 1) Days After Week 12 Visit | | |
| Outpatient visits | X | X | X | X | X | X | X | X | X |
| Randomization[d] | | X | | | | | | | |
| Demographics | X | | | | | | | | |
| Medical history | X | | | | | | | | |
| Weight[e] | X | X | X | X | X | X | | X | X |
| Height[e] | X | | | | | | | | |
| Vital signs[f] | X | X | X | X | X | X | X | X | X |
| Pulse oximetry[f] | X | X | X | X | X | X | X | X | X |
| Physical examination[g] | Complete | Abbrev. | | Abbrev. | Abbrev. | Abbrev. | | Abbrev. | Abbrev. |
| Standard 12-lead ECG[h] | X | X | | X | | | | X | X |
| Sweat chloride[i, j] | X | X | X | X | X | X | X | X | X |

[a] All assessments will be performed before dosing, unless noted otherwise. Assessments may be performed in any order when more than 1 assessment is required at a particular time point. Assessments that are collected before and after dosing will only be collected once if study drug is not administered on the day of the visit (i.e., premature discontinuation of study drug treatment).

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

[c] If the subject prematurely discontinues study drug, an ETT Visit should be scheduled as soon as possible after the decision to terminate study drug treatment. Additional PK samples and safety assessments may also be performed at the discretion of the investigator. See Section 9.1.5 for additional details.

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

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

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

[g] Complete and abbreviated PEs are described in Section 11.5.3.

[h] Standard 12-lead ECGs will be performed in the supine position after the subject has been at rest for at least 5 minutes. See Section 8.2 for information about the ECG assessment for study eligibility.

[i] Sweat chloride assessments should be performed at approximately the same time at every visit. See Section 8.1 for information about the sweat chloride assessment for study eligibility.

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

## Table 3-1 Study VX18-561-101: Screening Visit, Treatment Period, Washout Visit, and Safety Follow-up Visit

| Event/Assessment[a] | Screening Visit[b] | Treatment Period | | | | | Washout Visit | ETT Visit[c] | Safety Follow-up 28 (± 7) Days After Last Dose of Study Drug |
|---|---|---|---|---|---|---|---|---|---|
| | Day -28 to Day -1 | Day 1 | Day 15 (± 3 day) | Week 4 (± 5 days) | Week 8 (± 5 days) | Week 12 (± 5 days) | 4 (± 1) Days After Week 12 Visit | | |
| Spirometry[k] | X | X | X | X | X | X | X | X | X |
| Urinalysis[j] | X | X | | | | | | X | X |
| β-hCG[l] | Serum | Urine | | Urine | | | | Serum | Serum |
| *CFTR* genotype[m] | X | | | | | | | | |
| FSH[n] | X | | | | | | | | |
| Serum chemistry and hematology[j] | X | X | X | X | X | X | | X | X |
| Coagulation[j] | X | X | | | | X | | X | X |
| PK sampling[o] | X | X | X | X | X | X | X | X | X |
| VX-561 or IVA dosing[p] | | Day 1 through Week 12 | | | | | | | |
| Adverse events | Continuous from signing of ICF through Safety Follow-up Visit | | | | | | | | |
| Medications review[q] | Continuous from signing of ICF through Safety Follow-up Visit | | | | | | | | |
| Treatment and procedures review | Continuous from signing of ICF through Safety Follow-up Visit | | | | | | | | |

[k] Spirometry may be performed pre- or post-bronchodilator at the Screening Visit. At other study visits, spirometry will be done pre-bronchodilator, before the morning dose of study drug, and should be performed at approximately the same time at every visit.

[l] The serum β-hCG test is to be performed for all female subjects at Screening. Subsequent urine or serum β-hCG tests are to be performed as indicated for women of childbearing potential. A definition of non-childbearing potential is provided in Section 11.5.5.1.

[m] *CFTR* genotyping will be performed for all subjects. If the screening *CFTR* genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used to establish eligibility. Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study.

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

[o] Blood samples will be collected for PK analysis of VX-561 and metabolites or IVA and metabolites. The sample collected at Screening will be collected without regard to time of IVA dosing. On Day 1, samples will be collected before dosing (0 hours) and at 4 hours after dosing (relative to the morning dose). At Day 15, Week 4, Week 8, and Week 12, a predose sample will be collected before the morning dose. In a subset of subjects (up to approximately 20 subjects), additional samples will be collected at the Week 4 visit at 1, 2, 4, and 6 hours after dosing (relative to the morning dose). At the Washout Visit, a single sample will be collected prior to resumption of IVA. A single sample will be collected at the Safety Follow-up Visit for analysis of IVA for those subjects who resume IVA therapy. Acceptable PK sampling windows are provided in Table 11-1. At the ETT Visit, a single blood sample for PK analysis will be collected.

[p] Study drug will be administered orally twice daily (Section 9.6). The last dose of study drug will be the morning dose on the Week 12 Visit. Subjects may resume their prior IVA therapy after the Washout Visit.

[q] All medications taken from 28 days before the Screening Period through the end of the study will be recorded (Section 9.5).

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## List of Tables



## List of Figures

## List of Abbreviations

| Abbreviation | Definition |
|---|---|
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine transaminase |
| AST | aspartate transaminase |
| AUC | area under the concentration versus time curve |
| $AUC_{0-24h}$ | AUC from the time of dosing to 24 hours |
| β-hCG | beta-human chorionic gonadotropin |
| BMI | body mass index |
| bpm | beats per minute |
| CD | compact disc |
| CF | cystic fibrosis |
| *CFTR* | *CF transmembrane conductance regulator gene* |
| CFTR | CF transmembrane conductance regulator protein |
| CI | confidence interval |
| $C_{max}$ | maximum observed concentration |
| CMC | chemistry, manufacturing, and controls |
| CPAP | clinical pharmacology analysis plan |
| CRF | case report form |
| CRO | contract research organization |
| CTCAE | Common Terminology Criteria for Adverse Events |
| $C_{trough}$ | predose concentration |
| CYP | cytochrome P450 |
| ECG | electrocardiogram |
| EDC | electronic data capture |
| EENT | eyes, ears, nose, and throat |
| ETT | Early Termination of Treatment |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| [redacted] | [redacted] |
| $FEV_1$ | forced expiratory volume in 1 second |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| GI | gastrointestinal |
| GLI | Global Lung Function Initiative |
| GPP | Good Publication Practices |
| GPS | Global Patient Safety |
| HBE | human bronchial epithelial |
| HIPAA | Health Insurance Portability and Accountability Act |
| HR | heart rate |
| ICF | informed consent form |
| ICH | International Council for Harmonization |
| IDMC | independent data monitoring committee |

| Abbreviation | Definition |
|---|---|
| ICMJE | International Committee of Medical Journal Editors |
| IEC | independent ethics committee |
| IRB | institutional review board |
| IVA | ivacaftor |
| IWRS | interactive web response system |
| LUM | lumacaftor |
| max | maximum value |
| MedDRA | Medical Dictionary for Regulatory Activities |
| min | minimum value |
| MMRM | mixed-effects model for repeated measures |
| n | size of subsample |
| PC | publication committee |
| PD | pharmacodynamic, pharmacodynamics |
| PE | physical examination |
| PI | pancreatic insufficient |
| PK | pharmacokinetic, pharmacokinetics |
| $ppFEV_1$ | percent predicted forced expiratory volume in 1 second |
| PR | PR interval, segment |
| PT | Preferred Term |
| q12h | every 12 hours |
| qd | daily |
| QRS | the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization |
| QT | QT interval |
| QTc | QT interval corrected |
| QTcF | QT interval corrected by Fridericia's formula |
| RNA | ribonucleic acid |
| RR | interval from the onset of 1 QRS complex to the next |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SC | steering committee |
| SD | standard deviation |
| SET | study execution team |
| SI | SI units (International System of Units) |
| SOC | System Organ Class |
| SUSAR | suspected, unexpected, serious adverse reaction |
| TC | triple combination |
| TE | treatment-emergent |
| TEAE | treatment-emergent adverse event |
| TEZ | tezacaftor |
| ULN | upper limit of normal |
| USA | United States of America |
| WHO-DD | World Health Organization-Drug Dictionary |

