

1

**TITLE PAGE**



***VERTEX PHARMACEUTICALS INCORPORATED***

# **Clinical Study Protocol**

**A Phase 3b Open-label Study Evaluating the Safety  
of Elexacaftor/Tezacaftor/Ivacaftor Combination  
Therapy in Subjects With Cystic Fibrosis**

**Vertex Study Number: VX20-445-121**

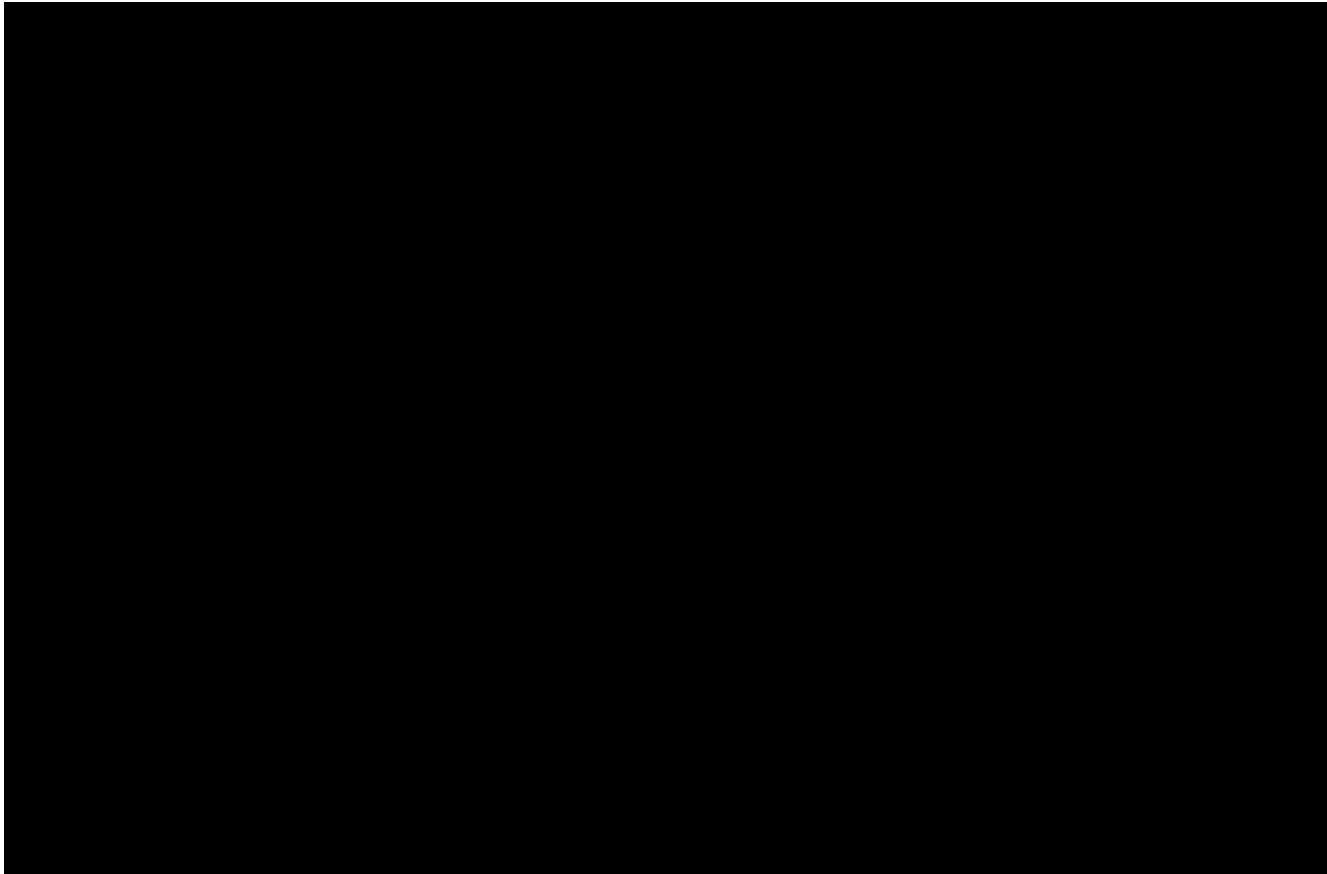
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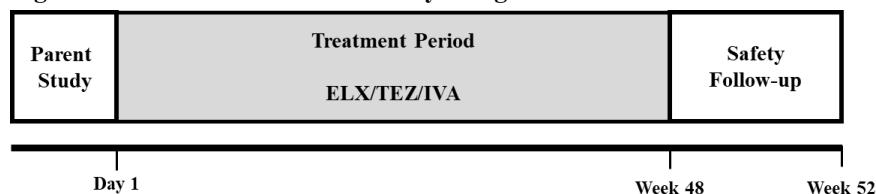
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## 2 PROTOCOL SYNOPSIS

|                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title</b>                                  | A Phase 3b Open-label Study Evaluating the Safety of Elexacaftor/Tezacaftor/Ivacaftor Combination Therapy in Subjects With Cystic Fibrosis                                                                                                                                                                                                                                                                                              |
| <b>Brief Title</b>                            | A Study Evaluating the Safety of Elexacaftor/Tezacaftor/Ivacaftor in Subjects With Cystic Fibrosis                                                                                                                                                                                                                                                                                                                                      |
| <b>Clinical Phase and Clinical Study Type</b> | Phase 3b, safety                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Objectives</b>                             | <b>Primary Objective</b><br>To evaluate the safety and tolerability of Elexacaftor (ELX)/Tezacaftor (TEZ)/Ivacaftor (IVA) in subjects with Cystic Fibrosis (CF)                                                                                                                                                                                                                                                                         |
| <b>Endpoints</b>                              | <b>Primary Endpoint</b><br>Safety and tolerability of ELX/TEZ/IVA based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry                                                                                                                                                                                                                                                                      |
| <b>Number of Subjects</b>                     | Subjects who participated in a parent study (VX19-445-117 or VX20-445-126) and meet the eligibility criteria may enroll. Up to approximately 160 subjects are expected to enroll in this open-label extension study.                                                                                                                                                                                                                    |
| <b>Study Population</b>                       | Male and female subjects with CF who are 12 years of age or older                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Investigational Drug</b>                   | <b>Active substance:</b> ELX (VX-445)/TEZ (VX-661)/IVA (VX-770)<br><b>Activity:</b> CFTR correctors (ELX and TEZ) and potentiator (IVA)<br><b>Strength and route of administration:</b> 100-mg ELX/50-mg TEZ/75-mg IVA FDC tablets for oral administration<br><br><b>Active substance:</b> IVA (VX-770)<br><b>Activity:</b> CFTR potentiator<br><b>Strength and route of administration:</b> 150-mg IVA tablets for oral administration |
| <b>Study Duration</b>                         | The total study duration is approximately 52 weeks (from the first dose of study drug in this study), including a Treatment Period of 48 weeks and a Safety Follow-up Visit 4 weeks after the last dose of study drug.                                                                                                                                                                                                                  |
| <b>Study Design</b>                           | This is a Phase 3b, multicenter, open-label study for subjects who complete a parent study (VX19-445-117 or VX20-445-126) and meet eligibility criteria. A schematic of the study design is shown in Figure 2-1.                                                                                                                                                                                                                        |

**Figure 2-1** VX20-445-121 Study Design

ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor

Note: Figure is not drawn to scale.

Subjects will receive a dose of ELX 200 mg once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h).

For treatment continuity in regions where ELX/TEZ/IVA is not commercially available, an option to return to this study will be offered to subjects who depart this study to enroll in another Vertex study of investigational CFTR modulators (hereafter referred to as “another qualified Vertex study”) based on the following:

- Subjects have received open-label ELX/TEZ/IVA during the other study’s Run-in Period but have not received study drug in the Treatment Period of the other study, and
- Meet all eligibility criteria for this study at their Returning Visit

Subjects who resume participation in this study will resume treatment with study drug after completion of a Returning Visit. Resumption of participation in this study following departure to another qualified Vertex study will be permitted only once.

**Assessments** Safety: AEs, clinical laboratory assessments, ECGs, vital signs and pulse oximetry, physical examinations (PES), and ophthalmologic examinations

**Statistical Analyses** The safety analysis will be conducted for subjects who have received at least 1 dose of study drug in this open-label study. The safety analysis will be descriptive only.

### **3 SCHEDULE OF ASSESSMENTS**

Schedules of assessments is in Table 3-1. All visits will be scheduled relative to the Day 1 Visit in this study.

Assessments may be performed in any order when more than 1 assessment is required at a particular time point, unless noted otherwise. All assessments should be performed before study drug dosing (Section 9.6), unless noted otherwise.

Subjects who depart this study to enroll in another qualified Vertex study, and who meet the eligibility criteria in Section 8, may resume participation in this study only once.

