1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan

(Methods)

Protocol Number VX15-371-101, Version 3.0

(Final Analysis)

A Phase 2a, Randomized, Double-blind, Placebo-controlled, Incomplete Block, Crossover Study to Evaluate the Safety and Efficacy of VX-371 in Subjects Aged 12 Years or Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation, and Being Treated With Orkambi

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Version: 1.0

Version Date of SAP: 27July2017

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2 TABLE OF CONTENTS

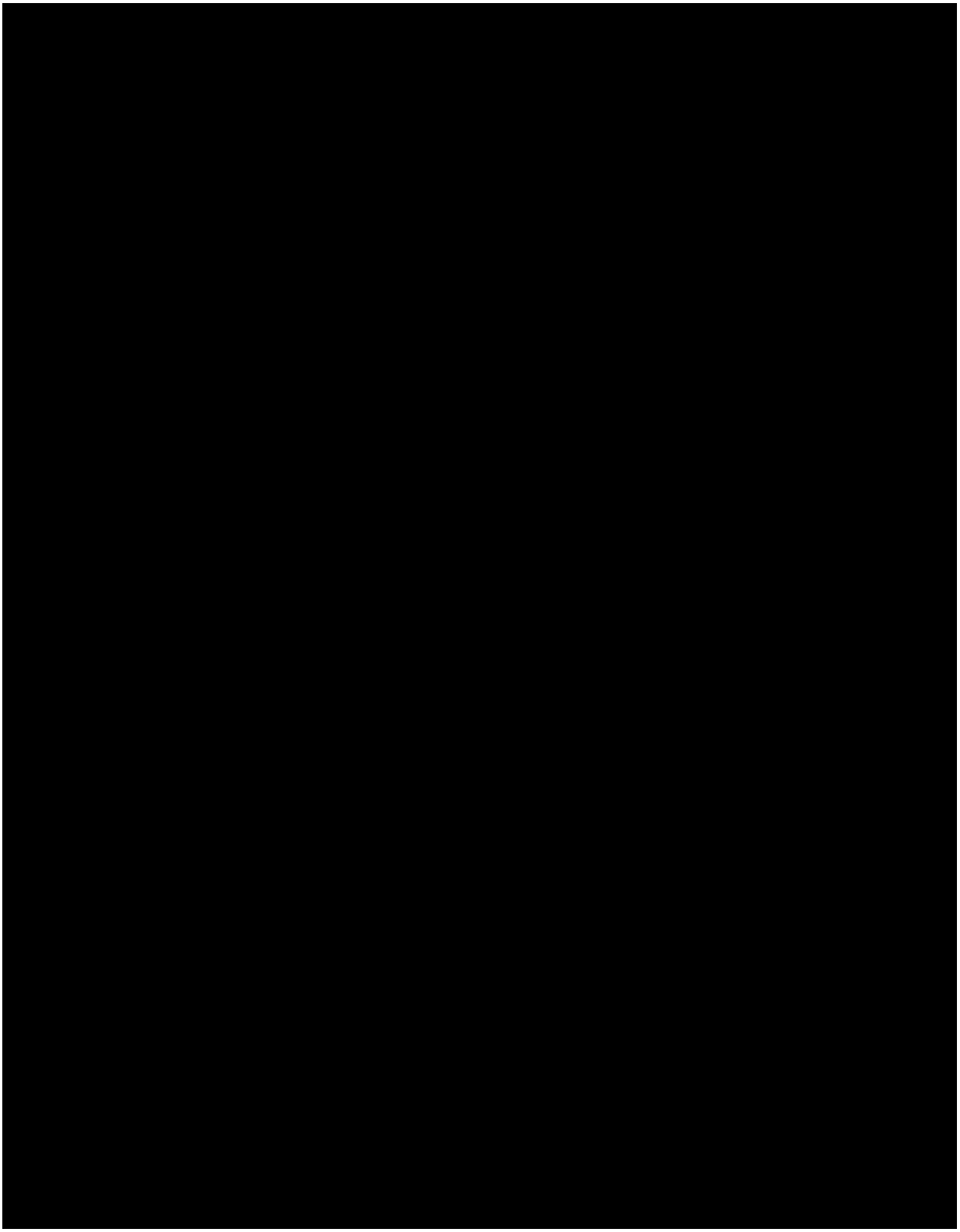
List of Tables

List of Figures

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ATC	Anatomic class
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	Body mass index (kg/m2)
Bid	Bis in die (twice a day)
Bpm	Beats per minute
CF	Cystic fibrosis
[redacted]	[redacted]
CFTR	Cystic fibrosis transmembrane conductance regulator gene
CI	Confidence Interval
CPAP	Clinical Pharmacology Analysis Plan
CRO	Contract research organization
CSP	Clinical study protocol
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ETT	Early Termination of Treatment
FAS	Full Analysis Set
$FEF_{25-75\%}$	Forced midexpiratory flow rate (L/sec)
FEV_1	Forced expiratory volume (L) in 1 second
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity (L)
GLI	Global Lung Initiative
GPS	Global Patient Safety
HS	Hypertonic Saline
ICF	Informed consent form
IDMC	Independent Data Monitoring Committee
IPD	Important Protocol Deviation
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LFT	Liver function test
LLN	Lower limit of normal
max	Maximum value
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
min	Minimum value
MMRM	Mixed Model for Repeated Measures
PI	Principal Investigator
PK	Pharmacokinetic/pharmacokinetics
$ppFEV_1$	Percent predicted forced expiratory volume in 1 second
PT	Preferred Term
q12h	Every 12 hours
QRS	Q, R, and S-wave define the QRS-complex in an ECG
QT	QT interval represents the duration of ventricular depolarization and subsequent repolarization; it is measured from the beginning of the QRS complex to the end of the T wave
QTcF	QT interval corrected for heart rate with Fridericia's correction [$QTcF = QT/RR^{0.33}$]
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SI	Système international
SOC	System organ class
TBILI	Total bilirubin
TE	Treatment Emergent
TEAE	Treatment-emergent adverse event
TFL	Tables, figures and listings
UB	Unblinded Biostatistician
ULN	Upper limit of normal



4 INTRODUCTION

This SAP, which describes the planned final analyses for the Study VX15-371-101 (Study 101) data, is based on the following:

- clinical study protocol (CSP) for Study 101 (Version 3.0, dated 22 July 2016).
- approved electronic case report forms (eCRF) for Study 101 (Version 5.0, dated 4 April 2017).

Study 101 is a Phase 2a, randomized, double-blind, placebo-controlled, incomplete block, crossover, multicenter, study in subjects ≥12 years of age with cystic fibrosis (CF) who are homozygous for the *F508del-CFTR* mutation and who are being treated with Orkambi (lumacaftor/ivacaftor). All subjects must be receiving stable treatment with Orkambi before the first dose of inhaled study drug and through the Safety Follow-up Telephone Contact or Safety Follow-up Visit.

This SAP (Methods) documents the planned final statistical analyses of efficacy and safety endpoints defined in the study protocol for Study 101 and describes the corresponding data presentations. It also documents analyses for additional efficacy and safety variables not specified in the protocol, which will provide supportive information to enhance the scientific understanding of the drug entity.

The study will also evaluate the pharmacokinetic (PK) characteristics of VX-371, [redacted] in this patient population. PK analyses will be documented separately in the clinical pharmacology analysis plan (CPAP) for the study.

The Vertex Biometrics department will perform the statistical analysis of the efficacy and safety data. SAS (Version 9.4) will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the database lock and treatment unblinding for the study.

5 STUDY OBJECTIVES

5.1 Primary Objectives

To evaluate the safety and efficacy of treatment with VX-371 in hypertonic saline (HS) compared to HS alone in subjects with CF who are ≥12 years of age, homozygous for the *F508del-CFTR* mutation, and being treated with Orkambi

5.2 Secondary Objectives

- To evaluate the efficacy of treatment with VX-371 in HS compared with placebo in subjects with CF who are ≥12 years of age, homozygous for the *F508del-CFTR* mutation, and being treated with Orkambi
- To evaluate the efficacy of treatment with VX-371 in HS compared with VX-371 in placebo in subjects with CF who are ≥12 years of age, homozygous for the *F508del-CFTR* mutation, and being treated with Orkambi

- To evaluate the efficacy of treatment with VX-371 in placebo compared with placebo in subjects with CF who are ≥12 years of age, homozygous for the *F508del-CFTR* mutation, and being treated with Orkambi
- To investigate the pharmacokinetics of VX-371 in subjects with CF who are ≥12 years of age, homozygous for the *F508del-CFTR* mutation, and being treated with Orkambi

6 STUDY ENDPOINTS

6.1 Primary Endpoint

- Results of safety and tolerability assessments of adverse events (AEs), spirometry, clinical laboratory values (urine, serum and plasma chemistry, hematology, and coagulation studies), standard 12-lead electrocardiograms (ECGs), vital signs, and ophthalmologic examinations
- Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from study baseline at Day 28 in each Treatment Period

6.2 Secondary Endpoints

- PK parameters for VX-371

7 STUDY DESIGN

7.1 Overall Design

This is a Phase 2a, randomized, double-blind, placebo-controlled, incomplete block, crossover, multicenter, study in subjects ≥12 years of age with CF who are homozygous for the *F508del-CFTR* mutation and who are being treated with Orkambi. All subjects must be receiving stable treatment with Orkambi before the first dose of inhaled study drug (i.e. VX-371 + placebo, VX-371 + HS, HS and placebo administered by nebulizer) and through the Safety Follow-up Telephone Contact or Safety Follow-up Visit.

Table 7-1 Study VX15-371-101 Treatment Sequences

Sequence	Treatment Period 1	Treatment Period 2	N
1	VX-371 + 4.2% HS	4.2% HS	50
2	4.2% HS	VX-371 + 4.2% HS	50
3	VX-371 + 0.17% saline (placebo)	Placebo (0.17% saline)	25
4	Placebo (0.17% saline)	VX-371 + 0.17% saline (placebo)	25

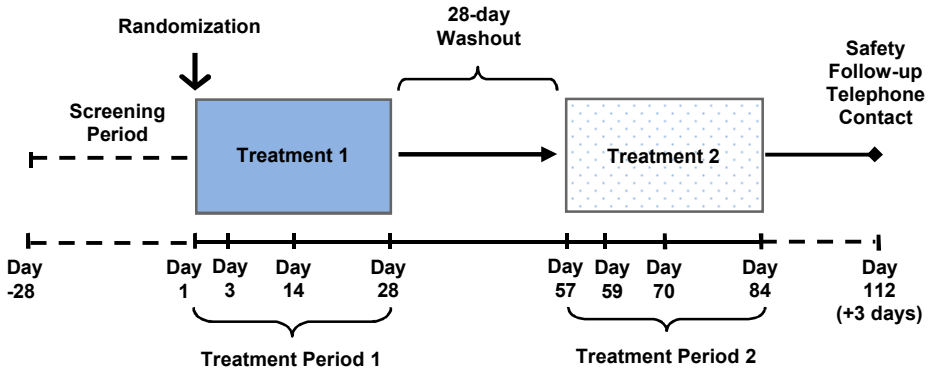
Approximately 150 subjects will be randomized (2:2:1:1) to 1 of the 4 treatment sequences as described in Table 7-1Study VX15-371-101 Treatment Sequences. Each treatment sequence will comprise:

Treatment Period 1 → Washout → Treatment Period 2

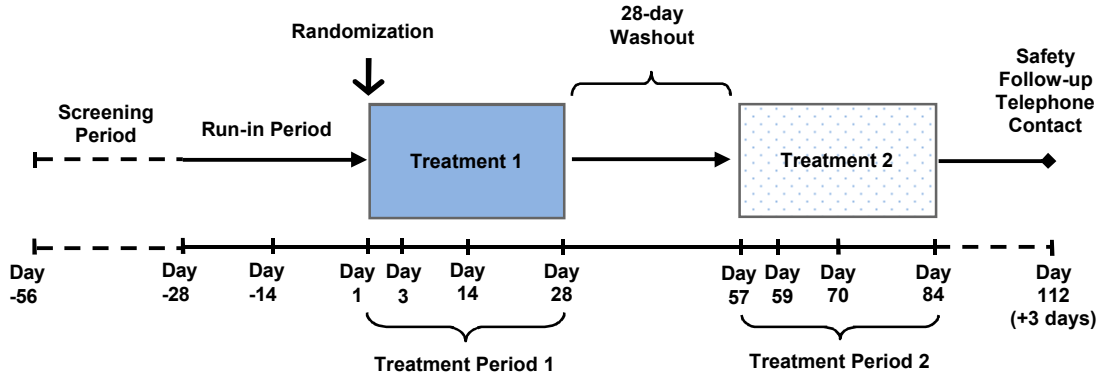
A schematic of the study design is provided in Figure 7-1.