# 5 INTRODUCTION

## 5.1 Background

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

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

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

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

The therapeutic activity of CFTR correctors and potentiators has been established with products that were developed by Vertex and approved for the treatment of CF: ivacaftor (IVA) monotherapy (Kalydeco®), lumacaftor (LUM) in combination with IVA (Orkambi®), and tezacaftor (TEZ) in combination with IVA (Symdeko™, Symkevi®). Kalydeco, Orkambi, and Symdeko are approved to treat CF in patients with specific *CFTR* genotypes. TEZ and LUM are first-generation CFTR correctors that improve the processing and trafficking of mutated CFTR protein, resulting in an increase in the quantity of protein at the cell surface. IVA increases the open-channel probability of the mutated CFTR protein that has been delivered to the cell surface, thereby enhancing total chloride transport. For the most common CF-causing mutation, *F508del*, the combined effect of either LUM and IVA or TEZ and IVA is increased quantity and function of F508del-CFTR at the cell surface.

VX-561 is a deuterated isotope of IVA with a specific pattern of 9 substituted deuteriums. In vitro data indicate similar potency of VX-561 in human bronchial epithelial (HBE) cells relative to IVA. Safety pharmacology and nonclinical toxicology studies of VX-561 demonstrate a similar safety profile relative to IVA. Phase 1 clinical studies in healthy subjects have shown that VX-561 had a reduced rate of clearance, increased exposure, greater plasma levels at 24 hours, and a longer half-life compared to IVA, thereby supporting once daily dosing (refer to VX-561 Investigator's Brochure). In healthy subject studies to date, the safety profile of VX-561 is considered similar to IVA.

## 5.2 Study Rationale

This study is being conducted to evaluate the efficacy and pharmacodynamic (PD) effect (i.e., change in sweat chloride) for a range of VX-561 doses to support VX-561 dose selection for future studies, including studies of VX-561 in triple combination (TC) with CFTR correctors, such as VX-121 and TEZ. Subjects will be on stable IVA treatment at baseline and will be randomized to study drug treatment groups on Day 1 (VX-561 or IVA). Change in $ppFEV_1$ from IVA baseline is the primary endpoint. However, dose selection of VX-561 for future studies may consider the totality of data, including exposure-response analyses for efficacy (percent predicted forced expiratory volume in 1 second [$ppFEV_1$]) and PD (sweat chloride) endpoints.

# 6 STUDY OBJECTIVES

## 6.1 Primary Objective

- To evaluate the efficacy of VX-561

## 6.2 Secondary Objectives

- To evaluate the PD effect of VX-561
- To evaluate the pharmacokinetics (PK) of VX-561, IVA, and relevant metabolites
- To evaluate the safety and tolerability of VX-561

# 7 STUDY ENDPOINTS

## 7.1 Primary Endpoint

- Absolute change in $ppFEV_1$ from baseline at Week 12

## 7.2 Secondary Endpoints

- Absolute change in sweat chloride concentrations from baseline at Week 12
- PK parameters of VX-561, IVA, and relevant metabolites
- Safety and tolerability, based on the assessment of adverse events (AEs), laboratory test results, standard 12-lead ECGs, vital signs, and pulse oximetry

# 8 STUDY POPULATION

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

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

## 8.1 Inclusion Criteria

1. Subject will sign and date an informed consent form (ICF).
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Subjects (males and females) aged 18 years or older on the date of informed consent.

4. Receiving IVA treatment with no interruptions for at least 28 days before screening.
5. Tolerating IVA therapy as judged by the investigator.
6. Female subjects must have a negative pregnancy test at Screening.
7. Body weight ≥35 kg.
8. Subjects must be able to produce a valid (quantity-sufficient) sweat sample at screening. If the initial screening collection results in insufficient sweat volume, then the sweat chloride collection may be repeated.
9. Confirmed diagnosis of CF as determined by the investigator.
10. Has 1 of the following mutations in their CF gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R*. If the screening *CFTR* genotype result is not received before randomization, a previous *CFTR* genotype laboratory report may be used to establish eligibility. Subjects who have been enrolled and whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9).
11. Subjects must have a forced expiratory volume in 1 second ($FEV_1$) ≥40% and ≤100% of predicted normal for age, sex, and height (equations of the Global Lung Function Initiative [GLI])[8] at the Screening Visit. Spirometry measurements must meet American Thoracic Society/European Respiratory Society criteria[9] for acceptability and repeatability.
12. Stable CF disease as judged by the investigator.
13. Willing to remain on a stable CF treatment regimen (other than protocol-specified changes in CFTR modulator regimen) through the Safety Follow-up Visit (Section 9.5).

## 8.2 Exclusion Criteria

1. History of any comorbidity that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject.
2. History of clinically significant cirrhosis with or without portal hypertension.
3. Any of the following abnormal laboratory values at screening:
   - Hemoglobin <10 g/dL
   - Total bilirubin ≥2 × upper limit of normal (ULN)
   - Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP) ≥3 × ULN
   - Abnormal renal function defined as glomerular filtration rate ≤50 mL/min/1.73 $m^2$ (calculated by the Modification of Diet in Renal Disease Study Equation)[10,11] for subjects ≥18 years of age
4. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for sinopulmonary disease within 28 days before the first dose of study drug.
5. Lung infection with organisms associated with a more rapid decline in pulmonary status (e.g., *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*). For

subjects who have had a history of a positive culture, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:

- The subject has not had a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent.
- The subject has had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent 1 within the 6 months before the date of informed consent.

6. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug.
7. Standard 12-lead ECG demonstrating QTcF >450 msec at screening. If QTcF exceeds 450 msec, the ECG will be repeated 2 more times, and the average of the 3 QTcF values will be used to determine the subject's eligibility.
8. History of solid organ or hematological transplantation.
9. History of alcohol or drug abuse in the past year, including, but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator.
10. Ongoing or prior participation in a study of an investigational treatment with the exception of the following:
    - Ongoing or prior participation in an investigational study of a Vertex CFTR modulator. A washout period of 28 days must elapse before Day 1.
    - For prospective subjects with ongoing or prior participation in all other interventional studies, a washout period of 28 days or 5 terminal half-lives (whichever is longer) must elapse before screening. The duration of the elapsed time may be longer if required by local regulations.
    - Ongoing participation in a noninterventional study (including observational studies and studies requiring assessments without administration of study drug or assignment to other interventions) is permitted.
11. Use of prohibited medications as defined in Table 9-1, within the specified window before the first dose of study drug.
12. Pregnant or nursing female subjects.
13. Subject, or close relative of the subject, is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site. However, an adult (aged 18 years or older) who is a relative of a study staff member may be enrolled in the study provided that:
    - the adult lives independently of and does not reside with the study staff member, and
    - the adult participates in the study at a site other than the site at which the family member is employed