**Table 3-1 Study VX20-445-121: Treatment Period and Safety Follow-up Visit**

| Event/Assessment <sup>a</sup>    | Treatment Period                          |                                                          |                                     |                            | ETT Visit/<br>Departing<br>Visit <sup>b</sup> | Safety Follow-up<br>28 ( $\pm$ 7) Days<br>After Last Dose<br>of Study Drug <sup>c</sup> | Comments                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------------------|-------------------------------------------|----------------------------------------------------------|-------------------------------------|----------------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                  | Day 1/<br>Returning<br>Visit <sup>d</sup> | Weeks 4, 8, 16, 20,<br>28, 32, 40, 44<br>( $\pm$ 5 Days) | Weeks 12, 24, 36<br>( $\pm$ 5 Days) | Week 48<br>( $\pm$ 5 Days) |                                               |                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                             |
| ICF and assent (when applicable) | X                                         |                                                          |                                     |                            |                                               |                                                                                         | ICF and assent are not required for Returning Visit                                                                                                                                                                                                                                                                                                                                         |
| Study visit                      | X                                         |                                                          | X                                   | X                          | X                                             | X                                                                                       | All visits may be performed as home health visits (if permitted by local regulations) or in the clinic at the discretion of the investigator (Section 9.1.6). All visits must have a consultation between the subject and investigator (i.e., in person, phone, or telemedicine video conference) within 1 business day after the home health visit, which can be outside the visit window. |
| Telephone contact                |                                           | X                                                        |                                     |                            |                                               |                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                             |

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

<sup>b</sup> If the subject prematurely discontinues study drug treatment, an ETT Visit should be scheduled as soon as possible after the decision to discontinue treatment (Section 9.1.3). If the subject prematurely discontinues treatment to participate in another qualified Vertex study, the Departing Visit should be completed before or on the same day as the visit at which they receive the first dose of study drug in the Run-in Period of the other qualified Vertex study. The Safety Follow-up Visit will not be required if the subject enrolls in the other qualified Vertex study within 28 days of the last dose of study drug in this study.

<sup>c</sup> The Safety Follow-up Visit is required for all subjects, unless otherwise specified. For subjects who complete an ETT Visit 3 weeks or later following the last dose of study drug, the ETT Visit will replace the Safety Follow-up Visit (Section 9.1.2).

<sup>d</sup> The Day 1 Visit should be on the same day as the last scheduled visit of a parent study (Section 9.1.1). Subjects whose Day 1 Visit is NOT within 1 day of the last scheduled visit of a parent study will repeat all Day 1 assessments. Subjects whose Day 1 Visit is within 1 day of the last scheduled visit of a parent study will NOT have to repeat any Day 1 assessments that were specified to be performed at the last scheduled visit in a parent study. Subjects who resume participation in this study after discontinuation from another qualified Vertex study will complete the Returning Visit (which will consist of all assessments in the Day 1 Visit) and will resume treatment with ELX/TEZ/IVA after completion of the Returning Visit. Study visit numbering for returning subjects will resume based on the last study visit before the Departing Visit in this study. If the subject's Returning Visit window coincides with a scheduled study visit in this study, only the Returning Visit assessments will be completed, after which subjects will resume study visits in this study. Subjects who resume participation but have their first dose of study drug in this study delayed will repeat the safety assessments specified to be performed at the Returning Visit before receiving their first dose of study drug.

**Table 3-1 Study VX20-445-121: Treatment Period and Safety Follow-up Visit**

| Event/Assessment <sup>a</sup>  | Treatment Period                          |                                                          |                                     |                            | ETT Visit/<br>Departing<br>Visit <sup>b</sup> | Safety Follow-up<br>28 ( $\pm$ 7) Days<br>After Last Dose<br>of Study Drug <sup>c</sup> | Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|--------------------------------|-------------------------------------------|----------------------------------------------------------|-------------------------------------|----------------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                | Day 1/<br>Returning<br>Visit <sup>d</sup> | Weeks 4, 8, 16, 20,<br>28, 32, 40, 44<br>( $\pm$ 5 Days) | Weeks 12, 24, 36<br>( $\pm$ 5 Days) | Week 48<br>( $\pm$ 5 Days) |                                               |                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Height and weight              | X                                         |                                                          | X                                   | X                          | X                                             | X                                                                                       | Height and weight will be measured with shoes off (Section 11.2.4). For subjects whose date of informed consent occurs after their 21st birthday, height will not be collected in this study. For subjects whose date of informed consent occurs on or before their 21st birthday, height will be collected through the first visit after the subject's 21st birthday and does not need to be collected at future visits.                                   |
| Vital signs and pulse oximetry | X                                         |                                                          | X                                   | X                          | X                                             | X                                                                                       | Complete before other assessments after subject has rested for at least 5 minutes (Sections 11.2.3 and 11.2.5).                                                                                                                                                                                                                                                                                                                                             |
| Standard 12-lead ECG           | X                                         |                                                          |                                     | X                          | X                                             | X                                                                                       | Complete before other assessments after subject has rested for at least 5 minutes (Section 11.2.6)                                                                                                                                                                                                                                                                                                                                                          |
| Physical examination           | X                                         |                                                          |                                     | X                          | X                                             | X                                                                                       | Section 11.2.3                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Ophthalmologic examination     |                                           |                                                          |                                     | X                          | X                                             |                                                                                         | Subjects <18 years of age on the date of informed consent in a parent study will have an ophthalmologic examination by the Week 48 Visit or the ETT Visit/Departing Visit (for subjects who prematurely discontinue study drug if the subject has received at least 12 weeks of study drug [in a parent study and current study] since their last ophthalmologic examination), whichever comes first. See Section 11.2.7 for acceptable assessment windows. |
| Pregnancy test                 | urine                                     | urine                                                    | urine                               | serum                      | serum                                         | serum                                                                                   | For all female subjects, at telephone contacts, a urine pregnancy test will be performed with a home kit provided by the study site. Results of the home pregnancy test will be reported to the site by telephone (Section 11.2.2).                                                                                                                                                                                                                         |

**Table 3-1 Study VX20-445-121: Treatment Period and Safety Follow-up Visit**

| Event/Assessment <sup>a</sup>      | Treatment Period                                                         |                                                          |                                     |                            | ETT Visit/<br>Departing<br>Visit <sup>b</sup> | Safety Follow-up<br>28 ( $\pm$ 7) Days<br>After Last Dose<br>of Study Drug <sup>c</sup> | Comments                                                                                                                                                                                                                             |
|------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------|-------------------------------------|----------------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                    | Day 1/<br>Returning<br>Visit <sup>d</sup>                                | Weeks 4, 8, 16, 20,<br>28, 32, 40, 44<br>( $\pm$ 5 Days) | Weeks 12, 24, 36<br>( $\pm$ 5 Days) | Week 48<br>( $\pm$ 5 Days) |                                               |                                                                                         |                                                                                                                                                                                                                                      |
| Serum chemistry                    | X                                                                        |                                                          | X                                   | X                          | X                                             | X                                                                                       | Section 11.2.2                                                                                                                                                                                                                       |
| Hematology                         | X                                                                        |                                                          | X                                   | X                          | X                                             | X                                                                                       |                                                                                                                                                                                                                                      |
| Coagulation                        | X                                                                        |                                                          | Week 24                             | X                          | X                                             | X                                                                                       |                                                                                                                                                                                                                                      |
| Urinalysis                         | X                                                                        |                                                          |                                     | X                          | X                                             | X                                                                                       |                                                                                                                                                                                                                                      |
| Study drug count                   | X                                                                        |                                                          | X                                   | X                          | X                                             | X                                                                                       |                                                                                                                                                                                                                                      |
| Study drug dosing                  | Day 1 through evening before Week 48 Visit                               |                                                          |                                     |                            |                                               |                                                                                         | Subjects on study drug interruption from a parent study or another qualified Vertex study may NOT begin dosing until they meet the resumption criteria in Section 9.8. Refer to Section 9.6.1 for study drug administration details. |
| Adverse events                     | Continuous from signing of ICF through completion of study participation |                                                          |                                     |                            |                                               |                                                                                         | Section 11.2.1                                                                                                                                                                                                                       |
| Medications review                 | Continuous from signing of ICF through completion of study participation |                                                          |                                     |                            |                                               |                                                                                         | Section 9.5                                                                                                                                                                                                                          |
| Treatment and<br>procedures review | Continuous from signing of ICF through completion of study participation |                                                          |                                     |                            |                                               |                                                                                         |                                                                                                                                                                                                                                      |

ECG: electrocardiogram; ETT: early termination of treatment; ICF: informed consent form

**4 TABLE OF CONTENTS**

|           |                                                        |           |
|-----------|--------------------------------------------------------|-----------|
| <b>1</b>  | <b>Title Page .....</b>                                | <b>1</b>  |
| <b>2</b>  | <b>Protocol Synopsis .....</b>                         | <b>3</b>  |
| <b>3</b>  | <b>Schedule of Assessments.....</b>                    | <b>5</b>  |
| <b>4</b>  | <b>Table of Contents.....</b>                          | <b>9</b>  |
|           | List of Tables .....                                   | 12        |
|           | List of Figures .....                                  | 12        |
|           | List of Abbreviations .....                            | 13        |
| <b>5</b>  | <b>Introduction.....</b>                               | <b>15</b> |
| 5.1       | Background.....                                        | 15        |
| 5.2       | Study Rationale .....                                  | 15        |
| <b>6</b>  | <b>Study Objectives .....</b>                          | <b>15</b> |
| 6.1       | Primary Objective.....                                 | 15        |
| <b>7</b>  | <b>Study Endpoints.....</b>                            | <b>16</b> |
| 7.1       | Primary Endpoint.....                                  | 16        |
| <b>8</b>  | <b>Study Population.....</b>                           | <b>16</b> |
| 8.1       | Inclusion Criteria .....                               | 16        |
| 8.2       | Exclusion Criteria.....                                | 16        |
| <b>9</b>  | <b>Study Implementation.....</b>                       | <b>17</b> |
| 9.1       | Study Design .....                                     | 17        |
| 9.1.1     | Treatment Period .....                                 | 18        |
| 9.1.2     | Follow-up.....                                         | 18        |
| 9.1.3     | Early Termination of Treatment.....                    | 19        |
| 9.1.4     | Lost to Follow-up .....                                | 19        |
| 9.1.5     | Completion of Study Participation .....                | 20        |
| 9.1.6     | Use of Remote Measures .....                           | 20        |
| 9.2       | Method of Assigning Subjects to Treatment Groups ..... | 20        |
| 9.3       | Rationale for Study Elements .....                     | 20        |
| 9.3.1     | Study Design and Population .....                      | 20        |
| 9.3.2     | Study Drug Dose and Duration .....                     | 21        |
| 9.3.3     | Rationale for Study Assessments .....                  | 21        |
| 9.4       | Study Restrictions.....                                | 21        |
| 9.5       | Prior and Concomitant Medications.....                 | 21        |
| 9.6       | Administration .....                                   | 22        |
| 9.6.1     | Dosing.....                                            | 22        |
| 9.6.2     | Missed Doses.....                                      | 23        |
| 9.7       | Dose Modification for Toxicity.....                    | 23        |
| 9.8       | Study Drug Interruption and Stopping Rules .....       | 23        |
| 9.8.1     | Liver Function Tests.....                              | 23        |
| 9.8.2     | Rash .....                                             | 24        |
| 9.9       | Removal of Subjects.....                               | 24        |
| 9.10      | Replacement of Subjects .....                          | 25        |
| <b>10</b> | <b>Study Drug Information and Management.....</b>      | <b>25</b> |
|           | 10.1 Preparation and Dispensing.....                   | 25        |