Figure 7-1 Schematic of Study Design VX15-371-101

A. For Orkambi+/HS- Subjects



B. For Orkambi-/HS-, Orkambi-/HS+, and Orkambi+/HS+ Subjects



This study includes the following periods:

- Screening Period:
  - Day -28 to Day -1 relative to the first dose of inhaled study drug for Orkambi+/HS- subjects
  - Day -56 to Day -29 relative to the first dose of inhaled study drug for Orkambi-/HS-, Orkambi-/HS+, and Orkambi+/HS+ subjects
- Run-in Period: Day -28 to Day -1 relative to the first dose of inhaled study drug (for Orkambi-/HS-, Orkambi-/HS+, and Orkambi+/HS+ subjects)
- Treatment Period
  - Treatment Period 1: Day 1 (first dose of inhaled study drug) through Day 28
  - Washout Period: Day 29 through Day 56

- Treatment Period 2: Day 57 through Day 84

- Early Termination of Treatment (ETT) Visit for a subject who discontinues from study drug treatment(s) and who does not complete the remaining assessments in the treatment period during which study drug treatment(s) is discontinued.
- Safety Follow-up Telephone Contact will occur 28 days (+ 3 days) after the Day 84 Visit; or 28 days (+ 3 days) after the Day 28 Visit for a subject who completes this visit but who will not be continuing into Treatment Period 2. (Note: Under certain circumstances, a safety Follow-up Telephone Contact may not be appropriate, and a SFUV may be required.)
- A SFUV will occur 28 days (+ 3 days) after a subject's last dose of study drug (whether inhaled study drug or lumacaftor/ivacaftor) in subjects who:
  - prematurely discontinue one or both study drugs during the course of either treatment period and do not complete the remaining assessments in the treatment period in which discontinuation occurred. In this circumstance, an ETT Visit is required in addition to the SFUV.
  - have a clinical finding during the treatment period or during the 28-day Safety Follow-up Period that requires follow-up in the estimation of the Principal Investigator (PI). An ETT Visit may or may not be required in this circumstance.

7.2 Sample Size and Power

The primary efficacy endpoint is the absolute change in $ppFEV_1$ from study baseline to the Day 28 measurements in each Treatment Period.

The null hypothesis to be tested is that the mean change from study baseline in $ppFEV_1$ to the Day 28 measurements is the same for VX-371 in combination with HS versus HS alone.

To have a feasible sample size and study duration, this study uses a crossover design. Assuming a standard deviation (SD) of 7 percentage points, 50 subjects per sequence (VX-371 + 4.2% HS followed by 4.2% HS; 4.2% HS followed by VX-371 + 4.2% HS) are needed to have approximately 81% power to detect a 3 percentage point treatment difference in the mean absolute change in $ppFEV_1$ from study baseline at Day 28 between VX-371 + HS and HS alone. The study will have approximately 80% power to detect a 3 percentage point (within treatment) change from study baseline at Day 28 in $ppFEV_1$ for VX-371. A 2-sided significance level of 0.05 was used in the sample size calculations. The sample size took into account an assumed dropout rate of 10%.

7.3 Randomization

Approximately 150 subjects will be randomized to 1 of 4 treatment sequences when they are determined to have met all eligibility criteria. Subjects will be randomized in a 2:2:1:1 ratio (VX-371 + 4.2% HS followed by 4.2% HS; 4.2% HS followed by VX-371 + 4.2% HS; VX-371 + placebo followed by placebo; placebo followed by VX-371 + placebo), stratifying by $ppFEV_1$ severity (<70 or ≥ 70).

The 4 treatment sequences are provided in Table 7-1.

An interactive web response system (IWRS) will be used for randomization following a list of randomization codes generated by a designated vendor (Cytel, Inc.).

7.4 Blinding and Unblinding

This is a double-blind study.

7.4.1 Blinding

The subjects and all site personnel, including the investigator, the site monitor, and the study team, will be blinded with the exception of the following:

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of the subject and the fetus in the event of a pregnancy
- Vertex Global Patient Safety (GPS) and Regulatory Affairs personnel to satisfy Serious Adverse Event (SAE) processing and reporting regulations
- External vendor (unblinded) statistician preparing the final (production) randomization list who is not part of the study team
- Vertex IXRS Management for IXRS oversight and system administration
- Independent Monitoring Committee (IDMC)
- Vendor preparing the unblinded analysis for the IDMC
- The bioanalytical external vendor personnel assigned to the study and Vertex Bioanalysis Contract Research Organization (CRO) Monitors who will not be participating in the study team
- The medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time

Spirometry Data Blinding:

Despite treatment blinding, knowledge of the spirometry results has the potential to suggest whether a subject has been administered active inhaled study drug or placebo. Therefore, during the conduct of the study, the Vertex study team will have no access to the postdose (i.e. on or after Day 1) spirometry data. The vendor for central reading of the spirometry data will send only the blinded spirometry files (blinded treatment, with real values for screening and baseline, but with dummy values for all the spirometry assessments after baseline) to Vertex to be used for developing the statistical programs. However, approximately 2 weeks before database lock, during the process of locking the clinical database, a small group of individuals (a biostatistician, a statistical programmer, and a validation statistical programmer) who could be part of the Vertex study team will access the treatment-blinded post-dose spirometry data to ensure there are no significant data issues and to refine the statistical programs. These team members will not have access to the unblinded treatment codes until database lock occurred. Subjects and their caregivers should not be informed of

their study-related spirometry results during the Treatment Period regardless of whether the subject has prematurely discontinued treatment.

7.4.2 Unblinding

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

Unblinding of an individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, investigators will use their best judgment as to whether to unblind without first attempting to contact the medical monitor to discuss and agree to the need for unblinding. If investigators deem it not necessary to unblind immediately, they will first attempt to contact the medical monitor to discuss and agree to the need for unblinding. If investigators have tried but are unable to reach the medical monitor, they will use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding without having successfully reached and discussed the situation with the medical monitor.

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

In addition, the Vertex Medical Information Call Center [redacted] will answer calls 24 hours a day, 7 days a week, 365 days of the year, and will triage these calls to the study medical monitor or appropriate backup.

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor will be notified within 24 hours of the unblinding event. The reason and the date of the unblinding will be documented clearly in the subject's study file. Information about the treatment assignment obtained from the unblinding will be maintained in a secure location with controlled access and will not be shared with the sponsor (Vertex), CRO, or any site personnel (other than the physician treating the subject). In addition, the investigator will consider whether the clinical event that prompted unblinding will be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to Vertex GPS or designee, per section 13.1 of the CSP.

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

8 ANALYSIS SETS

The following analysis sets will be defined: All Subjects Set, Randomized Set, Full Analysis Set (FAS), Safety Set and Run-in Subjects Set.

The **All Subjects Set** is defined as all subjects who have been randomized or have received at least 1 dose of inhaled study drug.

The **Randomized Set** is defined as all subjects who have been randomized.

The **Full Analysis Set (FAS)** is defined as all randomized subjects who carry the intended homozygous *F508del-CFTR* mutation and have received at least 1 dose of inhaled study drug.

The **Safety Set** is defined as all subjects who received at least 1 dose of inhaled study drug.

The **Run-in Subjects Set** is defined as all subjects who received orkambi during the run-in period.

9 STATISTICAL ANALYSIS

9.1 General Considerations

All individual subject data for those randomized or exposed to inhaled study drug will be presented in data listings. Study drug exposure, discontinuations and adverse events during the run-in period will be listed. The Schedule of Assessments is provided in Section 12.1. The precision standards are provided in Section 12.7.

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

Categorical variables will be summarized using counts and percentages.

Study periods: The study period will be divided into 3 segments based on the treatment of inhaled study drug:

- **Pre-treatment period** is defined as the period after the informed consent/assent date and before the initial dosing of inhaled study drug in treatment period 1. For the Orkambi+/HS- subjects, this corresponds to the Screening Period. While for Orkambi-/HS-, Orkambi-/HS+, and Orkambi+/HS+ subjects, it will also include the Run-in Period.

- **Treatment emergent (TE) period**
  - TE period for Treatment Period 1 will correspond to the period from the first dose of inhaled study drug in Treatment Period 1 to 28 days after the last dose of inhaled study drug in Treatment Period 1 and prior to the first dose of Treatment Period 2, or the Safety Follow-up Telephone Contact or Visit, whichever occurs first.
  - TE period for Treatment Period 2 will correspond to data from the first dose of inhaled study drug in Treatment Period 2 through the Safety Follow-up Telephone Contact or Visit , or 28 days after the last dose of inhaled study drug in Treatment Period 2, whichever occurs first.

- **Post-treatment period** is defined as the period after the last date of TE period for Treatment Period 2 to the date of the last study record in the clinical database or the period between the end of TE period for Treatment Period 1 and the start of TE period for

Treatment Period 2. For subjects who do not have Treatment Period 2, the period after the last date of TE period for Treatment Period 1 to the date of the last study record in the clinical database will be considered as post-treatment period.

Baseline: For this crossover study, 2 types of baseline will be defined.

- The **study baseline** is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of inhaled study drug in the study. Study baseline will be used for all summaries of demographics, background, and baseline characteristics, ECG, as well as all efficacy data analyses, including the primary efficacy endpoint analysis.
- The **period baseline** is defined as the most recent nonmissing measurement (scheduled or unscheduled) collected before the first dose of inhaled study drug in each treatment period. For Treatment Period 2, the baseline value should be from an assessment measured after the TE period for Treatment Period 1. Period baseline will be used for all safety data analyses except ECG. Since all ECG assessments will be performed 60 (± 30) minutes after completion of inhaled study drug dosing except measurements at Screening, the study baseline will be used for analysis for both periods.

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

Relative change from study baseline will be calculated as 100 x (post-baseline value - study baseline value)/study baseline value.

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

Relative change from period baseline will be calculated as 100 x (post-baseline value - period baseline value)/period baseline value.

Unscheduled Visits: Unscheduled visit measurements will be included in listings, for derivation of visit windows and computation of baseline, and for the analysis of maximum/minimum values and maximum/minimum changes from baseline values.

Visit Windows: Section 12.2 defines the visit window mapping rules to derive the analysis visits.

Analysis visit selection rules:

- For all efficacy parameters if there are multiple measurements within a visit window, the record at the corresponding scheduled visit will be used. If there is no measurement at the corresponding scheduled visit, then 1) the record closest to the target day will be used; or 2) if there are multiple records with the same distance to the target day, the earliest record will be used.
- For all safety parameters, if there are multiple measurements within a visit window, then 1) the record closest to the target day will be used; or 2) if there are multiple records with the same distance to the target day, the earliest record will be used.

Incomplete/Missing data: will not be imputed, unless otherwise specified.

Outliers: No formal statistical analyses will be performed to detect and/or remedy the presence of statistical outliers.

9.2 Background Characteristics

Subject disposition, demographic and baseline characteristics, prior and concomitant medications, study drug exposure and compliance, and other background characteristics will be summarized using descriptive statistics for continuous variables and counts and percentages for categorical variables. Additionally, all subject data will be presented in subject data listings. All summaries will be based on the FAS unless otherwise specified. No statistical hypothesis testing will be performed on background characteristics.

9.2.1 Subject Disposition

The number of subjects in the run-in period who were not randomized or dosed with the inhaled study drug screen failures during the Run-in Period, number of subjects randomized or dosed with inhaled study drug, and the total number of subjects will be tabulated for the following groups and overall based on their Orkambi and HS status at Screening:

- Orkambi+/HS-
- Orkambi-/HS-
- Orkambi+/HS+
- Orkambi-/HS+

The number of subjects in the following categories will be summarized by treatment group:

- All Subjects Set (Randomized or dosed with Inhaled Study Drug)
- Randomized
- Randomized but never dosed
- Full Analysis Set (FAS)
- Safety Set

The number of subjects in the following categories will be presented by treatment group for each period (Period 1 and Period 2):

- FAS
- Safety Set

The number and percentage (based on Safety Set) of subjects in each of the following disposition categories will be presented by treatment group for each period (Period 1 and Period 2):

- Completed treatment regimen
- Prematurely discontinued the treatment regimen and the reasons for discontinuations
- Prematurely discontinued inhaled study drug and the reasons for discontinuations

- Prematurely discontinued orkambi and the reasons for discontinuations
- Prematurely discontinued the study and the reasons for discontinuations

The number and percentage (based on the overall Safety Set) of subjects in each of the following disposition categories will be presented by treatment group:

- Completed treatment regimen in both periods
- Completed study

A listing will be provided for subjects who discontinued treatment or who discontinued study, along with reasons for discontinuations.

The number and percentage of randomized subjects will be summarized by stratification factor ($ppFEV_1$ at screening), by country and by site, using the number of subjects being randomized in each treatment sequence as the denominator. A randomization listing ordered by randomization date also will be provided.

9.2.2 Demographics and Baseline Characteristics

Demographic and study baseline characteristics data will be summarized by treatment group and overall based on the FAS for each period (Period 1 and Period 2).