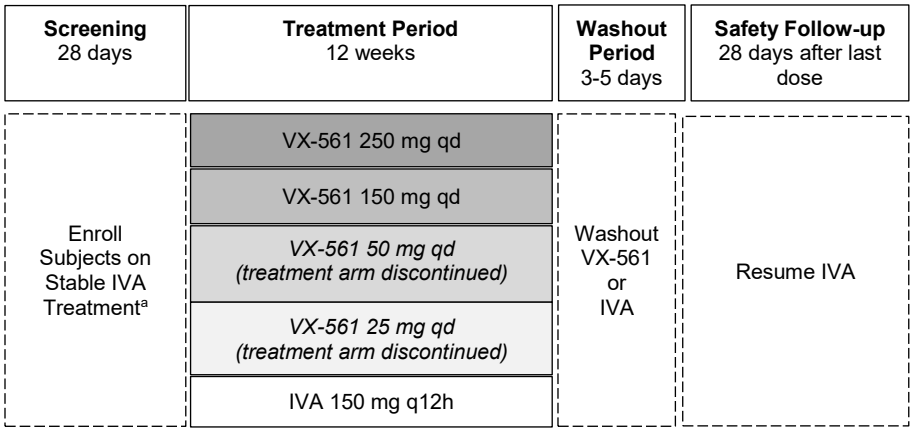
# 9 STUDY IMPLEMENTATION

## 9.1 Study Design

This is a Phase 2 study of VX-561 monotherapy. A schematic of the study design is shown in Figure 9-1, which is randomized, double-blind, parallel-group, and active-controlled. The study will evaluate 4 dose levels of VX-561 in subjects with CF who have a gating mutation and were previously taking a stable dose of IVA. Randomization will be stratified by ppFEV$_1$ value at screening (<70 versus ≥70).

The original protocol included 25 mg once daily (qd) and 50 mg qd VX-561 treatment arms; both were discontinued in the current protocol ([redacted]).

**Figure 9-1 VX18-561-101 Study Design**




[a] Approximately 88 subjects were planned to enroll in 5 treatment arms (25 mg qd VX-561, 50 mg qd VX-561, 150 mg qd VX-561, 250 mg qd VX-561, and IVA 150 mg every 12 hours [q12h]) in a ratio of 1:2:2:2:1 under the original protocol. The 25 mg qd VX-561 and 50 mg qd VX-561 treatment arms were discontinued; 44 subjects had been enrolled and randomized to the 5 treatment arms at this point. The remaining subjects planned to enroll will be randomized 2:2:1 to 3 treatment arms (250 mg qd VX-561, 150 mg qd VX-561, and IVA 150 mg q12h).

### 9.1.1 Screening

Screening Visit assessments are listed in Table 3-1.

The Screening Period will occur within 28 days before administration of study drug. Screening assessments will be used to confirm that subjects meet eligibility criteria. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent from each subject before any study procedures takes place.

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

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

#### 9.1.1.2 Rescreening

Subjects may be rescreened only once. If a subject is rescreened, all screening assessments will be repeated except for *CFTR* genotyping, follicle-stimulating hormone (FSH) level (if serum

FSH level was ≥40 mIU/mL during prior screening), and sweat chloride level. If a subject is rescreened, the new screening window will begin once the first rescreening assessment has been initiated.

#### 9.1.1.3 Extension of Screening Period Window

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

- Repetition of the Screening assessments (Section 9.1.1.1)
- Unexpected operational or logistic delays, or to meet the eligibility criteria
- Repetition of spirometry assessment if results are of poor quality

### 9.1.2 Treatment Period

The Treatment Period will last approximately 12 weeks. Treatment Period assessments are listed in Table 3-1. Dosing details are in Section 9.6.

### 9.1.3 Washout Period

The Washout Period will last approximately 4 days.

The study visits during the Washout Period will occur as shown in Table 3-1.

### 9.1.4 Follow-up

Subjects will have a Safety Follow-up Visit 28 (± 7) days after the last dose of study drug. Safety Follow-up Visit assessments are listed in Table 3-1.

### 9.1.5 Early Termination of Treatment OR Early Discontinuation

If a subject prematurely discontinues study treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. Subjects who prematurely discontinue treatment will also be required to complete the Safety Follow-up Visit, approximately 28 (± 7) days after their last dose of study drug. The assessments performed at the Safety Follow-up Visit are listed in Table 3-1.

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

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

If a subject withdraws consent for the study, no further assessments will be performed, and no additional data should be collected. Vertex may retain and continue to use any data and samples collected before such withdrawal of consent.

### 9.1.6 Lost to Follow-up

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

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

### 9.1.7 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 12.3.6). 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

An interactive web response system (IWRS) will be used to assign subjects to treatment. A randomization list will be produced by Vertex Biostatistics or a qualified randomization vendor. The Vertex study biostatistician will review and approve the dummy randomization list. The final randomization list will be reviewed and approved by a designated unblinded biostatistician who is not a member of the study execution team (SET).

Subjects will be assigned a unique subject number. Only subjects who have completed screening assessments and are eligible for participation in the study will be randomized to receive study drug during the Treatment Period. Randomization will be stratified by ppFEV$_1$ (<70 versus ≥70) determined during screening.

Approximately 88 subjects were planned to enroll in 5 treatment arms (25 mg qd VX-561, 50 mg qd VX-561, 150 mg qd VX-561, 250 mg qd VX-561, and IVA 150 mg q12h) in a ratio of 1:2:2:2:1 under the original protocol. The 25 mg qd VX-561 and 50 mg qd VX-561 treatment arms were discontinued; 44 subjects had been enrolled and randomized to the 5 treatment arms at this point. The remaining subjects planned to enroll will be randomized 2:2:1 to 3 treatment arms (250 mg qd VX-561, 150 mg qd VX-561, and IVA 150 mg q12h).

## 9.3 Rationale for Study Elements

### 9.3.1 Study Design

Subjects will continue their stable IVA treatment through screening, and then be randomized to study drug treatment groups on Day 1 (VX-561 or IVA). The efficacy and PD of VX-561 will be assessed after 12 weeks of randomized treatment. IVA (150 mg every 12 hours [q12h]) is included as a reference arm, but with unequal randomization to provide greater information on VX-561 dose-ranging. After the Treatment Period, a 3- to 5-day Washout Period where subjects will take no CFTR modulators is included to collect additional PK and PD data and enable a more thorough evaluation of VX-561 exposure-response relationships.

Following completion of the Washout Period, subjects will resume their prior therapy with commercial IVA.

### 9.3.2 Study Population

The study will enroll subjects with CF with a gating mutation (see Section 8.1) to ensure a relatively homogenous population to evaluate the efficacy, PK, and PD of VX-561 across a range of doses relative to IVA.

### 9.3.3 Study Drug Dose and Duration

**VX-561**

Four dose levels of VX-561 will be evaluated to provide a broad range of exposure for exposure-response analyses. The original protocol included 25 mg qd VX-561 and 50 mg qd VX-561 treatment arms; both treatment arms were discontinued in the current protocol [redacted]. A VX-561 dose regimen of 150 mg qd provides exposure similar to IVA 150 mg q12h, including $C_{max}$, $AUC_{0\text{-}24h}$, and $C_{trough}$. Based on the similarity of VX-561 and IVA in vitro potency and efficacy in HBE cells, this dose is predicted to provide the same effect as IVA on CFTR potentiation, and thus is also expected to result in a similar PD (i.e., sweat chloride) and efficacy (i.e., $ppFEV_1$) response. The 250 mg qd dose of VX-561 is included to provide a range of exposures to enable a more robust exposure-response analysis.