|           |                                                                                              |           |
|-----------|----------------------------------------------------------------------------------------------|-----------|
| 10.2      | Packaging and Labeling .....                                                                 | 25        |
| 10.3      | Study Drug Supply, Storage, and Handling .....                                               | 25        |
| 10.4      | Drug Accountability .....                                                                    | 26        |
| 10.5      | Disposal, Return, or Retention of Unused Drug.....                                           | 26        |
| 10.6      | Compliance.....                                                                              | 26        |
| 10.7      | Blinding and Unblinding .....                                                                | 26        |
| <b>11</b> | <b>Assessments .....</b>                                                                     | <b>27</b> |
| 11.1      | Subject and Disease Characteristics .....                                                    | 27        |
| 11.2      | Safety .....                                                                                 | 27        |
| 11.2.1    | Adverse Events .....                                                                         | 27        |
| 11.2.2    | Clinical Laboratory Assessments .....                                                        | 27        |
| 11.2.3    | Physical Examinations and Vital Signs .....                                                  | 29        |
| 11.2.4    | Height and Weight.....                                                                       | 29        |
| 11.2.5    | Pulse Oximetry .....                                                                         | 29        |
| 11.2.6    | Electrocardiograms.....                                                                      | 29        |
| 11.2.7    | Ophthalmologic Examination.....                                                              | 30        |
| 11.2.8    | Contraception and Pregnancy .....                                                            | 30        |
| 11.2.8.1  | Contraception .....                                                                          | 30        |
| 11.2.8.2  | Pregnancy .....                                                                              | 32        |
| <b>12</b> | <b>Statistical Analysis .....</b>                                                            | <b>32</b> |
| 12.1      | Sample Size .....                                                                            | 32        |
| 12.2      | Analysis Sets .....                                                                          | 32        |
| 12.3      | Statistical Analysis .....                                                                   | 32        |
| 12.3.1    | General Considerations.....                                                                  | 32        |
| 12.3.2    | Background Characteristics .....                                                             | 33        |
| 12.3.2.1  | Subject Disposition .....                                                                    | 33        |
| 12.3.2.2  | Demographics and Baseline Characteristics .....                                              | 33        |
| 12.3.2.3  | Prior and Concomitant Medications .....                                                      | 33        |
| 12.3.2.4  | Study Drug Exposure and Compliance.....                                                      | 34        |
| 12.3.2.5  | Important Protocol Deviations .....                                                          | 34        |
| 12.3.3    | Efficacy Analysis.....                                                                       | 34        |
| 12.3.4    | Safety Analysis .....                                                                        | 34        |
| 12.3.4.1  | Adverse Events .....                                                                         | 35        |
| 12.3.4.2  | Clinical Laboratory Assessments.....                                                         | 36        |
| 12.3.4.3  | Electrocardiogram.....                                                                       | 36        |
| 12.3.4.4  | Vital Signs.....                                                                             | 36        |
| 12.3.4.5  | Pulse Oximetry .....                                                                         | 37        |
| 12.3.4.6  | Other Safety Analyses.....                                                                   | 37        |
| 12.4      | Interim Analysis .....                                                                       | 37        |
| 12.5      | Data Monitoring Committee Analysis.....                                                      | 37        |
| <b>13</b> | <b>Procedural, Ethical, Regulatory, and Administrative Considerations .....</b>              | <b>37</b> |
| 13.1      | Adverse Event and Serious Adverse Event Documentation, Severity Grading, and Reporting ..... | 37        |
| 13.1.1    | Adverse Events .....                                                                         | 37        |
| 13.1.1.1  | Definition of an Adverse Event.....                                                          | 37        |
| 13.1.1.2  | Clinically Significant Assessments .....                                                     | 37        |

|                                                                     |           |
|---------------------------------------------------------------------|-----------|
| 13.1.1.3 Documentation of Adverse Events.....                       | 38        |
| 13.1.1.4 Adverse Event Severity.....                                | 39        |
| 13.1.1.5 Adverse Event Causality .....                              | 39        |
| 13.1.1.6 Study Drug Action Taken .....                              | 40        |
| 13.1.1.7 Adverse Event Outcome .....                                | 40        |
| 13.1.1.8 Treatment Given.....                                       | 40        |
| 13.1.2 Serious Adverse Events .....                                 | 41        |
| 13.1.2.1 Definition of a Serious Adverse Event.....                 | 41        |
| 13.1.2.2 Reporting and Documentation of Serious Adverse Events..... | 41        |
| 13.1.2.3 Expedited Reporting and Investigator Safety Letters .....  | 42        |
| 13.2 Administrative Requirements .....                              | 42        |
| 13.2.1 Product Complaints .....                                     | 42        |
| 13.2.2 Ethical Considerations.....                                  | 42        |
| 13.2.3 Subject Information and Informed Consent .....               | 43        |
| 13.2.4 Investigator Compliance .....                                | 43        |
| 13.2.5 Access to Records.....                                       | 43        |
| 13.2.6 Subject Privacy .....                                        | 43        |
| 13.2.7 Record Retention .....                                       | 44        |
| 13.2.8 Study Termination .....                                      | 44        |
| 13.2.9 End of Study .....                                           | 44        |
| 13.3 Data Quality Assurance .....                                   | 44        |
| 13.4 Monitoring.....                                                | 45        |
| 13.5 Electronic Data Capture .....                                  | 45        |
| 13.6 Confidentiality and Disclosure .....                           | 45        |
| 13.7 Publications and Clinical Study Report.....                    | 45        |
| 13.7.2 Clinical Study Report .....                                  | 46        |
| <b>14 References.....</b>                                           | <b>47</b> |
| <b>15 Protocol Signature Pages .....</b>                            | <b>48</b> |
| 15.1 Sponsor Signature Page .....                                   | 48        |
| 15.2 Investigator Signature Page .....                              | 49        |

**List of Tables**

|            |                                                                        |    |
|------------|------------------------------------------------------------------------|----|
| Table 3-1  | Study VX20-445-121: Treatment Period and Safety Follow-up Visit .....  | 6  |
| Table 9-1  | Prohibited Medications .....                                           | 21 |
| Table 10-1 | Study Drug: Dosing Form/Route/Strength .....                           | 26 |
| Table 11-1 | Safety Laboratory Test Panels .....                                    | 28 |
| Table 11-2 | Acceptable Methods of Contraception.....                               | 31 |
| Table 13-1 | Grading of AE Severity .....                                           | 39 |
| Table 13-2 | Classifications for AE Causality .....                                 | 39 |
| Table 13-3 | Classifications for Study Drug Action Taken With Regard to an AE ..... | 40 |
| Table 13-4 | Classifications for Outcome of an AE .....                             | 40 |

**List of Figures**

|            |                                 |    |
|------------|---------------------------------|----|
| Figure 2-1 | VX20-445-121 Study Design ..... | 4  |
| Figure 9-1 | VX20-445-121 Study Design ..... | 17 |

## List of Abbreviations

| Abbreviation   | Definition                                                                                                                          |
|----------------|-------------------------------------------------------------------------------------------------------------------------------------|
| ADL            | activities of daily living                                                                                                          |
| AE             | adverse event                                                                                                                       |
| ALT            | alanine transaminase                                                                                                                |
| AST            | aspartate transaminase                                                                                                              |
| BMI            | body mass index                                                                                                                     |
| CF             | cystic fibrosis                                                                                                                     |
| <i>CFTR</i>    | cystic fibrosis transmembrane conductance regulator gene                                                                            |
| CFTR           | cystic fibrosis transmembrane conductance regulator protein                                                                         |
| CRF            | case report form                                                                                                                    |
| CSR            | clinical study report                                                                                                               |
| CTCAE          | Common Terminology Criteria for Adverse Events                                                                                      |
| CYP            | cytochrome P450                                                                                                                     |
| ECG            | electrocardiogram                                                                                                                   |
| EDC            | electronic data capture                                                                                                             |
| EENT           | eyes, ears, nose, and throat                                                                                                        |
| ELX            | ellexacaftor                                                                                                                        |
| ETT            | Early Termination of Treatment                                                                                                      |
| EU             | European Union                                                                                                                      |
| <i>F508del</i> | <i>CFTR</i> gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein |
| FDA            | Food and Drug Administration                                                                                                        |
| FDC            | fixed-dose combination                                                                                                              |
| FSH            | follicle-stimulating hormone                                                                                                        |
| GCP            | Good Clinical Practice                                                                                                              |
| GPS            | Global Patient Safety                                                                                                               |
| HIPAA          | Health Insurance Portability and Accountability Act                                                                                 |
| HR             | heart rate                                                                                                                          |
| ICF            | informed consent form                                                                                                               |
| ICH            | International Council for Harmonization                                                                                             |
| IEC            | independent ethics committee                                                                                                        |
| IMP            | investigational medicinal product                                                                                                   |
| IND            | Investigational New Drug (application) (US)                                                                                         |
| IPD            | important protocol deviation                                                                                                        |
| IRB            | institutional review board                                                                                                          |
| IVA            | ivacaftor                                                                                                                           |
| LUM            | lumacaftor                                                                                                                          |
| max            | maximum value                                                                                                                       |
| min            | minimum value                                                                                                                       |
| n              | size of subsample                                                                                                                   |
| OATP1B1        | organic anion transporter protein 1B1                                                                                               |
| PE             | physical examination                                                                                                                |
| P-gp           | P-glycoprotein                                                                                                                      |