Demographic data will include the following:

- Age (years) at screening
- Age group at screening (12 to <18 years vs ≥18 years)
- Sex (Male and Female)
  - Female only: Child bearing potential
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, not collected per local regulations, and Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not collected per local regulations)
- Region (Europe or North America)

Study baseline characteristics will include the following:

- Weight (kg)
- Weight-for-age z-score (subjects < 20 years at screening)
- Height (cm)
- Height-for-age z-score (subjects < 20 years at screening)
- BMI (kg/m^2)
- BMI-for-age z-score (subjects < 20 years at screening)
- $ppFEV_1$ at Screening (<70, ≥70)

- ppFEV$_1$ at study baseline (<40, ≥40 to <70, ≥70 to ≤90 and >90)
- ppFEV$_1$ at study baseline
- FEV$_1$ (L)
- FVC (L)
- ppFVC (%)
- FEF$_{25-75\%}$ (L/sec)
- ppFEF$_{25-75\%}$ (%)
- FEV$_1$/FVC
- [redacted]
- Orkambi and HS Use at Screening (Orkambi+/HS-, Orkambi+/HS+, Orkambi-/HS-, Orkambi-/HS+)
- Use of Dornase Alfa
- Use of inhaled antibiotic
- Use of bronchodilator
- Use of inhaled bronchodilator (short-acting only, [short-acting and long-acting] or long-acting only)
- Use of inhaled corticosteroids

9.2.3 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For the FAS, medical history will be summarized descriptively by treatment group, system organ class (SOC) and preferred term (PT) for each period (Period 1 and Period 2). The corresponding data listing also will be provided.

Ophthalmology history will be presented in individual subject data listings only.

9.2.4 Prior and Concomitant Medications

Medications used in this study will be coded by using the World Health Organization Drug Dictionary - Enhanced and categorized as follows:

- **Prior medication:** any medication that started before the first dose of inhaled study drug in the study, regardless of when it ended.
- **Concomitant medication:** medication continued or newly received during the TE period for Treatment Period 1 or Treatment Period 2.
- **Post-treatment medication:** medication continued or newly received after the TE period for Treatment Period 2, or between the TE periods for Treatment Period 1 and Treatment

Period 2, or after the TE period for Treatment Period 1 for subjects who do not have Treatment Period 2.

A given medication can be classified as a prior medication, a concomitant medication, a post-treatment medication, or both prior and concomitant, both concomitant and post-treatment, or prior, concomitant, and post-treatment. If a medication has a missing or partial missing start/end date or time and it cannot be determined whether the medication was taken before initial dosing, concomitantly, or post-treatment, it will be considered as prior, concomitant, and post-treatment. Details for imputing missing or partial start and/or stop dates of medication are described in Section 12.3.

For the FAS, prior medications and concomitant medications will be summarized descriptively by: 1) treatment group, preferred name (PN); and 2) treatment group, anatomic class (ATC) level 1, ATC level 2, and PN. Prior medication summaries will be by period (Period 1 and Period 2). The summary tables by treatment group and PN will be repeated to include prior and concomitant medications with a frequency of ≥5% at the PN level. Post-treatment medications will be listed for each subject.

9.2.5 Study Drug Exposure

Exposure to inhaled study drug (i.e., duration of treatment in days) will be summarized by treatment group based on the FAS.

Duration of inhaled study drug exposure is defined as follows: last dose date of inhaled study drug – first dose date of inhaled study drug + 1 day within the treatment period, regardless of any interruption in dosing between the first and the last dose.

If the last dose date of inhaled study drug in the treatment period is missing, the subject's last available inhaled study drug administration date in that treatment period will be used for analysis purposes.

Duration of inhaled study drug exposure will be summarized by treatment using descriptive summary statistics. Duration of inhaled study drug will also be summarized by time interval (>0 to ≤14 days, >14 to ≤28 days, and >28 days) using counts and percentages.

Study drug administration information on Orkambi will be listed.

9.2.6 Study Drug Compliance

Inhaled study drug compliance within each treatment period will be calculated as follows:

$$100 \times [1 - (\text{Total number of days inhaled study drug interrupted in a treatment period}) / (\text{Duration of inhaled study drug exposure in that treatment period})]$$

The total number of days of inhaled study drug interrupted in a treatment period is defined as:

$$\text{sum of (number of days of inhaled study drug interrupted in each interruption interval in that treatment period)}$$

where number of days of inhaled study drug interrupted in each interval is defined as the interruption end date – the corresponding interruption start date + 1.

Note: A subject may have treatment interruption first, followed by decision of permanent treatment discontinuation. In such cases, last dose date is collected as the date before that treatment interruption and drug interruption would appear to be after the last dose date. For calculating compliance, the interruption end date will be restricted to the last dose date.

Inhaled study drug compliance will be summarized by treatment group using descriptive summary statistics, and will also be summarized by category (<80%, ≥80%) using counts and percentages. A list of subjects with <80% compliance rate will be provided.

Compliance on Orkambi will be defined as follows:

100 × [(Total number of days on Orkambi during the inhaled study drug exposure in a treatment period after excluding the number of days Orkambi was interrupted) / (Duration of inhaled study drug exposure in that treatment period)]

Note that the compliance for Orkambi will not consider the run-in period as well as the washout period. Compliance on Orkambi will be summarized using an approach similar to the inhaled study drug compliance.

Inhaled Study drug compliance and compliance on Orkambi will be summarized based on the FAS.

9.2.7 Important Protocol Deviations

Important protocol deviations (IPD) are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. IPD rules will be developed and finalized before database lock.

The protocol deviations that should be considered as potential IPDs include, but are not limited to:

- Violation of subjects rights, safety or well-being
- Subject entered the study despite violation of any inclusion or exclusion criteria
- Subject was less than 80% compliant with study medications
- Subject received excluded concomitant medications
- Subject received the wrong treatment or incorrect doses
- Subject remained in study despite meeting withdrawal criteria

Occurrence of any of these events should be considered as potential IPDs, but the blinded team should categorize them as IPDs only if they have the potential to affect interpretation of study results.

IPDs (from the clinical database or from the site deviation log) will be summarized descriptively based on the FAS and presented by treatment sequence. Additionally, IPDs will

be provided as a subject data listing. No subjects with IPDs will be excluded from any analysis.

9.3 Efficacy Analysis

The primary efficacy objective of this study is to evaluate the efficacy of VX-371+ HS versus HS alone. For efficacy analysis, the statistical inference will be based on change from study baseline. Unless otherwise defined, all efficacy analyses described in this section will be based on FAS. The efficacy analyses will be performed according to the treatment to which the subject was assigned in each period. Data for a period will be used provided that the subject received at least one dose of study drug in that treatment period.

9.3.1 Analysis of Primary Efficacy Endpoint

9.3.1.1 Definition of Primary Efficacy Endpoint

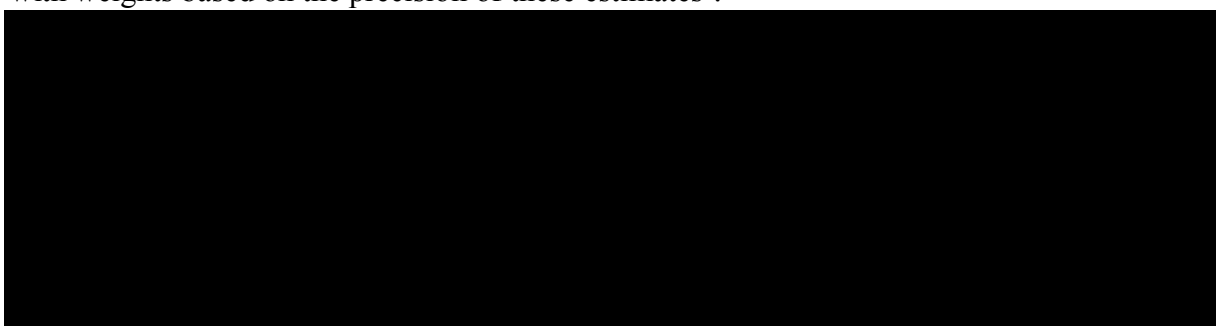
The primary efficacy endpoint is the absolute change in $ppFEV_1$ from study baseline at Day 28 in each treatment period. $ppFEV_1$ is the ratio of FEV_1 (L) to the predicted FEV_1 (L), expressed as a percentage. The predicted FEV_1 will be calculated according to the Global Lung Initiative (GLI) method[1]. The analysis will include all available measurements up to Day 28 during each treatment period, both on-treatment measurements and measurements after treatment discontinuation.

9.3.1.2 Primary Analysis of Primary Efficacy Endpoint

The null hypothesis to be tested is that the mean change from study baseline in $ppFEV_1$ at Day 28 is the same for VX-371 with HS versus HS alone.

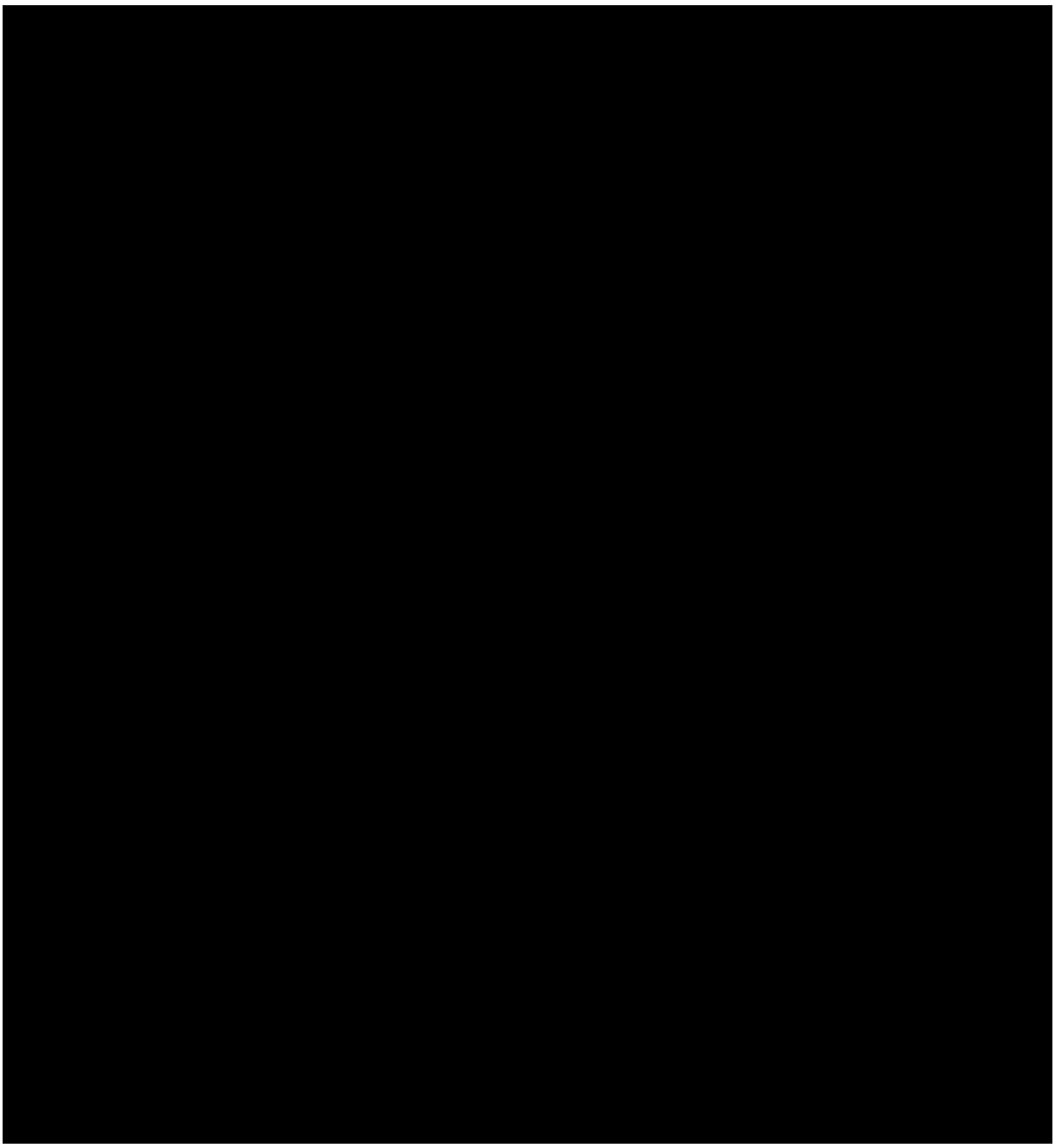
The primary analysis of the primary efficacy endpoint will be based on a mixed-effects model. This model will include the absolute change from study baseline in $ppFEV_1$ at Day 28 as the dependent variable and the following fixed effects: treatment, period and $ppFEV_1$ at study baseline and subject as a random effect. The within-subject covariance will be assumed to have the compound symmetry (CS) structure. Denominator degrees of freedom for the F-test for fixed effects will be estimated using the Kenward-Roger approximation.