The 12-week treatment duration is considered sufficient to avoid any carryover of the efficacy or PD effect from stable IVA treatment and avoid the need for an extended washout of IVA before the start of the Treatment Period.

**IVA**

The IVA dose regimen of 150 mg q12h is the approved regimen for treatment of CF in subjects aged 6 years and older who have 1 mutation in the *CFTR* gene that is responsive to IVA based on clinical and/or in vitro assay data.

### 9.3.4 Rationale for Study Assessments

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

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

## 9.4 Study Restrictions

Study restrictions are summarized in Table 9-1. VX-561 and IVA are metabolized extensively via CYP3A. Therefore, use of moderate and strong inducers or inhibitors of CYP3A, which have the potential to alter the exposure of VX-561 or IVA will be prohibited.

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

**Table 9-1 Study Restrictions**

| Restricted Medication/Food/Activity [a] | Timing of Restriction | |
|---|---|---|
| | **Start** | **Stop** |
| Moderate and strong CYP3A inducers or inhibitors (except ciprofloxacin), including grapefruit or grapefruit juice | None allowed within 14 days before the first dose of study drug | None allowed through the Safety Follow-up Visit |
| CFTR modulators other than study drug (e.g., Symdeko/ Symkevi) | None allowed within 28 days before first dose of study drug | None allowed through the Safety Follow-up Visit |

[a] See Section 9.5 for guidance on concomitant medications.

## 9.5 Prior and Concomitant Medications

Subjects will abstain from all concomitant medications as described in the exclusion criteria (Section 8.2) and Study Restrictions (Table 9-1).

All medications taken from 28 days before the Screening Period through the end of the study will be recorded with indication, route of administration, and start and stop dates of administration. All subjects will be questioned about medications from signing of the ICF through the Safety Follow-up Visit.

- Subjects must remain on a stable CF medication (and supplement) regimen (other than protocol-specified changes in CFTR modulator regimen) for their CF from 28 days before the Day 1 Visit through the Safety Follow-up Visit. Stable CF medication regimen is defined as the current medication regimen for CF that subjects have been following for at least 28 days before the Day 1 Visit. Subjects must not initiate long-term treatment with new medication from 28 days before the Day 1 Visit through the Safety Follow-up Visit unless discussed and approved by the medical monitor.
- Subjects may receive doses of prednisone or prednisolone of up to 10 mg/day or equivalent (chronically), or prednisone or prednisolone 60 mg/day for up to 5 days, without prior approval of the medical monitor.
- Information about bronchodilator use during the study will be collected and documented. Subjects who are using a bronchodilator must have their spirometry assessments performed according to the guidelines provided in Section 11.4.

## 9.6 Administration

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

Study drug will be administered with a fat-containing meal or snack, consistent with the recommendations for administration of Kalydeco[12], according to the following guidelines:

- It is recommended that the dose be taken within 30 minutes of the start of the meal or snack.
- All study drug doses will be administered q12h to maintain the blind. All doses of study drug will be taken at approximately the same time each day. For example, the morning dose could

be taken at 08:00 every morning and the evening dose could be taken at 20:00 every evening throughout the study.

- The date, amount taken, and time of study drug administration, including whether food was taken with each dose, will be recorded for the 2 doses before PK sample collection and the dose received on the morning of PK sample collection.
- On days of scheduled visits, the morning dose of study drug will be administered at the site after predose assessments have been completed. The meal or snack will be provided by the site for the morning dose of study drug.
- A subject's morning dose can be delayed by up to 6 hours to accommodate predose assessments on clinic visit days.
- For visits after the Day 1 Visit, subjects will be instructed to bring all used and unused study drug to the site; study drug will be dispensed at each visit, as appropriate.

**Missed Doses**

- If a subject misses a dose and recalls the missed dose within 6 hours, the subject should take the dose with food. If more than 6 hours have elapsed after the usual dosing time, the subject should skip that dose and resume the normal schedule for the following dose.

## 9.7 Dose Modification for Toxicity

If any unacceptable toxicity arises, individual subjects will discontinue dosing (Section 9.1.5). No dose modifications for toxicity are allowed.

## 9.8 Study Drug Interruption and Stopping Rules

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

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

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

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

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

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

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

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

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

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

## 9.9 Removal of Subjects

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

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

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

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

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

request destruction of the samples collected from him/her during the study as long as those samples can be identified as his/her samples.

Stopping rules are presented in Section 9.8.

### 9.10 Replacement of Subjects

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

## 10 STUDY DRUG INFORMATION AND MANAGEMENT

Study drug refers to VX-561, IVA, and their matching placebos.

### 10.1 Preparation and Dispensing

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

### 10.2 Packaging and Labeling

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

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

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

VX-561 and matching placebo will be supplied as light blue film-coated tablets of similar size and appearance containing 50 mg VX-561, 25 mg VX-561, and 0 mg VX-561, respectively. Following discontinuation of the 25 mg qd VX-561 treatment arm, the 25 mg VX-561 tablet and matching placebo will no longer be distributed to subjects.

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

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

### 10.4 Drug Accountability

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

## 10.6 Compliance

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

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

## 10.7 Blinding and Unblinding

This will be a double-blind study.

### 10.7.1 Blinding

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

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

- Vertex medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time
- Vertex Quality Assurance, for the purposes of any audit or event investigations

Sweat Chloride and Spirometry Blinding:

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

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

### 10.7.2 Unblinding

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

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

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

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

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

# 11 ASSESSMENTS

The schedule of assessments is shown in Table 3-1.

## 11.1 Subject and Disease Characteristics

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

## 11.2 Pharmacokinetics

### 11.2.1 Blood Sampling

For the evaluation of plasma concentrations of VX-561 and IVA, blood samples will be collected from all subjects according to Table 3-1. These samples may also be used for evaluations of metabolites of VX-561 or IVA, for further evaluation of the bioanalytical method, and for analyses that provide information on the metabolic pathways used or impacted by VX-561 or IVA.

All efforts should 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 | Within 60 minutes before dosing |
| Post-dose, up to 6 hours after study drug dosing | ± 15 minutes |

### 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 Guideline.

### 11.2.3 Bioanalysis

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

## 11.3 Pharmacodynamics: Sweat Chloride

Collection of sweat samples will be performed using an approved collection device.

Each collection will occur before study drug dosing. At each time point, 2 samples will be collected, 1 from each arm (left and right). Additionally, sweat collections will be performed on any single day during screening.

Sweat samples will be sent to a central laboratory for testing and interpretation of results. Sweat chloride results for individual subjects will not be disclosed to the study sites.

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

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

## 11.4 Efficacy: Spirometry

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

Spirometry will be performed as outlined below:

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

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

During the Screening Period, spirometry assessments may be performed pre- or post-bronchodilator. At all other visits, all spirometry assessments should be performed "pre-bronchodilator". During the Treatment Period, spirometry assessments must be performed before the morning dose of study drug 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 Visit spirometry assessment is pre-bronchodilator but, on a subsequent visit, the subject forgets to withhold bronchodilator use, a post-bronchodilator spirometry assessment will be obtained for that visit only, and the visit will not be rescheduled.
- If, on the Day 1 Visit, the subject forgets to withhold his/her dose of bronchodilator, spirometry should be performed post-bronchodilator, and all subsequent spirometric measurements (according to the schedule of assessments detailed in Table 3-1) should be performed post-bronchodilator.
- Each spirometry assessment will be recorded in the source documents as pre- or post-bronchodilator.