| <b>Abbreviation</b> | <b>Definition</b>                                                                                        |
|---------------------|----------------------------------------------------------------------------------------------------------|
| PI                  | principal investigator                                                                                   |
| ppFEV <sub>1</sub>  | percent predicted forced expiratory volume in 1 second                                                   |
| PR                  | PR interval, segment                                                                                     |
| PT                  | Preferred Term                                                                                           |
| QRS                 | the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization |
| QT                  | QT interval                                                                                              |
| QTcF                | QT interval corrected by Fridericia's formula                                                            |
| RR                  | interval from the onset of 1 QRS complex to the next                                                     |
| SAE                 | serious adverse event                                                                                    |
| SAP                 | statistical analysis plan                                                                                |
| SD                  | standard deviation                                                                                       |
| SI                  | SI units (International System of Units)                                                                 |
| SOC                 | System Organ Class                                                                                       |
| SUSAR               | suspected, unexpected, serious adverse reaction                                                          |
| TE                  | treatment-emergent                                                                                       |
| TEAE                | treatment-emergent adverse event                                                                         |
| TEZ                 | tezacaftor                                                                                               |
| ULN                 | upper limit of normal                                                                                    |
| US                  | United States                                                                                            |
| USA                 | United States of America                                                                                 |

## 5 INTRODUCTION

### 5.1 Background

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

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

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

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

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

### 5.2 Study Rationale

This study will evaluate the safety of 48 weeks of treatment with ELX/TEZ/IVA in subjects with CF who complete a parent study (VX19-445-117 or VX20-445-126). The potential for benefit in these patients is supported by published Phase 2 and publicly disclosed Phase 3 clinical data in subjects with CF. In addition, ELX/TEZ/IVA is generally safe and well tolerated (refer to ELX/TEZ/IVA Investigator's Brochure).

Data from this study are intended to enrich the body of evidence showing that ELX/TEZ/IVA is safe and well tolerated in subjects with CF.

## 6 STUDY OBJECTIVES

### 6.1 Primary Objective

To evaluate the safety and tolerability of ELX/TEZ/IVA in subjects with CF

## 7 STUDY ENDPOINTS

### 7.1 Primary Endpoint

Safety and tolerability of ELX/TEZ/IVA based on adverse events (AEs), clinical laboratory values, 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. In the criteria below, "parent study" is defined as VX19-445-117 or VX20-445-126.

### 8.1 Inclusion Criteria

1. Subject (or his or her legally appointed and authorized representative) will sign and date an informed consent form (ICF) and, when appropriate, an assent form.
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Did not withdraw consent from a parent study.
4. Meets at least 1 of the following criteria:
  - Completed study drug treatment in a parent study.
  - Had study drug interruption(s) in a parent study, but did not permanently discontinue study drug, and completed study visits up to the last scheduled visit of the Treatment Period of a parent study.
5. For subjects being considered for resumption of participation in this study after enrolling in another Vertex study of investigational CFTR modulators (referred to as "another qualified Vertex study"): Completed the ETT visit in another qualified Vertex study before or on the same day as the Returning Visit in this study. If more than 30 days have elapsed since the ETT visit in the other qualified Vertex study, approval of the medical monitor is required.
6. Willing to remain on a stable CF treatment regimen (as defined in Section 9.5) through completion of study participation.

### 8.2 Exclusion Criteria

1. History of any comorbidity that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject.
2. History of drug intolerance in a parent study that would pose an additional risk to the subject in the opinion of the investigator (e.g., subjects with a history of allergy or hypersensitivity to the study drug).
3. Pregnant and breast-feeding females. Female subjects must have a negative pregnancy test at the Day 1 Visit before receiving the first dose of study drug.
4. Current participation in an investigational drug trial other than a parent study. Participation in a noninterventional study (including observational studies, registry studies, and studies

requiring blood collections without administration of study drug) and screening for another Vertex study is permitted.

5. For subjects being considered for resumption of participation in this study after enrolling in another qualified Vertex study, the following exclusion criteria also apply:

- Subject received the first dose of study drug in the Treatment Period of another qualified Vertex study,
- Subject has access to commercially available ELX/TEZ/IVA or is receiving managed-access-program-supplied ELX/TEZ/IVA, or
- Subject departed this study more than once to participate in another qualified Vertex study.

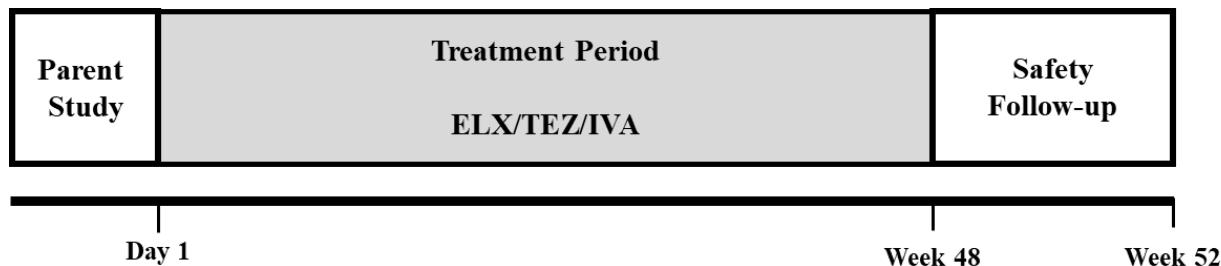
## 9 STUDY IMPLEMENTATION

### 9.1 Study Design

This is a Phase 3b, multicenter, open-label study for subjects who complete a parent study (VX19-445-117 or VX20-445-126) and meet eligibility criteria (Section 8). A schematic of the study design is shown in Figure 9-1.

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

**Figure 9-1 VX20-445-121 Study Design**



ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor

Note: Figure is not drawn to scale.

Subjects will receive a dose of ELX 200 mg once daily (qd)/TEZ 100 mg qd/IVA 150 mg every 12 hours (q12h).

For treatment continuity in regions where ELX/TEZ/IVA is not commercially available, an option to return to this study will be offered to subjects who depart this study to enroll in another qualified Vertex study based on the following:

- Subjects have received open-label ELX/TEZ/IVA during the other study's Run-in Period but have not received study drug in the Treatment Period of the other study, and
- Meet all eligibility criteria for this study (Section 8) at their Returning Visit.

Subjects who resume participation in this study will resume treatment with study drug after completion of a Returning Visit. Resumption of participation in this study following departure to another qualified Vertex study will be permitted only once.

### **9.1.1 Treatment Period**

Treatment Period assessments are listed in Table 3-1.

Subjects will receive the first dose of study drug on Day 1 after obtaining informed consent (and assent, when applicable) and confirming eligibility. Subjects who enroll in this study on a study drug interruption from a parent study or another qualified Vertex study will NOT receive the first dose of study drug until they meet the resumption criteria in Section 9.8; before receiving study drug, subjects will repeat all Day 1 assessments.

Study drug administration details are provided in Section 9.6.

The Day 1 Visit should be on the same day as the last scheduled visit of a parent study. Subjects whose Day 1 Visit is NOT within 1 day of the last scheduled visit of a parent study will repeat all Day 1 assessments.

Subjects whose Day 1 Visit is within 1 day of the last scheduled visit of a parent study will NOT have to repeat any Day 1 assessments that were specified to be performed at the last scheduled visit in a parent study.

### **Subjects Resuming Participation After Discontinuation From Another Qualified Vertex Study**

Subjects who resume participation in this study will complete the Returning Visit and resume treatment with ELX/TEZ/IVA after completion of the Returning Visit. Study visit numbering for returning subjects will resume based on the last study visit before the Departing Visit in this study.

The Early Termination of Treatment (ETT) Visit in another qualified Vertex study and the Returning Visit in this study may occur on the same day. If completed on the same day or within 1 calendar day, any assessments completed at the ETT in the other qualified Vertex study do not have to be repeated at the Returning Visit in this study.

Subjects who resume participation but have their first dose of study drug in this study delayed will repeat the safety assessments specified to be performed at the Returning Visit before receiving their first dose of study drug (see Section 3).

If the subject's Returning Visit window coincides with a scheduled study visit in this study, only the Returning Visit assessments will be completed, after which subjects will resume study visits in this study.

### **9.1.2 Follow-up**

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

The Safety Follow-up Visit is required for all subjects. However, subjects who transition within 28 days of the last dose of study drug to either:

- a commercially available Vertex CFTR modulator regimen

- managed-access-program-supplied Vertex CFTR modulator regimen
- or, to another qualified Vertex study

will complete the Week 48 Visit (or the Early Termination of Treatment [ETT] Visit/Departing Visit, if the transition occurs before the Week 48 Visit). In these cases, the Week 48 Visit (or the ETT Visit/Departing Visit) will replace the Safety Follow-up Visit.