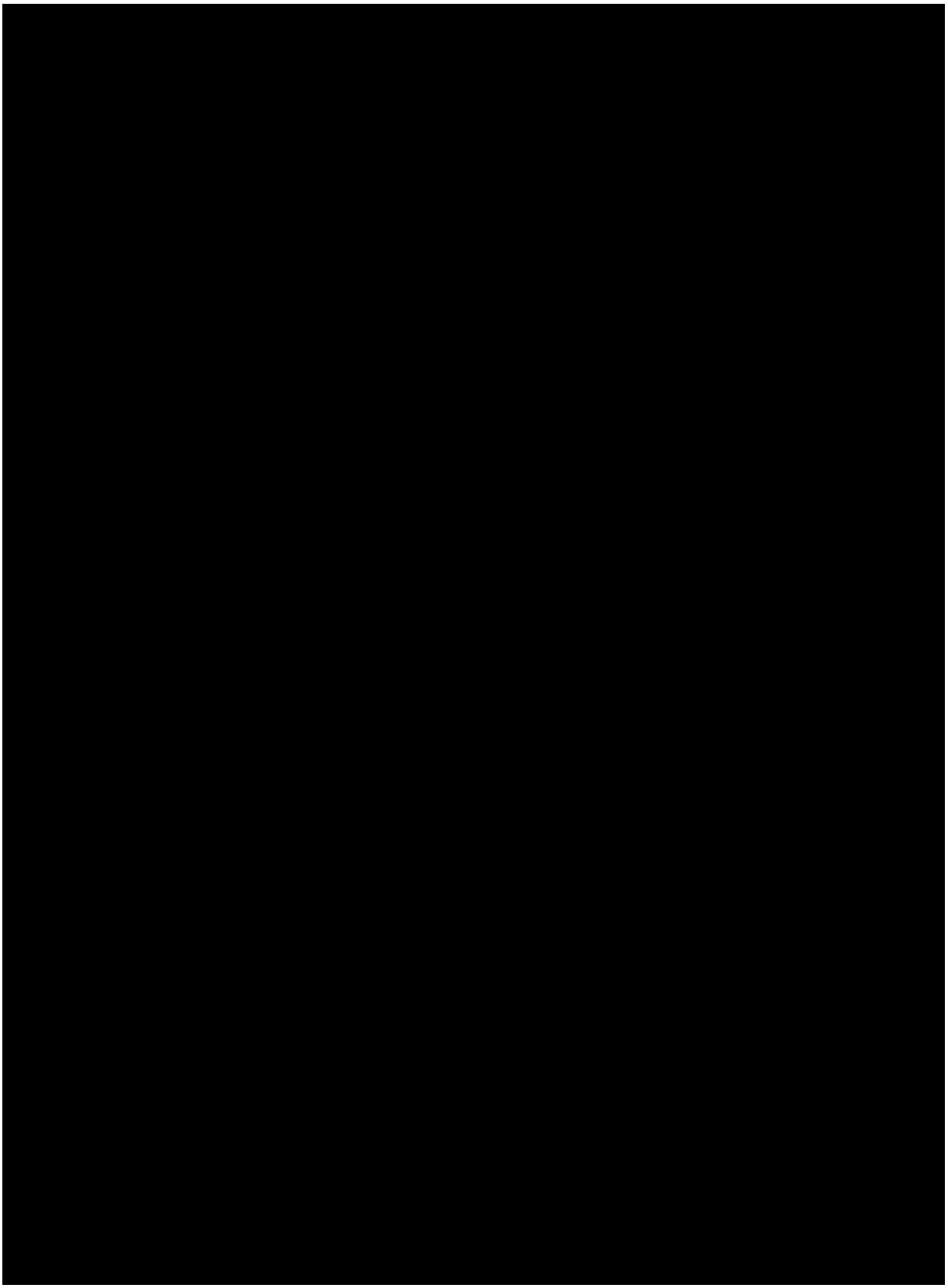
No imputation of missing data will be performed. Subjects who have data only for one of the periods will have a data structure similar to a parallel-group trial. Assuming that these subjects have dropped out at random, an estimate of treatment effect based on such subjects will be combined with the estimate from subjects who have data in both treatment periods with weights based on the precision of these estimates[2].

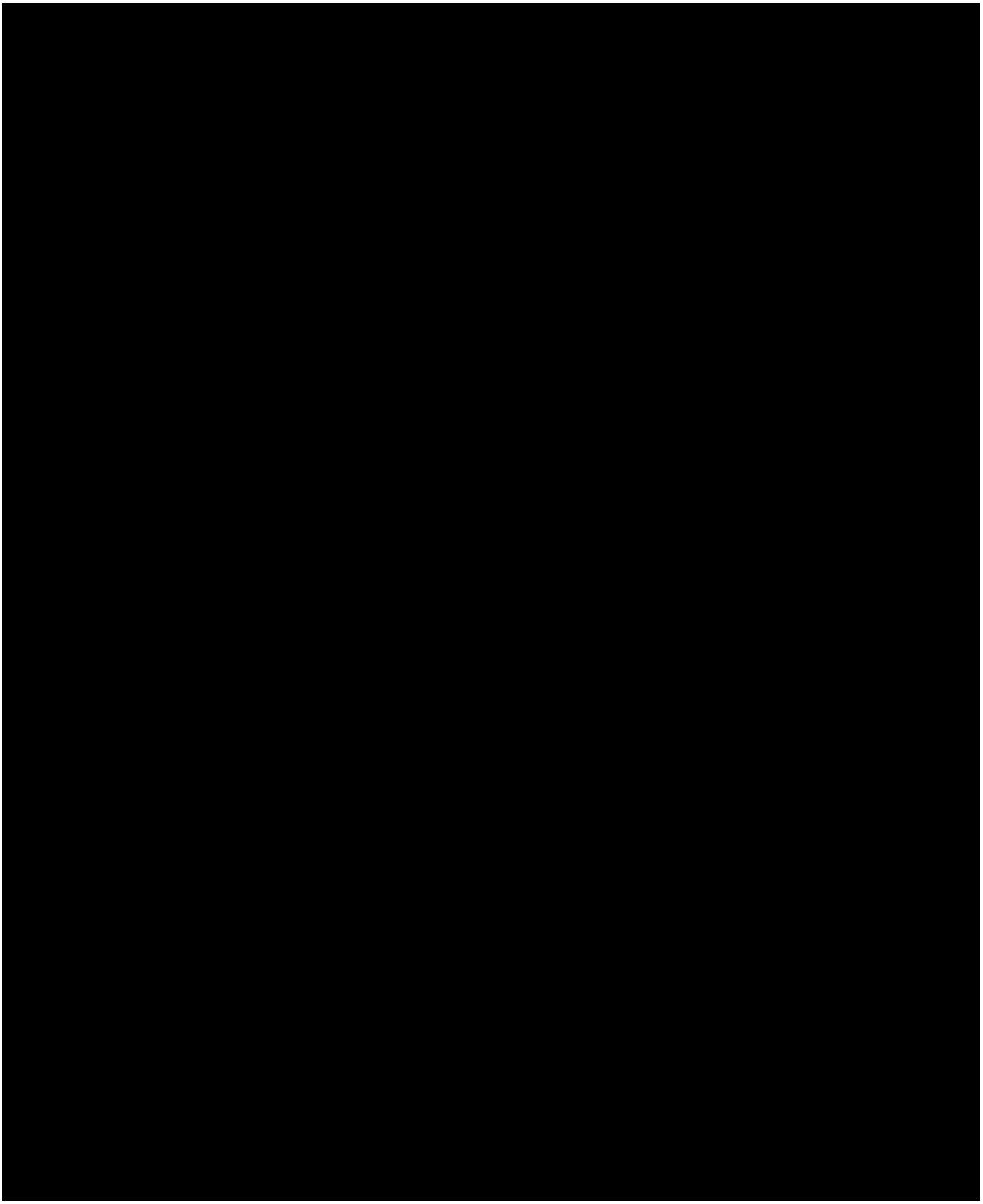


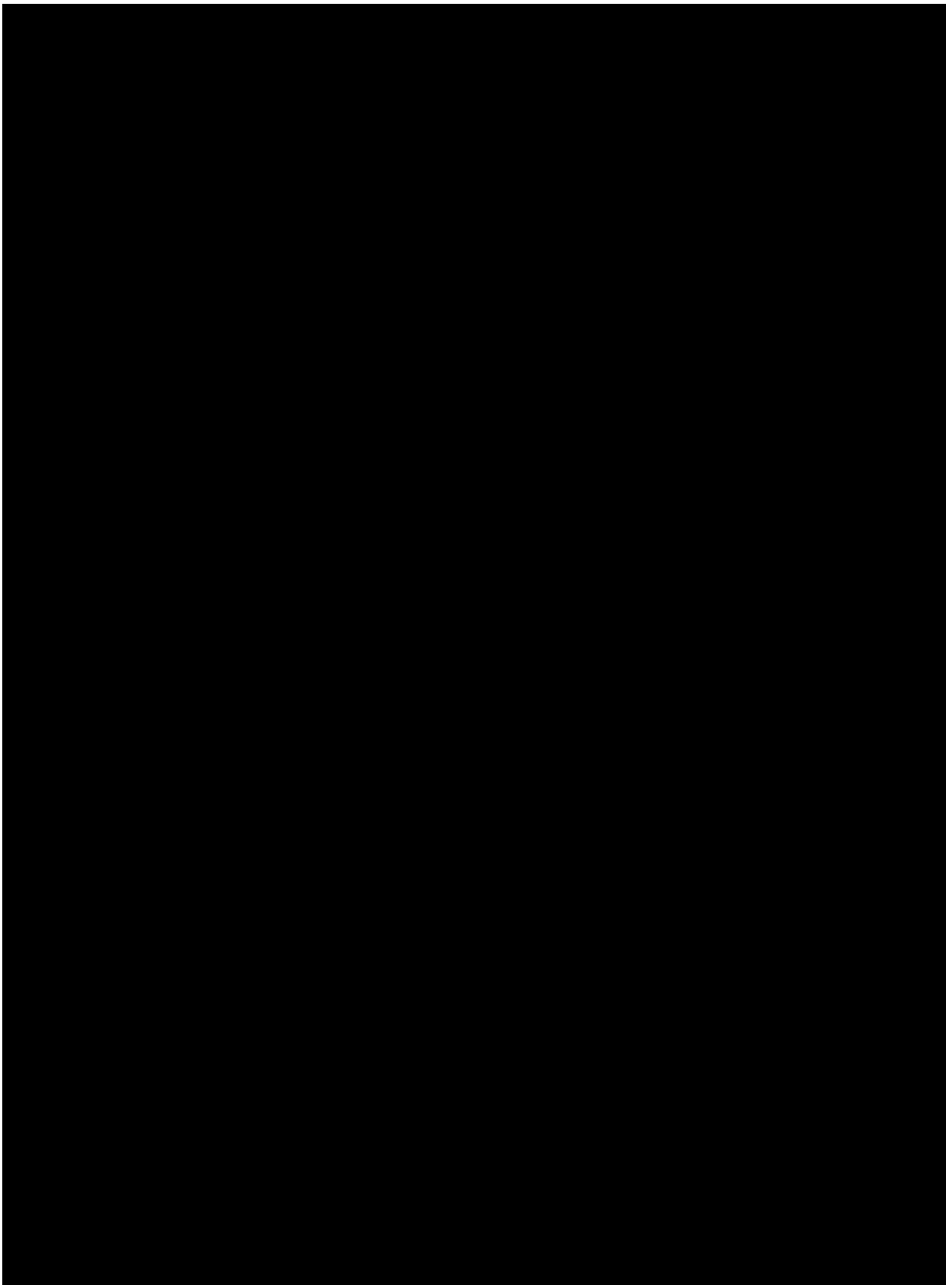
where "primary efficacy endpoint" is the absolute change from study baseline in $ppFEV_1$ at day 28.