If more than 1 spirometry assessment is required at a visit, bronchodilators will be withheld until completion of the last scheduled spirometry assessment.

All sites will be provided with spirometers to be used for all study assessments. Spirometry data will be transmitted to a centralized spirometry service for quality review. The investigator's assessment of the spirometry results will be used for the screening assessment and determination of eligibility.

See Section 10.7.1 for information about blinding of spirometry results.

## 11.5 Safety

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

### 11.5.1 Adverse Events

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

### 11.5.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory, with the exception of the urine pregnancy tests, which will be performed at the site. Blood and urine samples for clinical laboratory assessments will be collected as shown in Section 3.

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

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

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

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

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

[a] If urinalysis results are positive for leukocyte esterase, nitrite, protein, or blood, microscopic examination of urine will be 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.

Additional Tests at Screening: The following additional tests will be performed during screening to assess eligibility:

- Serum beta-human chorionic gonadotropin (β-hCG) for all female subjects

- Serum follicle-stimulating hormone (FSH) for suspected postmenopausal female subjects only. Levels will be within the laboratories range for postmenopausal for subjects to be considered of non-childbearing potential.

Pregnancy Testing (Female Subjects of Childbearing Potential):

- Serum and urine β-hCG as described in Table 3-1.

The pregnancy test at screening and Day 1 must be negative before receiving the first dose of study drug.

If a urine pregnancy test is positive, the pregnancy will be confirmed with a serum β-hCG test. If pregnancy is confirmed, the procedures outlined in Section 11.5.5.2 will be followed.

*CFTR* Genotype: *CFTR* genotyping will be performed for all subjects (Sections 8.1 and 9.9).

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

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

### 11.5.3 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. After screening, any clinically significant abnormal findings in PEs will be reported as AEs.

The abbreviated PE will include an assessment of the following body systems: head, neck, and thyroid; EENT; cardiovascular system; respiratory system; skin; and abdomen.
Vital signs include blood pressure (systolic and diastolic), temperature, pulse rate, and respiration rate. The subject will be instructed to rest for at least 5 minutes before vital signs are assessed.

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

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

See Section 8.2 for information about the ECG assessment for study eligibility.

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

### 11.5.5 Contraception and Pregnancy

#### 11.5.5.1 Contraception

Study participation requires compliance with the contraception guidelines outlined below.

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

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. True abstinence must be practiced from the Screening Visit through 90 days after the last dose of study drug.
- If the male is infertile (e.g., bilateral orchiectomy). If a male subject is assumed to have complete bilateral absence of the vas deferens, infertility must be documented before the first dose of study drug (e.g., examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound).
- If the female is of non-childbearing potential. To be considered of non-childbearing potential, the female must meet at least 1 of the following criteria:
  - Postmenopausal: Amenorrheic for at least 12 consecutive months and a serum FSH level within the laboratory's reference range for postmenopausal females.
  - Documented hysterectomy or bilateral oophorectomy/salpingo-oophorectomy.

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

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

**Table 11-3 Acceptable Methods of Contraception**

| Method | Male Subjects and Their Female (Non-study) Partners | Female Subjects and Their Male (Non-study) Partners |
|---|---|---|
| Vasectomy 6 months or more previously, with a documented negative postvasectomy semen analysis for sperm | Yes | Yes |
| Documented tubal ligation 4 weeks or more previously | Yes | Yes |
| Male or female condom with or without spermicide[a] | Yes | Yes |
| Female barrier contraception (such as diaphragm, cervical cap, or sponge) with spermicide | Yes | Yes |
| Continuous use of an intrauterine device for at least 90 days before the first dose of study drug. | | |
| Hormone-releasing | Yes | Yes |
| Non-hormone releasing | Yes | Yes |
| Hormonal methods of contraception (oral or patch), if successfully used for at least 60 days before the first dose of study drug | Yes | Yes |

Note: At least 1 acceptable method of contraception must be used by couples not exempt from the contraception requirement. Methods of contraception must be in successful use from signing of consent, approximately 28 days before the first dose of study drug (unless otherwise noted), and until 90 days following the last dose of study drug. Additional contraception requirements may need to be followed according to local regulations and/or requirements.

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

**Additional notes:**

- Male and female subjects who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study if they become sexually active with a partner of the opposite sex.
- Male subjects must not donate sperm from signing consent, throughout the study, and for 90 days following the last dose of study drug.
- Female subjects and female partners of male subjects should not plan to become pregnant from signing consent through 90 days following the last dose of study drug. For male subjects with a female partner of childbearing potential, the couple should not plan to become pregnant during the study or within 90 days after the last dose of study drug, with the exception of couples who plan to become pregnant by artificial insemination using sperm banked by the male subject before the first dose of study drug or sperm from another source.
- Male subjects whose female partner becomes pregnant through well-documented in vitro fertilization (donated sperm) or banked sperm (collected before the subject received study drug), or is otherwise already pregnant before the male subject's first dose of study drug, must be compliant with the contraception requirements. In this scenario, the male subject and his female partner must commit to using a male condom (to ensure there is no exposure of the fetus to study drug) from signing consent through 90 days after the last dose of study drug.
- Female subjects should not nurse a child from signing consent through 90 days following the last dose of study drug.

- Unique situations that may not fall within the above specifications may be discussed with the Vertex medical monitor or authorized designee on an individual basis.

#### 11.5.5.2 Pregnancy

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

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

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

## 12 STATISTICAL AND ANALYTICAL PLANS

This section presents a summary of the planned analyses of safety, efficacy, and clinical pharmacology results. Statistical analysis details on safety and efficacy will be provided in the statistical analysis plan (SAP), clinical pharmacologic analysis details will be provided in the clinical pharmacology analysis plan (CPAP), and population PK-PD analysis details will be provided in the Modeling and Simulation Plan, all of which will be finalized before clinical database lock.

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

### 12.1 Sample Size and Power

The primary objective is to evaluate efficacy of VX-561. The primary efficacy endpoint is the absolute change in ppFEV$_1$ from baseline at Week 12. Based on the initial study design that included 4 dose groups of VX-561 and an IVA 150 mg q12h dose group, assuming a within-group SD of 7 percentage points and a 10% dropout rate at Week 12: a sample size of 22 subjects in the 50, 150, and 250 mg qd VX-561 arms will provide a 95% CI of ± 3.4 percentage points around the observed mean absolute change in ppFEV$_1$ from baseline at Week 12, based on 2-sided, 1-sample t statistics; a sample size of 11 subjects in the other arms will provide a 95% CI of ± 5.4 percentage points around the observed mean.

Following discontinuation of the 25 mg qd VX-561 and 50 mg qd VX-561 treatment arms, the remaining subjects planned to enroll will be randomized in a 2:2:1 ratio to the 3 current treatment arms with a sample size of approximately 28 subjects for the 250 mg qd VX-561 treatment arm, approximately 28 subjects for the 150 mg qd VX-561 treatment arm, and approximately 14 subjects for the IVA 150 mg q12h treatment arm. The total study sample size including discontinued arms and current arms is approximately maintained as planned (N = 88). Under the same assumption as the original design (within-group SD of 7 percentage points and 10% dropout rate at Week 12): a sample size of 28 subjects in the 250 mg qd VX-561 and 150 mg qd

VX-561 arms will provide a 95% CI of ± 2.9 percentage points around the observed mean absolute change in ppFEV$_1$ from baseline at Week 12, based on 2-sided, 1-sample t statistics; a sample size of 14 subjects in the IVA 150 mg q12h arm will provide a 95% CI of ± 4.4 percentage points around the observed mean.