For subjects who complete an ETT Visit/Departing Visit 3 weeks or later following the last dose of study drug, the ETT Visit/Departing Visit will replace the Safety Follow-up Visit (Section 9.1.3).

### **9.1.3 Early Termination of Treatment**

#### **Departing Visit**

If a subject enrolls in another qualified Vertex study, the Departing Visit should be completed before or on the same day as the visit at which they receive the first dose of study drug in the Run-in Period of the other qualified Vertex study. If completed on the same day, the Schedule of Assessments in the other qualified Vertex study should be followed and study assessments in this study that were specified to be performed in the other qualified Vertex study do not have to be repeated. If the subject does not resume participation in this study, they will not be required to complete a separate ETT visit.

#### **ETT Visit**

If a subject prematurely discontinues study treatment for any reason other than to enroll in another qualified Vertex study, an ETT Visit should be scheduled as soon as possible after the subject decides to terminate study treatment.

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

If a subject withdraws consent for the study, no further assessments will be performed. Vertex may retain and continue using the study data and samples after the study ends, and may use the samples and information in the development of the study compound, for other drugs and diagnostics, in publications and presentations, and for education purposes. If a subject withdraws from the study, the study data and samples collected will remain part of the study (Section 9.9).

### **9.1.4 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 study 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.

### **9.1.5 Completion of Study Participation**

Completion of study participation for each individual subject is defined as: the Safety Follow-up Visit; or, in situations in which the ETT Visit, Departing Visit, or the Week 48 Visit replaces the Safety Follow-up Visit (Section 9.1.2), the ETT Visit, Departing Visit, or the Week 48 Visit.

If subjects withdraw consent or assent, completion of study participation is defined as date of withdrawal of consent or assent, whichever is earlier (Section 9.9).

If subjects are lost to follow-up (Section 9.1.4), the date of completion of study participation will be defined as the date of last contact.

The end of study is defined in Section 13.2.9.

### **9.1.6 Use of Remote Measures**

Remote measures may be used for a number of study visits as detailed in Table 3-1. The decision whether to conduct a study visit remotely or in clinic will be at the discretion of the investigator; if the investigator determines that study visits will be conducted remotely, the medical monitor should be notified.

Whenever local regulations or site practice do not allow remote measures, visits will be conducted at the site.

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

- Electronic or remote consent and reconsent may be used, as allowed by local regulations.
- Study drug may be shipped directly from the site to the subject, as applicable and as allowed by local regulations.
- Study visits may be conducted as in-home visits by qualified personnel. All visits must have a consultation between the subject and investigator (i.e., in person, phone, or telemedicine video conference) within 1 business day after the home health visit, which can be outside the visit window.
- Study assessments may be performed or overseen by qualified personnel conducting the in-home visits using Vertex supplied equipment, as applicable (e.g., weight measurement).
- Remote monitoring visits may be implemented as applicable (including remote source data verification) and as allowed per local regulations.

## **9.2 Method of Assigning Subjects to Treatment Groups**

This is an open-label study.

### **9.3 Rationale for Study Elements**

#### **9.3.1 Study Design and Population**

This Phase 3b study will enroll subjects who completed a parent study of ELX/TEZ/IVA and meet eligibility criteria. Results from this study will provide information on the safety of ELX/TEZ/IVA in subjects with CF who are 12 years of age and older.

### 9.3.2 Study Drug Dose and Duration

To evaluate safety and tolerability the study drug doses evaluated are the same as the doses evaluated in a parent study.

The overall treatment duration will be 48 weeks, which is considered sufficient for evaluating the safety of treatment with ELX/TEZ/IVA.

### 9.3.3 Rationale for Study Assessments

All safety assessments are standard parameters for clinical studies in drug development.

### 9.4 Study Restrictions

Table 9-1 lists prohibited medications. A non-exhaustive list of study prohibitions and cautions for medications will be provided in the Study Reference Manual. Guidance of concomitant medications is provided in Section 9.5.

**Table 9-1 Prohibited Medications**

| Medication                                                                                             | Timing of Restriction                                                                                                       |                                                        |                                                                                                                                                                                                                                                    |
|--------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                        | Start of Restriction                                                                                                        | End of Restriction                                     | Rationale                                                                                                                                                                                                                                          |
| Moderate and strong CYP3A inducers                                                                     | None allowed within 14 days before the first dose of the study drug on Day 1                                                | None allowed through completion of study participation | ELX, TEZ, and IVA are metabolized extensively via CYP3A4. Therefore, use of moderate and strong inducers of CYP3A and moderate and strong inhibitors of CYP3A, which have the potential to alter the exposure of ELX, TEZ, or IVA, are prohibited. |
| Moderate and strong CYP3A inhibitors (except ciprofloxacin) <sup>a</sup>                               | None allowed within 14 days before the first dose of the study drug on Day 1                                                | None allowed through completion of study participation |                                                                                                                                                                                                                                                    |
| CFTR modulators (investigational or approved), except for study drugs in a parent study and this study | None allowed within 28 days or 5 terminal half-lives (whichever is longer) before the first dose of the study drug on Day 1 | None allowed until after the last dose of study drug   | These agents may confound the results of this study.                                                                                                                                                                                               |

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

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

### 9.5 Prior and Concomitant Medications

Information regarding prior and concomitant medications, including CF medications, other medications, and herbal and naturopathic remedies, will be collected in each subject's source documentation for medications taken within the 56 days before the first dose of study drug in this study through completion of study participation, as defined in Section 9.1.5. For subjects who enroll in another qualified Vertex study and resume participation in this study, any new medications started after the subject first departs this study will be collected for the period after the Departing Visit and before study drug dosing resumes in this study, through completion of study participation.

- Subjects should remain on a stable treatment regimen for their CF through completion of study participation. Stable treatment regimen is defined as the current treatment regimen for CF that subjects have been following for at least 28 days before Day 1. Subjects should not

initiate long-term treatment with new medication from 28 days before the Day 1 Visit through completion of study participation. Guidelines for stable treatment regimens for CF are as follows:

- o Subjects who are taking inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the study.
- o Subjects who cycle onto and off of an inhaled antibiotic should continue on their prior schedule.
- o Subjects who alternate between 2 different inhaled antibiotics should remain on the same cycling schedule during the study.
- Subjects may receive doses of prednisone or prednisolone of up to 10 mg/day chronically, or up to 60 mg daily for up to 5 days.
- ELX may inhibit OATP1B1 and OATP1B3, which may increase the exposure of medicinal products that are substrates for these transporters. Substrates such as statins, glyburide, nateglinide, and repaglinide should be used with caution.
- IVA is a weak inhibitor of P-glycoprotein (P-gp). Administration of IVA may increase systemic exposure of medicinal products that are sensitive substrates of P-gp, which may increase or prolong their therapeutic effect and adverse reactions. Digoxin or other substrates of P-gp with a narrow therapeutic index, such as cyclosporine, everolimus, sirolimus, and tacrolimus, should be used with caution and appropriate monitoring.
- IVA may inhibit CYP2C9; therefore, during coadministration with warfarin, additional monitoring of the international normalized ratio is recommended. Other medicinal products that are CYP2C9 substrates for which exposure may be increased include glimepiride and glipizide; these should be used with caution.
- Information about bronchodilator use during the study will be collected and documented.

## **9.6 Administration**

### **9.6.1 Dosing**

Study drug tablets will be administered orally as ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h (e.g., 2 ELX/TEZ/IVA fixed-dose combination [FDC] tablets in the morning and 1 IVA tablet in the evening). Additional information is provided in the Pharmacy Manual.

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

1. It is recommended that the dose be taken within 30 minutes of the start of the meal or snack.
2. All doses of study drug (morning and evening, as applicable) should be administered at approximately every 12 hours ( $\pm$  2 hours) on each dosing occasion (e.g., if the morning doses of study drug are administered at 08:00 hour on Day 1, all subsequent morning doses should be administered between 06:00 hour and 10:00 hour).
3. On days of scheduled clinic visits, the morning dose of ELX/TEZ/IVA will be administered at the site after predose assessments have been completed, if applicable. The meal or snack will be provided by the site for the morning dose of ELX/TEZ/IVA.

4. Subjects will be instructed to bring all used and unused materials associated with the study drug to the site; study drug will be dispensed at each visit, as appropriate.

### **9.6.2 Missed Doses**

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

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

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

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

### **9.7 Dose Modification for Toxicity**

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

### **9.8 Study Drug Interruption and Stopping Rules**

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

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

#### **9.8.1 Liver Function Tests**

The central laboratory will notify the medical monitor of alanine transaminase (ALT) or aspartate transaminase (AST) >3 × upper limit of normal (ULN) and total bilirubin >2 × ULN that are derived from centrally submitted samples.

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

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

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

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

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

Subjects who enroll in this study on a drug interruption because of transaminase elevations in a parent study may NOT receive the first dose of study drug until transaminases return to baseline values or  $\leq 2 \times$  ULN, whichever is higher.

Study drug administration **must be discontinued** if the following criteria are met:

- Subsequent ALT or AST values confirm the initial elevation that satisfied the interruption rule (above), and no convincing alternative etiology (e.g., acetaminophen use, viral hepatitis, alcohol ingestion) is identified, regardless of whether transaminase levels have improved

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

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

### **9.8.2 Rash**

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

### **9.9 Removal of Subjects**

Subjects may withdraw from the study at any time at their own request or the request of the subject's parent or legal guardian. 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.

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

- Meets any of the stopping (discontinuation) criteria (Section 9.8)
- Becomes pregnant (Section 11.2.8.2)

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 9.1.2), and follow up with the subject regarding any unresolved AEs.

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

## **9.10 Replacement of Subjects**

Subjects who withdraw or are withdrawn during the study drug Treatment Period will not be replaced.