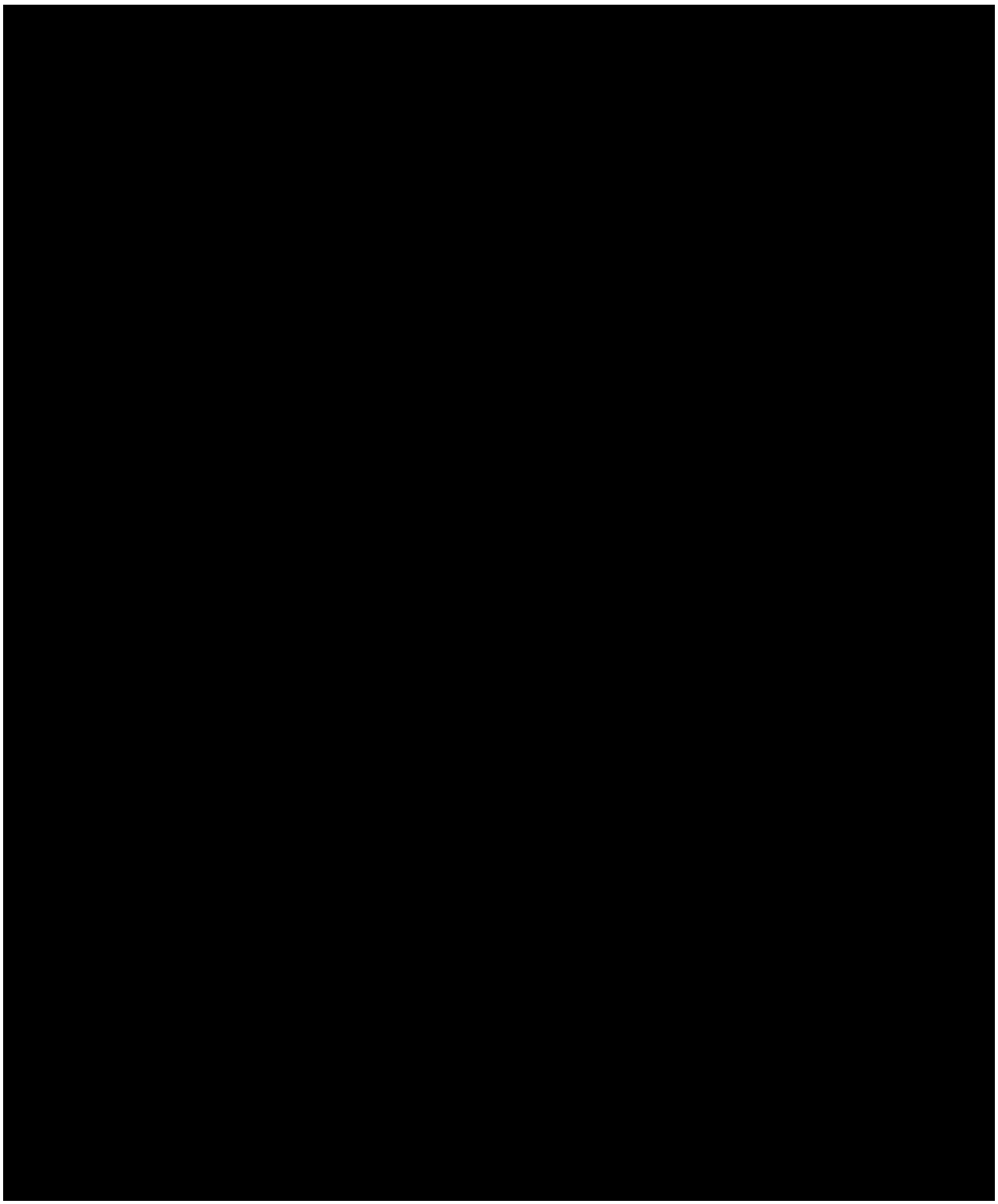
Descriptive summary statistics including n, mean, SD, and least-square means (LS means), along with its SE, 95% CI and the within-treatment 2-sided *P* value will be provided by treatment group. The between-treatment LS mean differences [VX-371 + HS versus HS, VX-371 + HS versus VX-371 + placebo, VX-371 + HS versus placebo, and VX-371 + placebo versus placebo] with the corresponding SE, 95% CIs and 2-sided *P* values will be presented. The cumulative distribution of the absolute change from study baseline in $ppFEV_1$ at Day 28 will be plotted by treatment group.

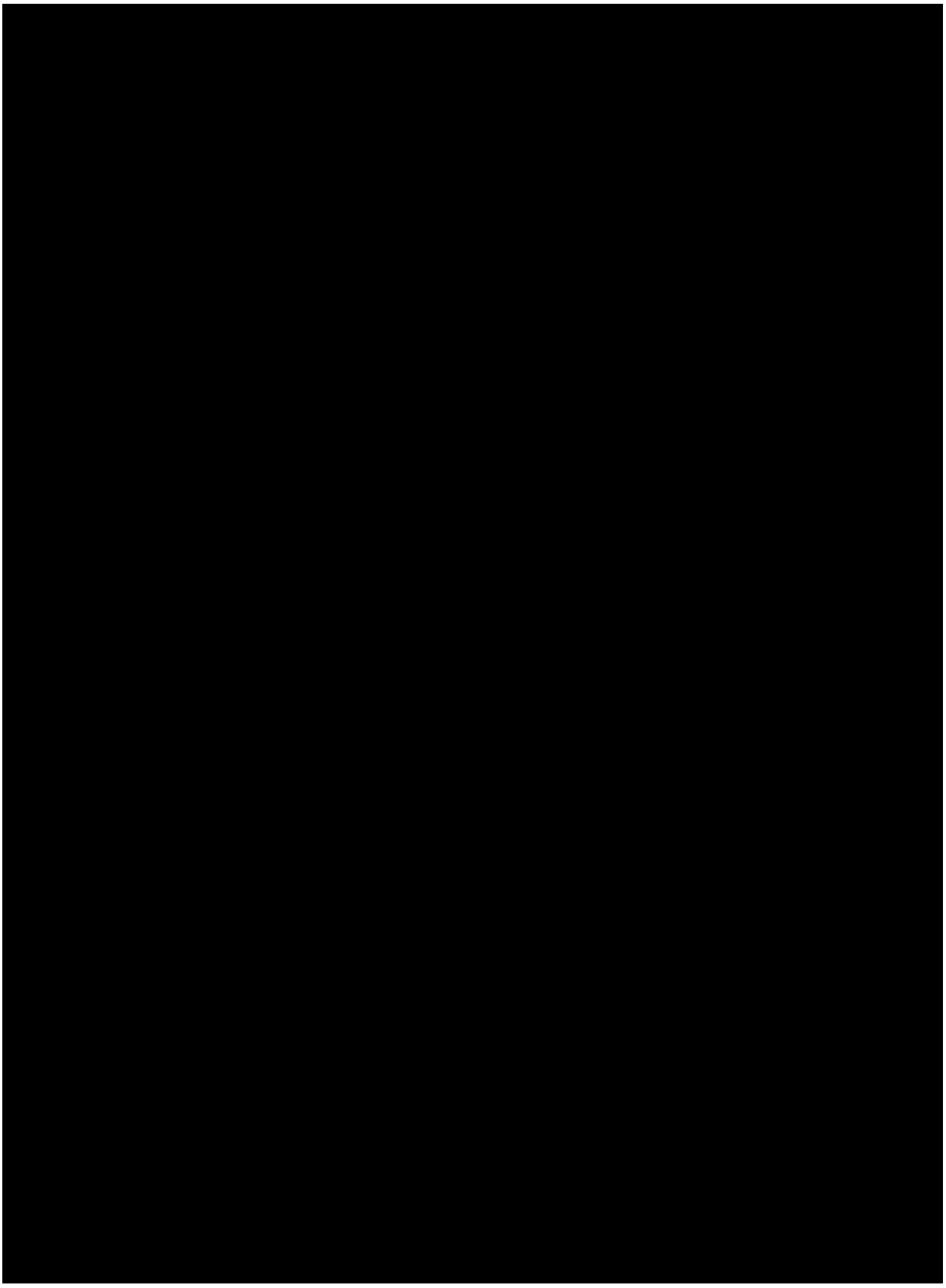


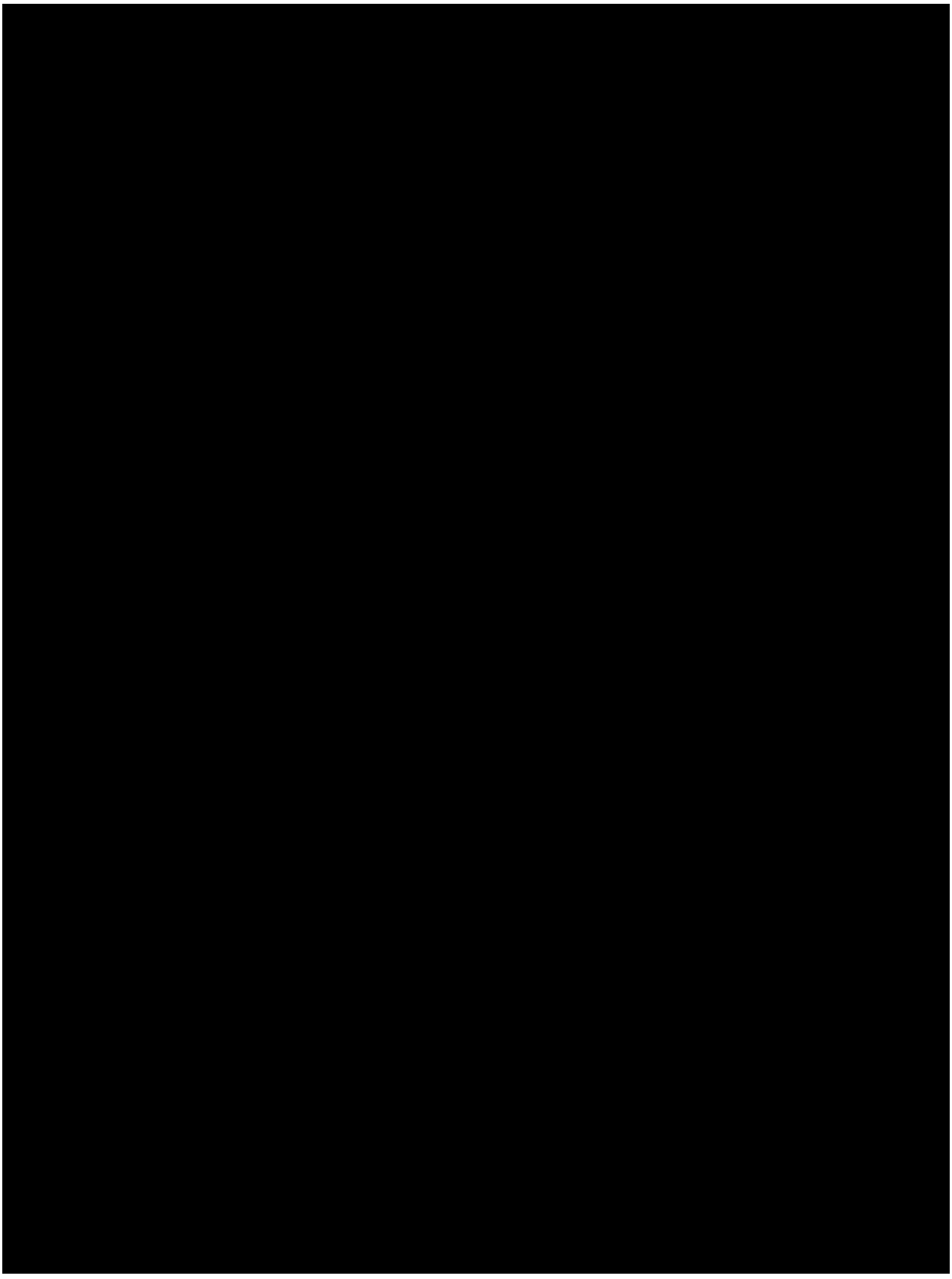












[redacted]

9.3.4 Multiplicity Adjustment

No multiplicity adjustment will be implemented.

9.4 Safety Analysis

All safety analyses will be based on the set of data associated with the TE period for Treatment Period 1 and the TE period for Treatment Period 2. Safety analyses will use the Safety Set. Subjects will be analyzed according to the treatment they actually received in a given treatment period. For subjects receiving study drug from more than one treatment group in the same treatment period, the treatment group allocation will be the determined using the following order: VX-371 + HS > VX-371 + Placebo > HS > Placebo. For safety analysis, the period baseline will be used.

All safety data will be presented in individual subject data listings.

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

- Incidence of treatment-emergent adverse event (TEAEs)
- Clinical laboratory values (i.e., hematology, serum and plasma chemistry, coagulation studies, and urine studies)
- ECG results
- Vital signs
- Ophthalmologic examination results (for pediatric subjects <18 years of age only)
- Spirometry

Only descriptive analysis of the safety data will be performed; no statistical testing is planned.

9.4.1 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 started before the start of inhaled study drug dosing in the study.

TEAE: any AE that increased in severity or that was newly developed during the TE period for Treatment Period 1 or Treatment Period 2. An AE that starts (or increases in severity) during a specific treatment period will be attributed to the inhaled study drug the subject was receiving during the treatment period.

Post-treatment AE: any AE that increased in severity or that was newly developed beyond the TE period for Treatment Period 2, or between the TE periods for Treatment Period 1 and Treatment Period 2, or beyond the TE period for Treatment Period 1 for subjects who do not have Treatment Period 2

For AEs with a missing or partially missing start date, if there is no clear evidence that the AE started (or increased in severity) before the first dose in Treatment Period 1, the start date will be imputed to the first dosing date in Treatment Period 1 and the AE will be assigned to the treatment in Treatment Period 1. For AEs with partially missing start date that indicates the AE started (or increased in severity) after the TE period of Treatment Period 1, but no clear evidence that it started before the first dose in Treatment Period 2, the start date will be imputed to the first dosing date in Treatment Period 2 and the AE will be assigned to the treatment in Treatment Period 2. Details for imputing missing or partial start date of AEs are described in Section 12.4.