## 12.2 Analysis Sets

The study will include the following analysis sets:

- The All Subjects Set is defined as all subjects who were randomized or received at least 1 dose of study drug. The All Subjects Set will be used for individual subject data listings and disposition summary tables, unless otherwise specified.
- The Full Analysis Set (FAS) will include all randomized subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug in the Treatment Period. The FAS will be used for all PD and efficacy analyses in which subjects will be analyzed according to their randomized treatment group, unless otherwise specified.
- The Safety Set will include all subjects who received at least 1 dose of study drug. All safety and study drug exposure will be summarized for the Safety Set.
- The PK Set will include all subjects who received at least 1 dose of study drug and for whom the primary PK data are considered sufficient and interpretable.

## 12.3 Statistical Analysis

This section summarizes the statistical analysis of safety and efficacy data. The Vertex Biometrics Department or designee will analyze the safety and efficacy data. Methodological and related details will be in the SAP.

### 12.3.1 General Considerations

The precision standards for reporting safety and efficacy variables are provided in an internal Biometrics document that specifies the programming rules, including the precision for derived variables.

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

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

**Baseline value**, unless specified otherwise, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug. For ECG, baseline will be defined as the most recent pretreatment measurement (or the average of triplicate measurements, if the most recent pretreatment measurement is obtained in triplicate) before the first dose of study drug. Further details on baseline definition will be provided in SAP.

**Absolute change from baseline** will be calculated as Post-baseline value − Baseline value.

**Relative change from baseline** will be calculated and expressed in percentage as 100% × (Post-baseline value − Baseline value)/Baseline value.

**Treatment-emergent (TE) Period** will include the time period starting from the date of the first dose of study drug to 28 days after the last dose date of study drug taken in the treatment period,

or the completion date of study participation, whichever comes earlier. The TE Period will be used for safety analyses unless specified otherwise.

**Visit windowing rules:** The analysis visit windows for protocol-defined visits will be in the SAP.

### 12.3.2 Background Characteristics

#### 12.3.2.1 Subject Disposition

The number of subjects in each category (including All Subjects Set, Randomized, FAS, Safety Set) will be summarized overall and by treatment group.

The number and percent (based on the FAS) of subjects in each disposition category (including completed treatment, completed study, and discontinued treatment or study with a breakdown of the reasons for discontinuation) will be summarized overall and by treatment group.

A listing will be provided for subjects who discontinued treatment or who discontinued study with reasons for discontinuation. A randomization listing of subjects will be provided.

#### 12.3.2.2 Demographics and Baseline Characteristics

Demographics, medical history, and baseline characteristics will be summarized overall and by treatment group based on the FAS. No statistical tests will be done to evaluate baseline imbalances between groups.

Demographic and baseline characteristics will include, but are not limited to age (in years), sex, ethnicity, race, weight (kg), height (cm), body mass index (BMI, in $kg/m^2$), baseline $ppFEV_1$, and baseline sweat chloride.

Medical history will be summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT).

#### 12.3.2.3 Prior and Concomitant Medications

Medications used will be coded using the World Health Organization-Drug Dictionary (WHO-DD) and categorized as the following:

**Prior medication:** any medication that started before the date of the first dose of study drug, regardless of when the medication ended.

**Concomitant medication:** medication continued or newly received on or after the date of the first dose of study drug through the end of the TE Period.

**Post-treatment medication:** medication continued or newly received after the TE Period.

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

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

Details for imputing missing or partial start and/or stop dates of medication will be in the SAP.

#### 12.3.2.4 Study Drug Exposure and Compliance

Study drug exposure will be summarized overall and by treatment, based on the Safety Set in terms of duration of treatment a subject received (in days), defined as: last dose date – first dose date + 1 day, regardless of study drug interruption.

Study drug compliance will be summarized overall and by treatment group based on the FAS, and will be calculated as: 100 × [1 − (total number of days of study drug interruption)/(duration of study drug exposure in days)].

In addition, percentage of tablets taken will also be summarized overall and by treatment group based on the FAS, and will be calculated as: 100 × [(total number of tablets dispensed) – (total number of tablets returned)]/(total number of tablets planned to be taken per day × duration of study drug exposure in days).

### 12.3.3 Efficacy and Pharmacodynamic Analyses

All efficacy and PD analyses described in this section will be based on the FAS, unless specified otherwise.

#### 12.3.3.1 Efficacy: Spirometry

The efficacy data from the discontinued arms (25 mg qd VX-561 and 50 mg qd VX-561) will not be included in the model and will be summarized descriptively.

The primary efficacy endpoint is the absolute change in $ppFEV_1$ from baseline at Week 12. The primary analysis (described below) is based on the within group mean of absolute change from baseline for 250 mg qd VX-561, 150 mg qd VX-561, and IVA 150 mg q12h treatment arms.

The primary analysis will be based on a mixed effects model for repeated measures (MMRM) using restricted maximum likelihood. The model will include the absolute change from baseline in $ppFEV_1$ at Day 15, Week 4, Week 8, and Week 12 from the current treatment arms (250 mg qd VX-561, 150 mg qd VX-561, and IVA 150 mg q12h) as the dependent variable; treatment group, visit, and treatment by visit as fixed effects; with continuous baseline $ppFEV_1$ as covariates; and an unstructured covariance structure for the within-subject errors. If the model estimation does not converge, a compound symmetry covariance structure will be used.

The primary results obtained from the model will be the within-group treatment effect estimate at Week 12 for each treatment arm. The adjusted mean with a 2-sided 95% CI will be presented in a table.

In addition, the adjusted mean and 95% CI of the treatment effect difference between each VX-561 arm and the IVA arm obtained from the MMRM model will be provided.

#### 12.3.3.2 Pharmacodynamics: Sweat Chloride

The secondary endpoint is the absolute change from baseline in sweat chloride at Week 12 and will be analyzed similarly to $ppFEV_1$ for 250 mg qd VX-561, 150 mg qd VX-561, and IVA 150 mg q12h treatment arms. Adjusted means and 95% CIs of the average treatment effects at Week 12 will be obtained for within-group (for each arm) and between-group comparisons (between each VX-561 arm and the IVA arm). Details will be provided in the SAP.

[redacted]

### 12.3.4 Safety Analysis

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

- AEs
- Clinical laboratory values (hematology, serum chemistry, coagulation studies, and urinalysis)
- Standard 12-lead ECGs
- Vital signs
- Pulse oximetry

Safety endpoints will be analyzed based on the Safety Set (including the 25 mg qd VX-561 and 50 mg qd VX-561 treatment arms that were discontinued). Only a descriptive analysis of safety will be performed.

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.

#### 12.3.4.1 Adverse Events

AEs will be classified as pretreatment AEs, treatment-emergent adverse events (TEAEs), or post-treatment AEs defined as follows:
**Pretreatment AE:** any AE that started before the first dose date of study drug.

**TEAE:** any AE that worsened (either in severity or seriousness) or that was newly developed on or after the first dose date of study drug through the end of the TE Period.

**Post-treatment AE**: any AE that worsened or that was newly developed beyond the TE Period.

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

Details for imputing missing or partial start dates of AEs are in the SAP.