# **10 STUDY DRUG INFORMATION AND MANAGEMENT**

## **10.1 Preparation and Dispensing**

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

## **10.2 Packaging and Labeling**

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

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

Table 10-1 provides the study drug information. The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for via the drug accountability forms as instructed by Vertex.

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

**Table 10-1 Study Drug: Dosing Form/Route/Strength**

| Drug Name, Dosing Form, Route | Tablet Strength |
|-------------------------------|-----------------|
| ELX/TEZ/IVA, FDC tablet, oral |                 |
| ELX                           | 100 mg          |
| TEZ                           | 50 mg           |
| IVA                           | 75 mg           |
| IVA, tablet, oral             | 150 mg          |

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

## **10.4 Drug Accountability**

The pharmacist or designated study site staff will maintain information about the dates and amounts of (1) study drug received; (2) study drug dispensed to the subjects; and (3) study drug returned by the subjects. Subjects will be instructed to return all used and unused materials associated with the study drug to the site. These materials will be retained at the site according to instructions provided by Vertex or its designee. The study monitor will review study drug records and inventory throughout the study. If a site uses a site-specific drug accountability system and/or process, including processes associated with the destruction of returned materials, the process must be documented and approved by Vertex. The study monitor should review the drug accountability documentation on a regular basis. The study monitor will promptly communicate to Vertex any discrepancies he/she is unable to resolve with the site.

## **10.5 Disposal, Return, or Retention of Unused Drug**

The study site staff or pharmacy personnel will retain all materials returned by the subjects until the study monitor has performed drug accountability. The investigator will ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Vertex. Destruction will be adequately documented.

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

## **10.6 Compliance**

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

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

## **10.7 Blinding and Unblinding**

This is an open-label study.

## **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. Select demographic and baseline characteristic and medical history will be derived from a parent study.

### **11.2 Safety**

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

For subjects <18 years of age on the date of informed consent in a parent study, ophthalmological examinations will be performed as specified in Table 3-1.

#### **11.2.1 Adverse Events**

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

#### **11.2.2 Clinical Laboratory Assessments**

Blood and urine samples will be analyzed at a central laboratory, with the exception of the urine pregnancy test. As described below, urine pregnancy tests will either be analyzed by the site or at home using a home pregnancy test kit. On Day 1 (and the Returning Visit if applicable), blood samples will be collected before the first dose of the study drug.

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 11-1.

**Table 11-1 Safety Laboratory Test Panels**

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

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

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

**Pregnancy ( $\beta$ -human chorionic gonadotropin) Tests for Female Subjects:** Female subjects must have a pregnancy test every 4 weeks. Serum pregnancy tests will be performed at the study site and analyzed at the central laboratory. Urine pregnancy tests will be performed and analyzed at the site or, at assessment time points when telephone contact takes the place of a study visit, at home by using a home kit provided by the study site. Results of a home urine pregnancy test will be reported to the site by telephone. The urine pregnancy test on Day 1 (and the Returning Visit if applicable) must be negative before the first dose of study drug is administered to the subject. Additional pregnancy tests may be required according to local regulations and/or requirements.

**Follicle-stimulating Hormone (FSH):** Blood samples for FSH may be measured as needed for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be in the postmenopausal range as determined by the laboratory performing the test.

**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.

### **11.2.3 Physical Examinations and Vital Signs**

A PE of all body systems and vital signs assessment will be performed at 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 Day 1, any clinically significant abnormal findings in PEs will be reported as AEs.

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.

### **11.2.4 Height and Weight**

Height and weight will be measured with shoes off. For subjects whose date of informed consent occurs after their 21<sup>st</sup> birthday, height will not be collected in this study. For subjects whose date of informed consent occurs on or before their 21<sup>st</sup> birthday, height will be collected through the first visit after the subject's 21<sup>st</sup> birthday and does not need to be collected at future visits.

### **11.2.5 Pulse Oximetry**

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

### **11.2.6 Electrocardiograms**

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

- The ECG will be done before any other procedures that may affect heart rate (HR), such as blood draws.
- 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 study completion will be recorded as AEs.

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

ECGs fall below the threshold value that triggered the repeat measurement. A subject with a QTcF value above the threshold value will discontinue dosing.

### **11.2.7 Ophthalmologic Examination**

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

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

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

Subjects who are <18 years of age on the date of informed consent in a parent study will have an ophthalmologic examination by the Week 48 Visit or the ETT Visit/Departing Visit (for subjects who prematurely discontinue study drug if the subject has received at least 12 weeks of study drug [in a parent study and current study] since their last ophthalmologic examination), whichever comes first; except for those subjects who have withdrawn consent or assent. This examination should be completed within 4 weeks before the Week 48 Visit, unless the subject prematurely discontinues study drug, in which case this examination should occur by the Safety Follow-up Visit (or ETT Visit/Departing Visit for subjects who do not complete a Safety Follow-up Visit), as described in Table 3-1.

Any clinically significant abnormal findings will be reported as AEs.

### **11.2.8 Contraception and Pregnancy**

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

#### **11.2.8.1 Contraception**

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

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. True abstinence must be practiced from the date of informed consent through 90 days after the last dose of study drug.
- If the subject is male and 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 subject is female and is of non-childbearing potential. To be considered of non-childbearing potential, the female must meet at least 1 of the following criteria:

- o Postmenopausal: Amenorrheic for at least 12 consecutive months and a serum FSH level within the laboratory's reference range for postmenopausal females
- o Documented hysterectomy or bilateral oophorectomy/salpingo-oophorectomy
- o Note: All other females (including females with tubal ligations and premenarchal females) 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. Methods of contraception must be in successful use from signing of consent (or assent, when applicable), approximately 28 days before the first dose of study drug (unless otherwise noted), and until 90 days following the last dose of study drug. Additional contraception requirements may need to be followed according to local regulations and/or requirements. Acceptable methods of contraception are listed in Table 11-2.

**Table 11-2    Acceptable Methods of Contraception**

|                                                                                                                                                     | Male Subjects and<br>Their Female<br>(Non-study) Partners | Female Subjects and<br>Their Male (Non-study)<br>Partners |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------|
| Vasectomy performed at least 6 months previously, with a documented negative postvasectomy semen analysis for sperm                                 | Yes                                                       | Yes                                                       |
| Bilateral tubal occlusion (e.g., ligation) performed at least 6 months previously                                                                   | Yes                                                       | Yes                                                       |
| Male or female condom with or without spermicide <sup>a</sup>                                                                                       | Yes                                                       | Yes                                                       |
| Female barrier contraception (such as diaphragm, cervical cap, or sponge) with spermicide                                                           | Yes                                                       | Yes                                                       |
| Continuous use of an intrauterine device for at least 90 days before the first dose of study drug                                                   |                                                           |                                                           |
| Hormone-releasing                                                                                                                                   | Yes                                                       | Yes                                                       |
| Non-hormone releasing                                                                                                                               | Yes                                                       | Yes                                                       |
| Oral, implanted, injected, or vaginal <b>hormonal</b> contraceptives, if successfully used for at least 60 days before the first dose of study drug | Yes                                                       | Yes                                                       |

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

#### **Additional notes:**

- If over the course of the study the subject meets the criteria for waiving the contraception requirements, the subject does not need to follow the contraceptive methods listed in Table 11-2.
- If over the course of the study the subject's status changes and the subject does not meet the criteria for waiving the contraception requirements, the subject must begin following the contraceptive methods listed in Table 11-2.
- Male subjects must not donate sperm during the period starting from the first dose of study drug until 90 days after the last dose of study drug.

- Female subjects should not nurse a child during the period starting from the first dose of study drug until 90 days after the last dose of study drug.
- Female partners of male subjects should not plan to become pregnant during the study or within 90 days after the last dose of study drug, with the exception of those 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.

### **11.2.8.2      Pregnancy**

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

If a female subject becomes pregnant during study participation, study drug will be permanently discontinued immediately. The investigator will notify the medical monitor and Vertex Global Patient Safety (GPS) within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy using the Pregnancy Information Collection Form. Male subjects with female partners who become pregnant during the study must use a male condom to avoid exposure of a potential embryo or fetus to study drug via the seminal fluid.

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

## **12            STATISTICAL ANALYSIS**

### **12.1           Sample Size**

The primary objective of the study is the evaluation of the safety of ELX/TEZ/IVA. This is an open-label extension study that will enroll the subjects from parent studies who meet eligibility criteria in this study.

Up to approximately 160 subjects are expected to enroll in this open-label extension study.

### **12.2           Analysis Sets**

The **All Subjects Set** is defined as all subjects who were enrolled (defined as subject having data in the clinical database) in this study. This analysis set will be used for individual subject data listings and disposition summary tables unless otherwise specified.

The **Safety Set** is defined as all subjects who have received at least 1 dose of study drug in this study. The Safety Set will be used for subject demographics and baseline characteristics and for all safety analyses unless otherwise specified.

### **12.3           Statistical Analysis**

#### **12.3.1        General Considerations**

All individual subject data for subjects who were enrolled or received at least 1 dose of study drug will be presented in individual subject data listings.

**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 ELX/TEZ/IVA either in a parent study or this study, as applicable. For assessments collected in duplicate or triplicate, the baseline value will be defined as the average of non-missing values.

**Change (absolute change) from baseline** will be calculated as Post-baseline value – Baseline value.

**TE Period** will include the time from the first dose of study drug in this study to 28 days after the last dose of study drug or to the completion of study participation (as defined in Section 9.1.5), whichever occurs first. For subjects who enroll in another qualified Vertex study before completing this study and resume participation in this study, the TE Period will exclude the time spent in the other study.