9.4.1.1 Over view of Treatment emergent AEs

An overview of all TEAEs will be summarized in the following categories:

- All TEAEs
- Grade 3/4 TEAEs
- TEAEs by relationship to study drug regimen
- TEAEs by relationship to study device
- TEAEs by maximum severity
- TEAEs leading to treatment interruption (this will include TEAEs leading to treatment interruption of inhaled study drug, Orkambi, and either inhaled study drug or Orkambi)
- TEAEs leading to treatment discontinuation (this will include TEAEs leading to discontinuation of inhaled study drug, Orkambi, and either inhaled study drug or Orkambi)
- Serious TEAEs
- Related serious TEAEs

- TEAEs leading to death

9.4.1.2 TEAEs and TE SAEs by System Organ Class and Preferred Term

The number and percentage of subjects with TEAEs will be summarized by treatment group, MedDRA system organ class (SOC) and preferred term (PT), where multiple occurrences of the same AE for the same subject will be counted only once. The summary table will be presented in descending order of frequencies in the VX-371 + HS treatment group. TE SAEs will be summarized similarly.

9.4.1.3 TEAEs and TE SAEs by PT

The number and percentage of subjects with TEAEs will be summarized by treatment group and PT, where multiple occurrences of the same AE for the same subject will be counted only once. TE SAEs will be summarized similarly.

9.4.1.4 Related TEAEs and TE SAEs by SOC, PT

The number and percentage of subjects with related TEAEs will be summarized by treatment group, SOC, and PT, where multiple occurrences of the same AE for the same subject will be counted only once. The summary table will be presented in descending order of frequencies in the VX-371 + HS treatment group. TEAEs in the following relationship to study drug regimen categories will be considered as related: Related, Possibly Related and Missing. TE SAEs will be summarized similarly.

In addition, related TEAEs pertaining to the study device will be summarized by treatment group and PT.

9.4.1.5 Grade 3/4 TEAEs by SOC, PT

The number and percentage of subjects with Grade 3/4 TEAEs will be summarized by treatment group, SOC, and PT, where multiple occurrences of the same AE for the same subject will be counted only once. The summary table will be presented in descending order of frequencies in the VX-371 + HS treatment group. Grade 3/4 TEAEs include severe and life-threatening adverse events.

9.4.1.6 Respiratory Events and Symptoms

Respiratory symptoms are defined as any TEAEs for the following 3 PTs:

- Chest discomfort
- Dyspnoea
- Respiration abnormal

Respiratory events are defined as any of the afore-mentioned respiratory symptoms, or any TEAEs for the following 4 additional PTs:

- Asthma
- Bronchial hyperreactivity
- Bronchospasm
- Wheezing

A summary of TE respiratory symptoms and events will be presented:

1. Showing number and percentage of subjects overall as well as by PT;
2. Showing number and percentage of subjects by maximum severity;
3. Summary of time-to-first onset (relative to first dose date of inhaled study drug in the treatment period)
4. Summary of duration of events (days) with descriptive summary;
5. Showing number and percentage of subjects with TEAE leading to treatment interruption of inhaled study drug, Orkambi, and either inhaled study drug or Orkambi; with TEAE leading to treatment discontinuation of inhaled study drug, Orkambi, and either inhaled study drug or Orkambi; with serious TEAEs; with related serious TEAEs; and with TEAE leading to death.

9.4.1.7 Hyperkalaemia

The following AE PTs will be selected for hyperkalaemia:

- Hyperkalaemia
- Blood potassium increased

A summary of hyperkalaemia will be presented using an approach similar to that for respiratory symptoms and events.

[redacted]

[redacted]

9.4.2 Clinical Laboratory

For treatment emergent laboratory measurements, the raw values and change from period baseline values of the continuous laboratory continuous laboratory measurements (chemistry, hematology, and coagulation) will be summarized in SI units using descriptive statistics by treatment group at each scheduled time point. Urine sodium to potassium ratios will be summarized by treatment group.

The number and percentage of subjects with abnormal high (>ULN) hematology and chemistry values will be summarized by visit, as will the number and percentage of subjects with abnormal low (<LLN) hematology and chemistry values.

The number and percentage of subjects with laboratory measurements meeting the threshold analysis criteria during the TE period will be presented. The threshold analysis criteria are provided in Section 12.5 (Table 12-8 Threshold Criteria for Laboratory Tests).

The incidence of LFTs meeting the threshold analysis criteria during the TE period against the period baseline threshold criteria will also be summarized by treatment group (only worsening of the shift from period baseline will be presented).

Mean values (± SD) will be plotted against visit for plasma potassium, ALT, AST, alkaline phosphatase, GGT, and total bilirubin.

A listing of subjects with elevated liver function test (LFT, alanine aminotransferase [ALT]>3 Upper Limit Normal [ULN], aspartate aminotransferase [AST]>3 ULN, serum alkaline phosphatase [ALP]>1.5 ULN, direct bilirubin>1.5 ULN, and total bilirubin>1.5 ULN) results during the TE period will be presented. The listing will include all parameters of the LFT assessment at all visits.

A listing of subjects with elevated plasma potassium level at any time point during the TE period will be provided. The listing will include all plasma potassium measurements at all visits.

Results of urinalysis and serum pregnancy tests will be listed in individual subject data listings only. In addition, a listing containing individual subject laboratory measurements outside the reference ranges will be provided. This listing will include data from scheduled and unscheduled time points.

9.4.3 Electrocardiogram

For treatment-emergent ECG measurements, a summary of raw values and change from study baseline values will be provided by treatment group at each scheduled time point for the following standard 12-lead ECG measurements: PR, QTc for HR intervals (QTcF), QRS duration, and HR. In addition, the mean value at each time point will be plotted by treatment group for QTcF and heart rate.

The number and percentage of subjects with ECG measurements meeting the threshold analysis criteria during the TE period will be presented. The threshold analysis criteria are provided in Section 12.5 (Table 12-9 Threshold Criteria for ECGs).

9.4.4 Vital Signs

The raw values and change from period baseline values will be summarized by treatment group at each scheduled time point for the following treatment-emergent vital signs measurements: systolic and diastolic blood pressure (mm Hg), body temperature (^{o}C), HR (beats per minute), weight, height, BMI and respiratory rate (breaths per minute). In addition, the mean value at each time point will be plotted by treatment group for systolic and diastolic blood pressure.

The number and percentage of subjects with vital signs meeting the threshold analysis criteria during the TE period will be presented. The threshold analysis criteria are provided in Section 12.5 (Table 12-10 Threshold Criteria for Vital Signs).

9.4.5 Physical Examination

Abnormal physical examination findings will be presented in a data listing.

9.4.6 Ophthalmologic Examinations

The results of ophthalmologic examinations for pediatric subjects <18 years of age will be presented in individual by-subject listings.

9.4.7 Spirometry

9.4.7.1 Decline in Postdose Spirometry

For the postdose measurements on Day 1, Day 14 and Day 28 of each treatment period, a summary of raw values for ppFEV$_1$ will be provided by treatment group. The absolute change from the predose value of ppFEV$_1$ to the postdose value on the same day will be provided by treatment group. In addition, a box plot by study day and treatment group will be provided. The above analyses will be repeated for FEV$_1$.

The following summaries regarding the decline in postdose spirometry will be provided:

- Number and percentage of subjects with ≥10, ≥15 or ≥20 percentage points decrease in absolute change from predose value of $ppFEV_1$.
- Number and percentage of subjects with ≥0.2 L decrease in absolute change from predose value of FEV_1.

Subjects with ≥10 percentage points decrease in absolute change from predose value of $ppFEV_1$ or ≥0.2 L decrease in the absolute change from predose value of FEV_1 will be listed.

9.4.7.2 Decline in Predose Spirometry

The following summaries regarding the decline in predose spirometry will be provided:

- Number and percentage of subjects with ≥10, ≥15 or ≥20 percentage points decrease in absolute change from period baseline in $ppFEV_1$ at each post-baseline visit.
- Number and percentage of subjects with ≥0.2 L decrease in absolute change from period baseline in FEV_1 at each post-baseline visit.

Subjects with ≥10 percentage points decrease in absolute change from period baseline in $ppFEV_1$ or ≥0.2 L decrease in the absolute change from period baseline in FEV_1 will be listed. The listing will include raw values and absolute/relative changes from period baseline in $ppFEV_1$ and FEV_1 at each visit from the period in which the decline criteria was met.

9.4.8 Other Safety Analyses

Not applicable.

10 INTERIM AND DMC ANALYSES

10.1 Interim Analysis

No interim analysis is planned or conducted.

10.2 DMC Analysis

An independent data monitoring committee (DMC) was formed. The DMC objectives and operational details are defined in a separate document (DMC Charter), which was finalized before the first subject is screened in the study. The DMC conducted planned reviews of study data as outlined in the DMC Charter. The DMC meeting schedule is as below:

- After ≥40% of subjects (60 subjects) have completed Treatment Period 1.
- Ad-hoc: Ad-hoc IDMC meetings will be teleconference on an as-needed basis. Timing of the data snapshot will be defined on an ad-hoc basis.

Overall, there is one DMC data review. Details of the DMC analyses are provided in the DMC Analysis Plan.

11 REFERENCES

1 Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.

2 Senn S. Cross-over Trials in Clinical Research. 2nd ed. Chichester, John Wiley & Sons. 2002.

[redacted]

12 APPENDICES

12.1 Schedule of Assessments

The Schedules of Assessments are shown in Tables 12-1 to 12-4.

All visits are to be scheduled relative to the Day 1 Visit (first dose of study drug).

Table 12-1 Study VX15-371-101: Screening Period for All Subjects

Event/Assessment	Screening Period (Day-28 to Day -1 for Orkambi+/HS- Subjects or Day -56 to Day -29 for Orkambi-/HS+, Orkambi-/HS-, and Orkambi+/HS+ Subjects[a])
Clinic visit	X
Informed consent/assent	X
Inclusion/exclusion criteria review	X
Demography	X
Medical history	X
Ophthalmologic history	X
Medications review	X
Height and weight[b]	X
Vital signs	X
Ophthalmologic examination (only for pediatric subjects <18 years of age)	X
Physical examination[c]	X
Standard 12-lead ECG[d]	X
Sweat chloride[e]	X
CFTR genotype[f]	X
Serum β-hCG[g]	X
Serum FSH[h]	X

[a] All Screening assessments must be completed before the Day 1 Visit for Orkambi+/HS- subjects and before the Day -28 Visit for Orkambi-/HS+, Orkambi-/HS-, and Orkambi+/HS+ subjects. Subjects may be rescreened after discussion with, and approval from, the medical monitor (see section 8.1.1.2 of CSP).

[b] Height and weight will be measured with shoes off.

[c] A full physical examination will be performed at the Screening Visit (see section 11.6.3 of CSP).

[d] A standard 12-lead ECG will be performed after the subject has been seated or supine for at least 5 minutes (see section 11.6.4 of CSP).

[e] A sweat chloride test must be performed at the Screening Visit if an eligible sweat chloride value is not available in the subject's medical records and the Screening Visit value is needed to establish eligibility. For subjects using sweat chloride values documented in their medical records to establish eligibility, the sweat chloride test at the Screening Visit is optional. Collection of sweat chloride will not overlap with any other study assessments.

[f] *CFTR* genotyping will be performed to confirm that the subject is homozygous for the *F508del-CFTR* mutation and the results of the genotyping should be confirmed during the Screening Period. If the *CFTR* screening genotype result is not received before randomization, a previous *CFTR* genotype lab report may be used to establish eligibility. Note: Subjects who have been randomized and whose screening genotype does not confirm study eligibility must be discontinued from the study.

[g] A pregnancy test will be performed for all female subjects of childbearing potential.

Table 12-1 Study VX15-371-101: Screening Period for All Subjects

Event/Assessment	Screening Period (Day-28 to Day -1 for Orkambi+/HS- Subjects or Day -56 to Day -29 for Orkambi-/HS+, Orkambi-/HS-, and Orkambi+/HS+ Subjects[a])
Urine tests	X
Serum and plasma chemistry	X
Hematology	X
Coagulation	X
Spirometry	X
Lumacaftor/ivacaftor dosing[i]	lumacaftor 400 mg/ivacaftor 250 mg q12h
[redacted]	[redacted]
AEs and SAEs	Continuous, from signing of ICF (and assent form, if applicable) through Safety Follow-up Telephone Contact

[h] Follicle-stimulating hormone (FSH) will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be ≥40 mIU/mL to be considered postmenopausal.

[i] Subjects are to take 2 tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) orally q12h with fat-containing food (see section 10.2.2 of CSP).