AE summary tables will be presented for TEAEs only, 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
- Serious TEAEs
- TEAEs leading to death

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 of individual subject AE data for TEAEs leading to treatment discontinuation, SAEs, and deaths will be provided separately. All AEs, including pretreatment AEs, will be in an individual subject data listing.

#### 12.3.4.2 Clinical Laboratory Assessments

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

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

Results of urinalysis and the urine/serum pregnancy test will be in individual subject data listings only.

#### 12.3.4.3 Electrocardiogram

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

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

#### 12.3.4.4 Vital Signs

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

The number and percentage of subjects meeting a threshold analysis criterion during the TE Period will be summarized overall and by treatment group. The threshold value criteria will be 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 for each part, at each scheduled visit for the percent of oxygen saturation by pulse oximetry.

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

#### 12.3.4.6 Physical Examination

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

[redacted]

### 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 will conduct safety reviews of study data. IDMC analyses will be conducted as outlined in the IDMC Charter. The planned IDMC reviews (with reference to number of subjects and duration of study) will be specified in the IDMC charter.

IDMC review will include relevant unblinded safety data. The IDMC may recommend stopping the study at any time. The IDMC may also recommend stopping individual dose groups, if there are increased safety findings in those groups.

## 12.4 Clinical Pharmacology Analysis

### 12.4.1 Pharmacokinetic Analysis

The PK of VX-561 and IVA will be described using summary statistics. Preliminary review and analyses of the drug concentrations may be done before database lock under the conditions of masked identifications of the subject concentrations.

Details of the analyses will be in the CPAP.

### 12.4.2 Pharmacokinetic/Pharmacodynamic Analyses

A sequential approach will be used to perform the population PK/PD analyses for VX-561. The Bayesian estimates of individual PK parameters from the final population PK model will be used to simulate PK profiles for each subject. The simulated VX-561 plasma concentrations will be used in the response models to describe changes in sweat chloride and $ppFEV_1$ from baseline. Fixed- and random-effect parameter estimates and the associated asymptotic standard error will be estimated. Descriptive statistics will be used to summarize Bayesian estimates of individual PK/PD parameters obtained from the population PK/PD model.

Details of the analyses will be described in the Modeling and Simulation Plan.

# 13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

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

### 13.1.1 Adverse Events

#### 13.1.1.1 Definition of an Adverse Event

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

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

#### 13.1.1.2 Clinically Significant Assessments

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

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

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

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

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

#### 13.1.1.3 Documentation of Adverse Events

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

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a Safety Follow-up Visit: through the Safety Follow-up Visit
- For enrolled subjects who do not have a Safety Follow-up Visit, the earliest of
    - 35 days after the last dose of study drug, or
    - the ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (see Section 9.1.5)

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." 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 |

#### 13.1.1.5 Adverse Event Causality

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

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

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

#### 13.1.1.6 Study Drug Action Taken

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

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

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

#### 13.1.1.7 Adverse Event Outcome

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

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

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

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

| Classification | Definition |
|---|---|

#### 13.1.1.8 Treatment Given

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

### 13.1.2 Serious Adverse Events

#### 13.1.2.1 Definition of a Serious Adverse Event

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

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

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

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

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

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

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

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (preferred choice)

Fax: [redacted]

For 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.

#### 13.1.2.3 Expedited Reporting and Investigator Safety Letters

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

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

### 13.2 Administrative Requirements

#### 13.2.1 Ethical Considerations

The study will be conducted in accordance with the current ICH GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and in accordance with local applicable laws and regulations. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, sample ICF, advertisements (if applicable), written information given to the subjects

(including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or Vertex, as allowable by local applicable laws and regulations.

### 13.2.2 Subject Information and Informed Consent

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

### 13.2.3 Investigator Compliance

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

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

### 13.2.4 Access to Records

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

### 13.2.5 Subject Privacy

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

For sites participating in the US, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated regulations, an executed HIPAA authorization will be obtained by the site from each subject (or the legal representative of the subject) before research activities may begin. Each HIPAA authorization will comply with all HIPAA requirements including authorization allowing the site access to and use of the subject's

personally identifiable health information, authorization for the site to disclose such information to Vertex, the FDA, and other parties requiring access under the protocol, and statements as to the purpose for which such information may be used and for how long.

### 13.2.6 Record Retention

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

### 13.2.7 Study Termination

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

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

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

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

### 13.2.8 End of Study

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

## 13.3 Data Quality Assurance

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

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each subject. Study data for each enrolled subject will be entered into a CRF by study site personnel using a secure, validated, web-based electronic data capture (EDC) application. Vertex will have read-only access to site-entered clinical data in the EDC application.

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

## 13.4 Monitoring

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

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

## 13.5 Electronic Data Capture

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

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

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

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

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

## 13.6 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

[redacted]

### 13.7.2 Clinical Study Report

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

## 14 REFERENCES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14 International Committee of Medical Journal Editors (ICMJE). December 2017. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. Available at: http://www.icmje.org/recommendations/. Accessed 03 August 2018.

# 15 PROTOCOL SIGNATURE PAGES

## 15.1 Sponsor Signature Page

| Protocol #: VX18-561-101 | Version #: 2.0 | Version Date: 03 October 2019 |
|---|---|---|
| Study Title: A Phase 2, Randomized, Double-blind Study to Evaluate the Efficacy and Safety of VX-561 in Subjects Aged 18 Years and Older With Cystic Fibrosis | | |

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

[redacted]

## 15.2 Investigator Signature Page

| Protocol #: VX18-561-101 | Version #: 2.0 | Version Date: 03 October 2019 |
|---|---|---|
| Study Title: A Phase 2, Randomized, Double-blind Study to Evaluate the Efficacy and Safety of VX-561 in Subjects Aged 18 Years and Older With Cystic Fibrosis | | |

I have read Protocol VX18-561-101, Version 2.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-561, IVA, and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date

## 1 TITLE PAGE

*VERTEX PHARMACEUTICALS INCORPORATED*

# Clinical Study Protocol Addendum for Cystic Fibrosis

## Cystic Fibrosis Studies for the Following Programs

**Ivacaftor (VX-770)**

[redacted]

**VX-561**

**Version and Date of Protocol Addendum:** Version 2.0, 15 May 2020
Replaces Version 1.0, dated 24 April 2020

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

## Summary of Changes to Cystic Fibrosis Clinical Study Protocols

Vertex is currently evaluating several CFTR modulators in clinical studies for the treatment of cystic fibrosis (CF), a serious and life-threatening disease. In completed studies, treatment with these CFTR modulators has generally resulted in rapid, robust, clinically meaningful, and statistically significant improvements in clinical measures, and are generally safe and well tolerated. Adverse events (AEs) seen with these treatments are mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects.

During this COVID-19 pandemic, the safety of the subjects, investigators, and site personnel participating in these clinical studies is Vertex's first priority, thus it is important to minimize any unnecessary risk to COVID-19 exposure through travel to study sites. This addendum summarizes the measures taken for ongoing CF clinical studies. These operational adjustments were implemented to align with Health Authority guidance ensuring the protection of subjects, investigators, and site personnel while maintaining compliance with GCP and minimizing impact to the integrity of the studies. Overall, the benefit-risk of these studies remains favorable.

Vertex recommends that subjects and sites refer to local guidance regarding travel restrictions. There are no operational changes to the study protocols for subjects who can travel to the study sites for their visits. However, to ensure continued safety of subjects who *cannot* travel to the study sites for their visits (for any reason due to COVID-19), specific alternative measures are being implemented to minimize the risk of exposure to COVID-19 (see table below). As the COVID-19 pandemic evolves, Vertex will continue to assess the need for additional actions to ensure the safety of all involved in these clinical studies.