### **12.3.2 Background Characteristics**

Subject disposition, demographic and baseline characteristics, prior and concomitant medications, exposure, compliance, and important protocol deviations (IPDs) will be summarized.

#### **12.3.2.1 Subject Disposition**

Subject disposition will be summarized for the All Subjects Set. The number and percentage of subjects in the following categories will be summarized as appropriate:

- All Subjects Set
- Safety Set
- Completed treatment
- Prematurely discontinued treatment and the reasons for discontinuation
- Completed study
- Prematurely discontinued the study and the reasons for discontinuation
- Departed this study to enroll in another qualified Vertex study
- Departed this study to enroll in another qualified Vertex study and returned to this study

#### **12.3.2.2 Demographics and Baseline Characteristics**

Demographics and baseline characteristics will be summarized by descriptive summary statistics. Demographics and baseline characteristics will be obtained from a parent study baseline.

The following demographics and baseline characteristics will be summarized for the Safety Set and will include (but are not limited to) sex, race, age, baseline weight, baseline height, and baseline body mass index (BMI), and baseline percent predicted forced expiratory volume in 1 second (ppFEV<sub>1</sub>).

Medical history will be summarized descriptively for the Safety Set.

#### **12.3.2.3 Prior and Concomitant Medications**

Medications used will summarized descriptively and categorized as the following:

- **Prior medication:** any medication that was administered within the 56 days before the first dose of study drug in this open-label study. For subjects who enroll in another qualified Vertex study and resume participation in this study, any new or changed medication administered after the Departing Visit and prior to the first dose of study drug after resuming participation in this study will also be considered prior medication.
- **Concomitant medication:** medication continued or newly received during the TE Period in this open-label study.
- **Post-treatment medication:** medication continued or newly received after the TE Period in this open-label study.

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

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

#### **12.3.2.4 Study Drug Exposure and Compliance**

Study drug exposure will be summarized based on the Safety Set, defined as the last day of study drug in this open-label study minus the first day of study drug in this open-label study plus 1, regardless of study drug interruption. For subjects who enroll in another qualified Vertex study and resume participation in this study, time spent in the other study will be excluded.

Study drug compliance will be summarized based on the Safety Set and will be calculated as:  $100 \times [1 - (\text{total number of days of study drug interruption in this open-label study}) / (\text{duration of study drug exposure in days in this open-label study})]$ . A study drug interruption on a given day is defined as an interruption of any study drug on that day. For subjects who enroll in another qualified Vertex study and resume participation in this study, time spent in the other study will be excluded.

#### **12.3.2.5 Important Protocol Deviations**

An IPD is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

All IPDs will be provided in an individual subject data listing, as appropriate.

#### **12.3.3 Efficacy Analysis**

Not applicable.

#### **12.3.4 Safety Analysis**

All safety analyses will be based on the TE Period in this open-label study for subjects in the Safety Set, unless otherwise specified.

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

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

All safety data will be presented in individual subject data listings. Only descriptive analyses of safety data will be performed. Additional details will be described in the statistical analysis plan (SAP).

#### **12.3.4.1 Adverse Events**

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

- **Pretreatment AE:** any AE that occurred since the end of the TE Period in a parent study and before the first dose of ELX/TEZ/IVA in the TE Period in the open-label study. For subjects who depart this study to enroll in another qualified Vertex study and resume participation in this study, details of pre-treatment AEs will be specified in the SAP.
- **TEAE:** any AE that worsened (either in severity or seriousness) or newly developed at or after the first dose date of ELX/TEZ/IVA in the TE Period in this open-label study.
- **Post-treatment AE:** any AE that worsened (either in severity or seriousness) or newly developed after the TE Period in this open-label study.

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

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

- Overview of TEAEs
- TEAEs
- Related TEAEs
- TEAEs by maximum severity
- TEAEs by strongest relationship
- Grade 3 and Grade 4 TEAEs
- Serious TEAEs
- Related serious TEAEs
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- TEAEs leading to death

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

Listings containing individual subject level AE data will be provided separately for:

- Serious TEAEs
- Grade 3/4 TEAEs
- TEAEs leading to treatment discontinuation
- TEAEs leading to treatment interruption
- TEAEs leading to death

In addition, all AEs, including pre- and post-treatment AEs, will be presented in individual subject data listings

#### **12.3.4.2 Clinical Laboratory Assessments**

For the TE laboratory measurements, the observed values and change from baseline values of the continuous laboratory parameters will be summarized in SI units at each time point during the TE Period.

For threshold analysis, the number and percentage of subjects with at least 1 threshold event during the TE Period will be summarized. The threshold criteria and selected parameters will be provided in the SAP.

Results of urinalysis and pregnancy tests will be listed in individual subject data listings only. In addition, a listing containing individual subject laboratory assessment values will be provided. This listing will include data from scheduled and unscheduled time points.

Additional safety laboratory data analyses may be described in the SAP.

#### **12.3.4.3 Electrocardiogram**

For the TE ECG measurements, a summary of observed values and change from baseline values will be provided at each time point during the TE Period, for the following ECG interval measurements (in msec): RR, PR, QT, QT corrected for HR intervals (QTcF), QRS duration, and HR (beats per minute).

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

Additional ECG analyses may be described in the SAP.

#### **12.3.4.4 Vital Signs**

For the TE vital signs measurements, the observed values and change from baseline values will be summarized at each time point during the TE Period in this open-label study. The following vital signs parameters will be summarized: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (beats per minute), and respiratory rate (breaths per minute).

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

Additional vital signs analyses may be described in the SAP.

#### **12.3.4.5 Pulse Oximetry**

For the TE pulse oximetry measurements, a summary of observed values and change from baseline values will be provided at each time point during the TE Period, for the percent of oxygen saturation by pulse oximetry.

#### **12.3.4.6 Other Safety Analyses**

Details of other safety analyses may be included in the SAP.

### **12.4 Interim Analysis**

Not applicable

### **12.5 Data Monitoring Committee Analysis**

Not applicable.

## **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
  - 28 days after the last dose of study drug, or
  - the ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (see Section 9.1.3)
- For subjects who depart this study to enroll in another qualified Vertex study: through the time of enrollment in another qualified Vertex study
- For subjects who depart this study to enroll in another qualified Vertex study and resume participation in this study, AEs will be collected from the time of the Returning Visit until the subject completes study participation in this study. AEs that fully occur (start and end) in the other qualified Vertex study will be recorded as medical history; AEs that started during participation in the other qualified Vertex study and are ongoing at the time of the Returning Visit in this study will be recorded as AEs in this study.

All subjects or the subjects' parents or legal guardians, as appropriate, 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](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm) (Accessed February 2022). When considering the severity of an AE in a pediatric subject, the investigator will consider that reference ranges for pediatric clinical laboratory parameters may differ from those in the CTCAE. The severity of an AE described by a term that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

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

| Classification                    | Description                                                                                                                                                                        |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Grade 1 (Mild)</b>             | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated                                                                          |
| <b>Grade 2 (Moderate)</b>         | Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL <sup>a</sup>                                                            |
| <b>Grade 3 (Severe)</b>           | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL <sup>b</sup> |
| <b>Grade 4 (Life-threatening)</b> | Life-threatening consequences; urgent intervention indicated                                                                                                                       |
| <b>Grade 5 (Death)</b>            | Death related to adverse event                                                                                                                                                     |

Source: [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm) (Accessed February 2022)

ADL: activities of daily living; AE: adverse event

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

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

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

### 13.1.1.5 Adverse Event Causality

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

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

| Classification          | Definition                                                                                                                                                                                                                                                                                                                                  |
|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Related</b>          | There is an association between the event and the administration of investigational study drug, a plausible mechanism for the event to be related to the investigational study drug and causes other than the investigational study drug have been ruled out, and/or the event reappeared on re-exposure to the investigational study drug. |
| <b>Possibly related</b> | There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.                |
| <b>Unlikely related</b> | The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.                                                                                                                                                                                            |

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

| Classification     | Definition                                                                                                                                                   |
|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Not related</b> | The event is related to an etiology other than the investigational study drug (the alternative etiology will be documented in the subject's medical record). |

AE: adverse event

**13.1.1.6 Study Drug Action Taken**

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

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

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

AE: adverse event

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

**13.1.1.7 Adverse Event Outcome**

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

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

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

AE: adverse event

**13.1.1.8 Treatment Given**

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

## **13.1.2      Serious Adverse Events**

### **13.1.2.1    Definition of a Serious Adverse Event**

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

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

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

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

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

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

For subjects who depart this study to participate in another qualified Vertex study, SAEs will be collected in the same manner as described for AEs (Section 13.1.1.3).

For SAEs that occur after obtaining informed consent and assent (where applicable) through completion of study participation, the SAE Form will be completed for new/initial events as well

as to report follow-up information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via:

Email: [REDACTED] (preferred choice)

Fax: [REDACTED]

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

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

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

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

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

## **13.2 Administrative Requirements**

### **13.2.1 Product Complaints**

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

Product complaints are to be reported to Vertex.

### **13.2.2 Ethical Considerations**

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

documents will be provided to the IRB/IEC by the investigator or Vertex, as allowable by local applicable laws and regulations.

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

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

### **13.2.4      Investigator Compliance**

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

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

### **13.2.5      Access to Records**

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

### **13.2.6      Subject Privacy**

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all data provided to Vertex, 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 and the review of the data collection process. The FDA and regulatory authorities in other jurisdictions, including the IRB/IEC, may also request access to all study records, including source documentation, for inspection.

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

requirements including authorization allowing the site access to and use of the subject's personally identifiable health information, authorization for the site to disclose such information to Vertex, the FDA, and other parties requiring access under the protocol, and statements as to the purpose for which such information may be used and for how long.