Table 12-2 Study VX15-371-101: Run-in Period for Orkambi-/HS-, Orkambi-/HS+, and Orkambi+/HS+ Subjects

	Run-in Period[a] (Day -28 to Day -1)	
Event/Assessment	**Day -28 (± 2 days)**	**Day -14 (± 2 days)**
Clinic visit	X	X
Vital signs	X	X
Physical examination[b]	X	X
Meal or snack at study center[c]	X	X
Lumacaftor/ivacaftor dosing[d]	lumacaftor 400 mg/ivacaftor 250 mg q12h	
[redacted]	[redacted]	
Adverse events and serious adverse events	Continuous, from signing of ICF (and assent form, if applicable) through Safety Follow-up Telephone Contact	

[a] During the Run-in Period, all subjects who are receiving HS as part of their CF standard of care will washout from HS for 28 days before dosing with study drug and will remain off HS through the Safety Follow-up Telephone Contact.
[b] An abbreviated physical examination will be performed at the Day -28 and Day -14 Visits (see section 11.6.3 of CSP).
[c] At the scheduled visits indicated, if the subject has not taken the morning dose of lumacaftor/ivacaftor before coming to the study visit, a fat-containing meal or snack will be provided with that dose.
[d] Subjects are to take 2 tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) orally q12h with fat-containing food (see section 10.2.2 of CSP).

Table 12-3 Study VX15-371-101: Treatment Period

	Treatment Period[a]								
	Treatment Period 1 (Day 1 to Day 28)				Washout[b] (Day 29 to Day 56) (+ 3 days)	Treatment Period 2 (Day 57 to Day 84)			
Event/Assessment	Day 1	Day 3 (± 1 day)	Day 14 (± 3 days)	Day 28 (- 2 days)		Day 57	Day 59 (± 1 day)	Day 70 (± 3 days)	Day 84 (- 2 days)
Clinic visit	X		X	X		X		X	X
Telephone contact[c]		X					X		
Inclusion/exclusion criteria review	X								
Randomization[d]	X								
[redacted]									
Height and weight[f]	X			X		X			X
Vital signs[g]	X		X	X		X		X	X
Physical examination[h]	X			X		X			X
Standard 12-lead ECG[i]	X		X	X		X		X	X

[a] See section 8.1.4 of CSP for guidance about discontinuation of study drug treatment.

[b] The Washout Period may be for acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) upon discussion with and approval by the medical monitor (see section 8.1.3.2 of CSP).

[c] A telephone contact will occur on Day 3 and Day 59 of the study for safety purposes (e.g., inquiry about adverse events).

[d] Randomization will occur after all inclusion and exclusion criteria are met. If the screening genotype result is not received before randomization, a previous *CFTR* genotype lab report may be used to establish eligibility. *Note: Subjects who have been randomized on the basis of a historical genotype lab report and whose screening genotype does not confirm study eligibility must be discontinued from the study.*

[redacted].

[f] Height and weight will be measured with shoes off.

[g] All vital signs will be collected within 60 minutes before inhaled study drug dosing. Only pulse rate and blood pressure will be collected 90 (± 30) minutes after inhaled study drug dosing. Vital signs will be assessed after the subject has been seated or supine for at least 5 minutes (see section 11.6.3 of CSP).

[h] An abbreviated physical examination will be performed before dosing with inhaled study drug (see section 11.6.3 of CSP).

[i] The ECG will be performed 60 (± 30) minutes after completion of inhaled study drug dosing and after the subject has been seated or supine for at least 5 minutes (see section 11.6.4 of CSP).

Table 12-3 Study VX15-371-101: Treatment Period

	Treatment Period[a]								
	Treatment Period 1 (Day 1 to Day 28)				Washout[b] (Day 29 to Day 56) (+ 3 days)	Treatment Period 2 (Day 57 to Day 84)			
Event/Assessment	Day 1	Day 3 (± 1 day)	Day 14 (± 3 days)	Day 28 (- 2 days)		Day 57	Day 59 (± 1 day)	Day 70 (± 3 days)	Day 84 (- 2 days)
[redacted]									
Spirometry[k]	X		X	X		X		X	X
Urine pregnancy test[l]	X			X		X			X
Urine tests[m]	X		X	X		X		X	X
[redacted]									
Serum and plasma chemistry[o]	X		X	X		X		X	X
Hematology	X			X		X			X
Coagulation	X			X		X			X

[redacted]

k The spirometry assessment will be performed within 60 (± 10) minutes before and 30 (± 5) minutes) after the dose of inhaled study drug is administered.

l Pregnancy tests will only be administered to female subjects of childbearing potential (see section 11.6.2 of CSP).

m On Day 1 and Day 57, a urine sample will be collected 90 (+ 5) minutes before dosing with inhaled study drug. A urine sample will also be collected at 90 (± 60) minutes after completion of dosing with inhaled study drug at the Day 14, Day 28, Day 70, and Day 84 Visits.

[redacted]

o Subjects with a potassium level that is ≤0.4 units below the ULN at the Day 1 or Day 57 Visit will be required to have a blood sample collected for a repeat evaluation of plasma potassium within 7 (± 2) days (see section 11.6.2.2 of CSP).

Table 12-3 Study VX15-371-101: Treatment Period

	Treatment Period[a]								
	Treatment Period 1 (Day 1 to Day 28)				Washout[b] (Day 29 to Day 56) (+ 3 days)	Treatment Period 2 (Day 57 to Day 84)			
Event/Assessment	Day 1	Day 3 (± 1 day)	Day 14 (± 3 days)	Day 28 (- 2 days)		Day 57	Day 59 (± 1 day)	Day 70 (± 3 days)	Day 84 (- 2 days)
Urine for PK analysis[p]	X		X	X		X		X	X
Blood for PK analysis[q]	X		X	X		X		X	X
Meal or snack at study center[r]	X		X	X		X		X	X
Inhaled study drug dosing[s]	X		X	**X**[t]		X		X	**X**[t]
Lumacaftor/ivacaftor dosing[u]	lumacaftor 400 mg/ivacaftor 250 mg q12h								
Inhaled study drug count	X		X	X		X		X	X
Lumacaftor/ivacaftor drug count	X		X	X		X		X	X

[p] A urine sample for evaluation of VX-371 will be collected within 90 (+ 5) minutes before and 90 (± 60) minutes after completion of dosing with inhaled study drug at the Day 1, Day 14, Day 28, Day 57, Day 70, and Day 84 Visits (see section 11.3.2 of CSP).

[q] Blood samples for the PK assessment will be analyzed for VX-371 [redacted]. For the evaluation of VX-371, a blood sample will be collected within 90 (+ 5) minutes before dosing with inhaled study drug and at 60 (± 30) minutes after completion of inhaled study drug dosing at the Day 1, Day 14, Day 28, Day 57, Day 70, and Day 84 Visits. [redacted]

[r] At the scheduled visits indicated, if the subject has not taken the morning dose of lumacaftor/ivacaftor before coming to the study visit, a meal or snack will be provided with that dose after all predose assessments have occurred.

[s] Inhaled study drug will be administered from Day 1 to Day 28 and from Day 57 to Day 84. Inhaled study drug should be administered by nebulization twice daily (bid) approximately 10 to 12 hours apart for oral inhalation (see section 10.2.1 of CSP). Inhaled study drug will be administered at the clinic at the Day 1, Day 14, Day 28, Day 57, Day 70, and Day 84 Visits.

[t] The last dose of inhaled study drug in Treatment Period 1 and Treatment Period 2 is the dose of study drug received at the Day 28 and Day 84 Visits, respectively.

[u] Subjects are to take 2 tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) orally q12h with fat-containing food (see section 10.2.2 of CSP). The last dose of Orkambi during the Run-in Period will be the morning dose of the Day 1 Visit (see section 8.1.2 of CSP).

Table 12-3 Study VX15-371-101: Treatment Period

	Treatment Period[a]							
	Treatment Period 1 (Day 1 to Day 28)				Washout[b] (Day 29 to Day 56) (+ 3 days)	Treatment Period 2 (Day 57 to Day 84)			
Event/Assessment	**Day 1**	**Day 3 (± 1 day)**	**Day 14 (± 3 days)**	**Day 28 (- 2 days)**		**Day 57**	**Day 59 (± 1 day)**	**Day 70 (± 3 days)**	**Day 84 (- 2 days)**
Dispense nebulizer and/or nebulizer handset[v]	X					X			
Collect nebulizer and/or nebulizer handset[w]				X					X
Medications review	X		X	X		X		X	X
Concomitant treatments and procedures	X		X	X		X		X	X
[redacted]									
Adverse events and serious adverse events	Continuous, from signing of ICF (and assent form, if applicable) through Safety Follow-up Telephone Contact								

[v] A nebulizer device (nebulizer and handset) will be dispensed at the Day 1 Visit. At the Day 57 Visit, a new nebulizer handset will be provided for replacement.

[w] The nebulizer handset used during Treatment Period 1 will be collected at the Day 28 Visit. At the Day 84 Visit, the nebulizer device (nebulizer and handset used during Treatment Period 2) will be collected.

Table 12-4 Study VX15-371-101: Early Termination of Treatment Visit, Safety Follow-up Visit, and Safety Follow-up Telephone Contact

Event/Assessment	Early Termination of Treatment Visit[37]	Safety Follow-up Visit 28 days (+ 3 days) After Last Dose of Study Drug[38]	Safety Follow-up Telephone Contact 28 days (+ 3 days) After the Day 28 or Day 84 Visit[39]
Clinic visit	X	X	
Telephone contact			X
Height and weight[40]	X	X	
Vital signs	X	X	
Physical examination	X	X	
Ophthalmologic examinations[41]	X	X	X
Standard 12-lead ECG[42]	X	X	
Urine pregnancy test[43]	X	X	
Hematology	X	X	
Coagulation	X	X	
Urine tests	X	X	
Serum and plasma chemistry	X	X	
Urine for PK analysis[44]	X		
Blood for PK analysis[45]	X		
Spirometry	X	X	
[redacted]			
Inhaled study drug count	X		
Lumacaftor/ivacaftor drug count	X	X	
Collect nebulizer and nebulizer handset	X		
Concomitant medications	X	X	
Concomitant treatments and procedures	X	X	

[37] See 8.1.4 of CSP for guidance about discontinuation of study drug treatment.
[38] See 8.1.6 of CSP.
[39] See 8.1.5 of CSP.
[40] Height and weight will be measured with shoes off.
[41] Pediatric subjects <18 years of age at the Screening Visit who discontinue study drug treatment will have an ophthalmologic examination that is to occur between their last dose of study drug and completion of either the ETT Visit or the Safety Follow-up Visit. Pediatric subjects who complete the Day 84 Visit will have an ophthalmologic examination that is to occur between the Day 84 Visit and the Safety Follow-up Telephone Contact. See 11.6.5 of CSP
[42] The ECG will be performed after the subject has been seated or supine for at least 5 minutes (11.6.4).
[43] Pregnancy tests will only be administered to female subjects of childbearing potential (see 11.6.2 of CSP).
[44] At the ETT Visit, a single urine sample for PK will be collected.
[45] At the ETT Visit, 2 blood samples for PK will be collected, 1 for the evaluation of VX-371 [redacted].

Table 12-4 Study VX15-371-101: Early Termination of Treatment Visit, Safety Follow-up Visit, and Safety Follow-up Telephone Contact

Event/Assessment	Early Termination of Treatment Visit[37]	Safety Follow-up Visit 28 days (+ 3 days) After Last Dose of Study Drug[38]	Safety Follow-up Telephone Contact 28 days (+ 3 days) After the Day 28 or Day 84 Visit[39]
[redacted]	[redacted]		
Adverse events and serious adverse events	Continuous, from signing of ICF (and assent form, if applicable) through Safety Follow-up Telephone Contact		

12.2 Analysis Visit Windows for Safety and Efficacy Assessments

Table 12-5 Visit Window Mapping Rules for Efficacy Assessments

Assessments	Analysis Period	Analysis Visit	Target Study Day	Visit Window (in study days)
[redacted]				
• Weight and Height	1	Baseline	1	[screening visit, Day 1]
	1	Day 28	28	[2, 35]
	2	Baseline	1	[end of TE period for first period +1 , Day 1]
	2	Day 28	28	[2, 35]
• Spirometry	1	Baseline	1	[screening visit, pre-dose Day 1]
	1	Day 14	14	(1*, 21]
	1	Day 28	28	[22, 35]
	2	Baseline	1	[end of TE period for Period 1+1, pre-dose Day 1]
	2	Day 14	14	(1*, 21]
	2	Day 28	28	[22, 35]

***** Day 1 post-dose measurement (unscheduled) in each period

Note:

1. All assessments including early termination visits, safety follow-up and unscheduled visits will follow the individual visit window to be mapped to individual visits
2. For spirometry use only pre-dose assessments.