Addendum Version 2.0 summarizes additional measures taken for these ongoing CF clinical studies (see table below) to ensure continued safety. In addition, administrative changes were made to provide clarifications (e.g., changed Addendum 1 to Addendum Version 1.0) and to provide examples of qualified personnel (e.g., personnel from site or qualified health care agency) who may conduct safety assessments, as indicated per protocol, during in-home visits.

## Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

| Protocol Change | Rationale for Change | Study Number |
|---|---|---|
| **Addendum Version 2.0, dated 15 May 2020** | | |
| **Assessments**<br><br>Weight and height/length/stature may be assessed by subjects or their caregivers using medical grade scales and stadiometers, as indicated per protocol and per local regulation. Sites and subjects will receive training and guidance as needed on these devices.<br><br>Subjects or caregivers will provide these measurements to site personnel by telephone or video call. Investigators will review results and contact subjects for follow-up as needed. All data will continue to be retained in the subject's source files. | To allow for collection of key data to assess safety and/or efficacy while maintaining study integrity and the safety of subjects and site personnel.<br><br>*Addendum 1 allowed for these assessments to be performed by qualified personnel conducting the in-home visits. Addendum 2 allows for these assessments to be performed by subjects or caregivers.* | [redacted]<br><br>VX18-561-101 |

## Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

| Protocol Change | Protocol Change | Protocol Change |
|---|---|---|
| **Addendum Version 1.0, dated 24 April 2020** | | |
| **Consenting of Subjects**<br>ICFs may be provided electronically or by post mail to subjects (and/or caregivers, as indicated per protocol). The subjects and/or caregivers will review the ICF with an appropriately qualified member of the investigator's team via telephone contact or video call. After this review, subjects and/or caregivers will consent (or assent, if applicable), and/or reconsent verbally and by signing and dating the ICF and returning it to the site via post mail. The signed and dated ICF will then be signed and dated by the investigator.<br><br>Subjects participating in select studies may have the opportunity to enroll in longterm extension studies. Informed consent (or assent, if applicable), and/or reconsent for subjects (and/or caregivers, as indicated per protocol) may be obtained per the same process described above, as applicable. | To provide alternative methods of obtaining reconsent or consent, as applicable, while ensuring subject safety. | [redacted] |
| **Study Drug Shipping**<br>Study drug may be shipped directly from the site to the subject, as applicable, and if permitted by local regulations; subject protected health information will not be released to Vertex.<br><br>Reconciliation, return, and destruction of study drug will continue to occur at the clinical site as indicated per protocol and in adherence to local regulations. | To ensure subjects can continue treatment with study drug without interruption while ensuring their safety.<br><br>To clarify that despite these alternative measures, reconciliation, return, and destruction of study drug will remain as indicated per protocol. | |
| **In-home Visits and/or Telephone Contact**<br>Study visits may be conducted as in-home visits by qualified personnel as requested by participating sites on a per-subject basis. In addition, all subjects may be contacted by site personnel by telephone or video call, irrespective of in-home visits. | To provide subjects the opportunity to continue participation in the clinical studies while ensuring their safety by minimizing the risk to COVID-19 exposure through travel. | VX18-561-101<br>[redacted] |

## Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

| Protocol Change | Protocol Change | Protocol Change |
|---|---|---|
| **Addendum Version 1.0, dated 24 April 2020** | | |
| **Safety Assessments and Reporting**<br>Safety assessments, as indicated per protocol, may be performed by qualified personnel conducting the in-home visits (e.g., personnel from site or qualified health care agency). These assessments may include the following, as indicated per protocol, and per local regulation:<br>• vital signs<br>• pulse oximetry<br>• height/length/stature<br>• weight<br>• physical examination (complete or abbreviated)<br>• pregnancy test (serum or urine)<br>• urinalysis<br>• blood draws for safety test panels (chemistry, LFT panel, lipid panel, hematology, coagulation).<br>Blood and/or urine samples for safety assessments are analyzed as indicated per protocol for subjects who have in-home visits.<br>Blood and/or urine samples for safety assessments may be collected and analyzed at local laboratories for subjects who do not have in-home visits, but do not complete the assessment at the site.<br>In addition, safety assessents will be evaluated by telephone. These assessments may include the review of the following:<br>• AEs<br>• signs and symptoms/systems for CF<br>• medications<br>• planned or unplanned hospitalizations for CF<br>• study drug administration<br>• outcomes related to PEx<br>• outcomes related to antibiotic treatment<br>Investigators will review results (in-home and telephone) and contact subjects for follow-up as needed.<br>All data will continue to be retained in the subject's source files.<br>Any clinically significant finding (e.g., AE, SAE, laboratory abnormalities) will continue to be reported as indicated per protocol. | To assess the safety and tolerability of the CFTR modulator evaluated in the specific clinical study while ensuring subject safety. These safety assessments will continue to provide safety data while minimizing burden to subjects and site personnel.<br><br>To clarify that despite these alternative measures, all adverse events and serious adverse events should be reported as indicated per protocol. | [redacted]<br>VX18-561-101<br>[redacted] |

## Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

| Protocol Change | Protocol Change | Protocol Change |
|---|---|---|
| **Addendum Version 1.0, dated 24 April 2020** | | |
| **Efficacy and Other Assessments**<br>Efficacy and other assessments, as indicated per protocol, may be performed by qualified personnel conducting the in-home visits. These assessments may include the following, as indicated per protocol, and per local regulation.<br><br>In-home Spirometry Assessment<br>A spirometry device may be provided to subjects for in-home assessments of lung function as indicated per protocol. Sites and subjects will receive training and guidance as needed.<br><br>Patient Reported Outcome<br>CFQ-R questionnaires may be provided to subjects (electronically or post mail) to be completed at home as indicated per protocol. Subjects will return these questionnaires to the site via post mail.<br><br>Other Assessments<br>• ECGs<br>• sweat chloride<br>• blood samples for *CFTR* genotype testing, [redacted], PK, FSH, [redacted], [redacted] | To be able to assess safety, treatment effectiveness, and quality of life measures of the CFTR modulator evaluated in the specific clinical study while ensuring subject safety. | All Efficacy and Other Assessments<br>[redacted]<br>VX18-561-101<br><br>*Note: CFQ-R does not apply for* [redacted] *VX18-561-101*<br><br>Other Outcomes Only<br>[redacted]<br>VX18-561-101 |

## Summary of Changes in Ongoing CF Clinical Studies for Subjects Who Cannot Travel to the Study Site

| Protocol Change | Protocol Change | Protocol Change |
|---|---|---|
| **Addendum Version 1.0, dated 24 April 2020** | | |
| **Remote Monitoring**<br>Vertex has implemented remote monitoring visits where applicable, including remote source data verification, as allowed per local regulations. Remote monitoring will focus on collection of safety data, and data supporting primary and key secondary endpoints. | To allow for review of key data to inform on the safety of subjects receiving treatment.<br><br>To allow for review of other key data to inform on the objectives of the study while maintaining study integrity and the safety of subjects and site personnel. | [redacted]<br>VX18-561-101 |

AE: adverse event; CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; ECG: electrocardiogram; [redacted]
FSH: follicle-stimulating hormone; GCP: Good Clinical Practice; ICF: informed consent form; [redacted]; LFT: liver function test;
PEx: pulmonary exacerbation; PK: pharmacokinetic; SAE: serious adverse event; [redacted]