### **13.2.7 Record Retention**

The investigator will maintain all study records according to current ICH E6 GCP Guidelines and/or applicable local regulatory requirement(s), whichever is longest, as described in the Clinical Trial Agreement. If the investigator withdraws from the responsibility of keeping the study records, custody will be transferred to a person willing to accept the responsibility and Vertex will be notified.

### **13.2.8 Study Termination**

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

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

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

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

### **13.2.9 End of Study**

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

## **13.3 Data Quality Assurance**

Vertex or its designated representative will conduct a study site visit to verify the qualifications of each investigator, inspect clinical study site facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct study documentation. Vertex will provide, or assess and approve, any electronic data capture (EDC) tools.

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

### **13.4 Monitoring**

The study will be monitored by Vertex or its designee in accordance with written procedures. Monitoring and auditing procedures developed or approved by Vertex for these activities comply with GCP regulatory requirements and guidelines. The monitoring strategy may include onsite, remote, and central monitoring activities, in accordance with local regulations. The study site monitor will ensure that the investigation is conducted according to the protocol design and regulatory requirements.

### **13.5 Electronic Data Capture**

Sites will use an EDC tool to record data for each enrolled subject.

It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported. 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, including the dates and details of study procedures, AEs, other observations, and subject status.

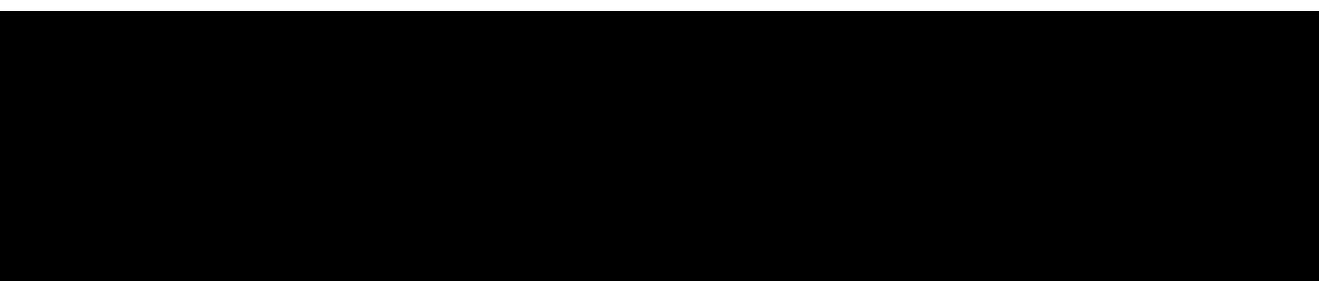
The audit trail entry will show the user's identification information and the date and time of any correction. The investigator will provide formal approval of all data reported to Vertex, including any changes made, to endorse the final submitted data for the subjects for whom the investigator is responsible.

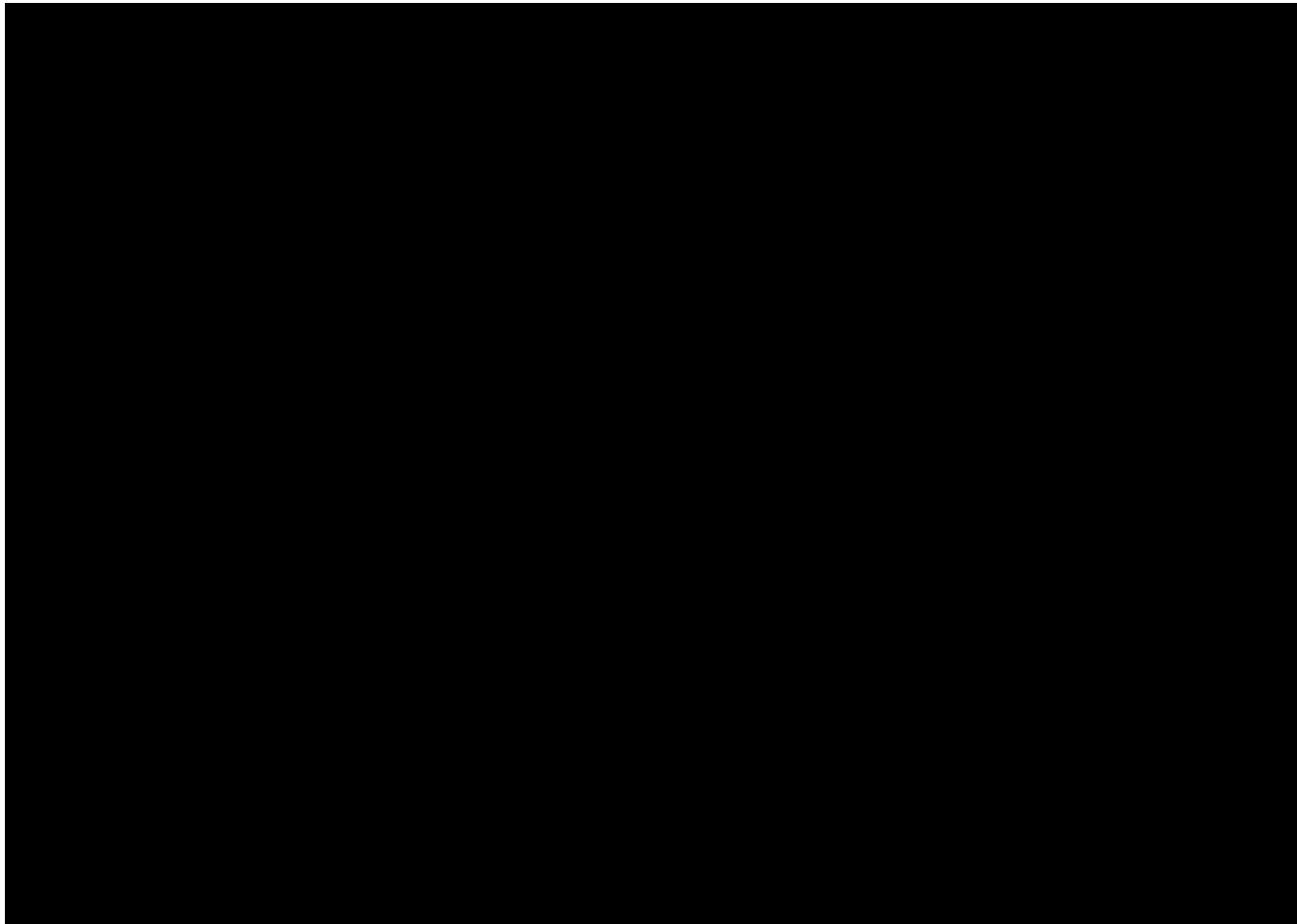
### **13.6 Confidentiality and Disclosure**

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

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

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





### **13.7.2 Clinical Study Report**

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

**14 REFERENCES**

- 1 Cystic Fibrosis Foundation. 2019 Patient Registry Annual Data Report. Bethesda, MD: 2020.
- 2 European Cystic Fibrosis Society. 2018 ECFS Patient Registry Annual Data Report. Karup, Denmark: 2020.
- 3 Ruseckaite R, Ahern S, Ranger T, Dean J, Gardam M, Bell S, et al. The Australian Cystic Fibrosis Data Registry Annual Report, 2017. Monash University: Department of Epidemiology and Preventative Medicine; March 2019, Report #20.
- 4 Cystic Fibrosis Canada. The Canadian Cystic Fibrosis Registry 2019 Annual Data Report. Toronto, Ontario: Cystic Fibrosis Canada; 2020.
- 5 Rommens JM, Iannuzzi MC, Kerem B, Drumm ML, Melmer G, Dean M, et al. Identification of the cystic fibrosis gene: Chromosome walking and jumping. *Science*. 1989;245(4922):1059-65.
- 6 Kreindler JL. Cystic fibrosis: Exploiting its genetic basis in the hunt for new therapies. *Pharmacol Ther*. 2010;125(2):219-29.
- 7 Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *Lancet Respir Med*. 2017;5(2):107-18.
- 8 Sawicki GS, McKone E, Pasta DJ, Wagener J, Johnson C, Konstan MW. The effect of ivacaftor on the rate of lung function decline in CF patients with a G551D-CFTR mutation. *J Cyst Fibros*. 2014;13:S6.
- 9 Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good publication practice for communicating company-sponsored medical research: GPP3. *Ann Intern Med*. 2015;163(6):461-4.
- 10 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 14 February 2022.

## 15 PROTOCOL SIGNATURE PAGES

## 15.1 Sponsor Signature Page

|                                                                                                                                                         |              |            |     |               |                  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|------------|-----|---------------|------------------|
| Protocol #:                                                                                                                                             | VX20-445-121 | Version #: | 2.0 | Version Date: | 14 February 2022 |
| Study Title: A Phase 3b Open-label Study Evaluating the Safety of Elexacaftor/Tezacaftor/Ivacaftor Combination Therapy in Subjects With Cystic Fibrosis |              |            |     |               |                  |

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

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Printed Name

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## Title

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Signature

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Date

**15.2           Investigator Signature Page**

|                                                                                                                                                         |              |            |     |               |                  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|------------|-----|---------------|------------------|
| Protocol #:                                                                                                                                             | VX20-445-121 | Version #: | 2.0 | Version Date: | 14 February 2022 |
| Study Title: A Phase 3b Open-label Study Evaluating the Safety of Elexacaftor/Tezacaftor/Ivacaftor Combination Therapy in Subjects With Cystic Fibrosis |              |            |     |               |                  |

I have read Protocol VX20-445-121, Version 2.0, and agree to conduct the study according to its terms. I understand that all information concerning ELX (VX-445)/TEZ (VX-661)/IVA (VX-770) and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

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Printed Name

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Signature

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Date