Table 12-6 Visit Window Mapping Rules for Safety Assessments

Assessments	Analysis Period	Analysis Visit	Target Study Day	Visit Window (in study days)
• Serum and plasma chemistry • Urine tests(sodium and potassium)§	1	Baseline	1	[screening visit, pre-dose Day 1]
	1	Day 14	14	(1*, 21]
	1	Day 28	28	[22, 35]
	2	Baseline	1	[end of TE period for first period +1 , pre-dose Day 1]
	2	Day 14	14	(1*, 21]
	2	Day 28	28	[22, 35]
		Safety Follow-up Visit	NA	Use the nominal visit if study day greater than 35
• Vital signs (respiratory rate and temperature)	1	Baseline	1	[screening visit, pre-dose Day 1]
	1	Day 14	14	[2, 21]
	1	Day 28	28	[22, 35]
	2	Baseline	1	[end of TE period for first period +1 , pre-dose Day 1]
	2	Day 14	14	[2, 21]
	2	Day 28	28	[22, 35]
		Safety Follow-up Visit	NA	Use the nominal visit if study day greater than 35
ECG	1	Baseline	1	[screening visit, pre-dose Day 1]
	1	Day 1	1	1†
	1	Day 14	14	(1*, 21]
	1	Day 28	28	[22, 35]
	2	Day 1	1	1†
	2	Day 14	14	(1*, 21]
	2	Day 28	28	[22, 35]
		Safety Follow-up Visit	NA	Use the nominal visit if study day greater than 35
• Hematology • Coagulation	1	Baseline	1	[screening visit, pre-dose Day 1]
	1	Day 28	28	(1*, 35]
	2	Baseline	1	[end of TE period for first period +1 , pre-dose Day 1]
	2	Day 28	28	(1*, 35]
		Safety Follow-up Visit	NA	Use the nominal visit if study day greater than 35

Assessments	Analysis Period	Analysis Visit	Target Study Day	Visit Window (in study days)
• Weight	1	Baseline	1	[screening visit, Day 1]
	1	Day 28	28	[2, 35]
	2	Baseline	1	[end of TE period for first period +1 , Day 1]
	2	Day 28	28	[2, 35]
		Safety Follow-up Visit	NA	Use the nominal visit if study day greater than 35
• Spirometry • Vital Sign (HR, SBP, and DBP)	1	Baseline	1	[screening visit, pre-dose Day 1]
	1	Day 1	1	1†
	1	Day 14	14	(1*, 21]
	1	Day 28	28	[22, 35]
	2	Baseline	1	[end of TE period for Period 1+1, pre-dose Day 1]
	2	Day 1	1	1†
	2	Day 14	14	(1*, 21]
	2	Day 28	28	[22, 35]
		Safety Follow-up Visit	NA	Use the nominal visit if study day greater than 35

***** Day 1 post-dose measurement (unscheduled) in each period
† Day 1 post-dose measurement (scheduled) in each period
§ Urine samples will also be collected post-dose on Day 14 and Day 28 in each period

Note:

1. All assessments including early termination visits, safety follow-up and unscheduled visits will follow the individual visit window to be mapped to individual visits.
2. Spirometry and vital sign assessments (heart rate, systolic blood pressure and diastolic blood pressure) taken at unscheduled visits or early termination visit or safety-follow-up visits will be considered as predose measurements and follow the visit window mapping rules to derive analysis visit.

12.3 Imputation Rules for Missing Prior/Concomitant Medication Dates

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
    a. If only DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use a date before the first dose date.
2. Missing or partial medication stop date:
    a. If only DAY is missing, use the last day of the month.
    b. If DAY and Month are both missing, use the last day of the year.
    c. If DAY, Month and year are all missing, assign 'continuing' status to stop date.

In summary, the prior, concomitant or post categorization of a medication is described below.

Table 12-7 Prior, Concomitant, and Post Categorization of a Medication

Medication start date	Medication end date				
	< Start date of TE Period 1	≥ Start date of TE Period 1 and ≤ End date of TE Period 1	> End date of TE Period 1 and < Start date of TE Period 2	≥ Start date of TE Period 2 and ≤ End date of TE Period 2	> End date of TE Period 2
< Start date of TE Period 1	P	PC1	PC1A	PC1C2	PC1C2A
≥ Start date of TE Period 1 and ≤ End date of TE Period 1	-	C1	C1A	C1C2A	C1C2A
> End date of TE Period 1 and < Start date of TE Period 2	-	-	A	C2A	C2A
≥ Start date of TE Period 2 and ≤ End date of TE Period 2	-	-	-	C2	C2A
> End date of TE Period 2	-	-	-	-	A

P – Prior; C1 – Concomitant for the Treatment in Period1; C2 – Concomitant for the Treatment in Period 2; A – Post-Treatment.

12.4 Imputation Rules for Missing Adverse Event Dates

Imputation rules for missing or partial AE start date are defined below:

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose date, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date; otherwise, impute the AE start day as 1.
- Otherwise, impute the AE start day as 1.

Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date; otherwise, impute the AE start Month as January and the Day as 1.
- Otherwise, impute the AE start MONTH as January and the DAY as 1.

Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE, TEAE or post-treatment AE.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing then query site with no imputation. Also compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date then the AE should be considered as a pretreatment AE. Otherwise, the AE will be considered as TEAE.

The imputation rule will be applied with respect to treatment start date for both periods and preference will be given to treatment in period 1 in case the AE is assigned to treatments in both periods. Missing or partially missing AE end date will not be imputed.

12.5 Threshold Analysis Criteria

Table 12-8 Threshold Criteria for Laboratory Tests

Parameter	Criteria	Comments
Clinical Chemistry		
CPK	>ULN - ≤ 2.5 x ULN >2.5 - ≤ 5 x ULN >5 - ≤ 10x ULN >10 x ULN	CTCAE grades 1-4
Creatinine	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN	CTCAE grades 1-4
Blood Urea Nitrogen	>ULN - ≤ 1.5 x ULN >1.5 - ≤ 3.0 x ULN >3.0 - ≤ 6.0 x ULN >6.0 x ULN	Same criteria as creatinine No CTCAE
Sodium	Hyponatremia <LLN - ≥130 mmol/L <130 – ≥120 mmol/L <120 mmol/L	CTCAE grade 1, 3, 4 (No CTCAE grade 2)
	Hypernatremia >ULN - ≤ 150 mmol/L >150 mmol/L- ≤155 mmol/L >155 mmol/L - ≤ 160 mmol/L >160 mmol/L	CTCAE grade 1-4
Potassium	Hypokalemia <LLN – ≥ 2.5 mmol/L <2.5 – ≥ 2.0 mmol/L <2.0 mmol/L	
	Hyperkalemia >ULN – ≤ 5.1 mmol/L >5.1 – ≤ 5.6 mmol/L >5.6 – ≤ 6.0 mmol/L >6.0 mmol/L	CTCAE grade 1-4
Glucose	Hypoglycemia <3.0 – ≥ 2.2 mmol/L <2.2 - ≥ 1.7 mmol/L <1.7 mmol/L	CTCAE grade 1-4
	Hyperglycemia >ULN - ≤ 8.9 mmol/L >8.9 – ≤ 13.9 mmol/L >13.9 – ≤ 27.8 mmol/L >27.8 mmol/L	CTCAE grade 1-4
Albumin	<35 - ≥ 30 g/L <30 – ≥ 20 g/L <20 g/L	CTCAE grade 1-3
Amylase	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.0 x ULN >2.0 – ≤ 5.0 x ULN >5.0 x ULN	CTCAE grade 1-4

Lipase	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.0 x ULN >2.0 – ≤ 5.0 x ULN >5.0 x ULN	CTCAE grade 1-4
Direct bilirubin	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2 x ULN >2 – ≤ 3 x ULN >3 – ≤ 10 x ULN >10 x ULN	Same Criteria as Total Bilirubin No CTCAE Not in DILI Guidance
GGT	>ULN - ≤ 2.5 x ULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	CTCAE grade 1-4
Calcium	Hypercalcemia >ULN - ≤ 2.9 mmol/L >2.9 – ≤ 3.1 mmol/L >3.1 – ≤ 3.4 mmol/L >3.4 mmol/L	CTCAE grade 1-4
	Hypocalcemia <LLN - ≥ 2.0 mmol/L <2.0 – ≥1.75 mmol/L <1.75 – ≥ 1.5 mmol/L <1.5 mmol/L	CTCAE grade 1-4
Magnesium	Hypermagnesemia >ULN - ≤ 1.23 mmol/L >1.23 – ≤ 3.30 mmol/L >3.30 mmol/L	CTCAE grade 1, 3, 4 No CTCAE grade 2
	Hypomagnesemia <LLN - ≥ 0.5 mmol/L <0.5 – ≥ 0.4 mmol/L <0.4 – ≥ 0.3 mmol/L <0.3 mmol/L	CTCAE grade 1-4
Inorganic phosphate	Hypophosphatemia <0.74 – ≥ 0.6mmol/L <0.6 – ≥ 0.3 mmol/L <0.3 mmol/L	CTCAE grade 1-4
ALT	>ULN - ≤ 3 xULN >3 – ≤ 5 xULN >5 – ≤ 8 xULN >8 – ≤ 20.0 xULN >20.0 x ULN	Per FDA DILI Guidance Jul 2009 and CTCAE
AST	>ULN - ≤ 3 xULN >3 – ≤ 5 xULN >5 – ≤ 8 xULN >8 – ≤ 20.0 xULN >20.0 x ULN	FDA DILI Guidance and CTCAE
ALT or AST	(ALT>ULN and ALT ≤ 3 xULN) or (AST>ULN and AST≤ 3 xULN) (ALT>3 xULN and ALT ≤ 5 xULN) or (AST>3xULN and AST≤ 5 xULN) (ALT>5 xULN and ALT ≤ 8 xULN) or (AST>5xULN and AST≤ 8 xULN) (ALT>8 xULN and ALT ≤ 20 xULN) or (AST>8xULN and AST≤ 20 xULN)	FDA DILI Guidance

	ALT>20 xULN or AST> 20 xULN	
Alkaline Phosphatase	>ULN - ≤ 1.5xULN >1.5 – ≤ 2.5 xULN >2.5 – ≤ 5.0 x ULN >5.0 – ≤ 20.0 x ULN >20.0 x ULN	FDA DILI Guidance and CTCAE
Total Bilirubin	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2 x ULN >2 – ≤ 3 x ULN >3 – ≤ 10 x ULN >10 x ULN	FDA DILI Guidance and CTCAE
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	FDA DILI Guidance Jul 2009
Hematology		
WBC	WBC decreased <LLN - ≥ 3.0 x 10e9 /L <3.0 – ≥ 2.0 x 10e9 /L <2.0 – ≥ 1.0 x 10e9 /L <1.0 x 10e9 /L	CTCAE grade 1-4
	Leukocytosis >100 x 10e9 /L	CTCAE grade 3 (only Grade available)
Lymphocytes	Lymphocyte decreased <LLN - ≥ 0.8 x10e9 /L <0.8 – ≥ 0.5 x10e9 /L <0.5 – ≥ 0.2 x10e9 /L <0.2 x10e9 /L	CTCAE grade 1-4
	Lymphocyte increased >4 – ≤ 20 x10e9/L >20 x10e9/L	CTCAE grade 2, 3 (only Grades available)
Neutrophils	Neutrophil decreased <LLN - ≥ 1.5 x10e9 /L <1.5 – ≥ 1.0 x10e9 /L <1.0 – ≥ 0.5 x10e9 /L <0.5 x10e9 /L	CTCAE grade 1-4
Hemoglobin	Hgb decreased (anemia) <LLN - ≥ 100 g/L <100 – ≥ 80 g/L < 80 g/L	CTCAE grade 1-3
	Hgb increased >ULN - ≤ 20 g/L above ULN >20 g/L above ULN - ≤ 40 g/L above ULN >40 g/L above ULN	CTCAE grade 1-3
Platelets	Platelet decreased <LLN - ≥ 75.0 x 10e9 /L <75.0 – ≥ 50.0 x 10e9 /L <50.0 – ≥ 25.0 x 10e9 /L <25.0 x 10e9 /L	CTCAE grade 1-4
Coagulation		
Activated partial thromboplastin time (PTT)	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.5 x ULN >2.5 x ULN	CTCAE grade 1-3

Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - ≤ 1.5 x ULN >1.5 – ≤ 2.5 x ULN >2.5 x ULN	CTCAE grade 1-3

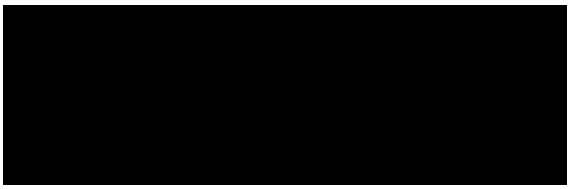
Table 12-9 Threshold Criteria for ECGs

Parameter	Criteria	Comments
HR	Bradycardia	Per HV grade 2, 3, plus shift change
	<50 bpm	
	<45 bpm	
	Decrease from baseline ≥10 bpm	
	Decrease from baseline ≥20 bpm	
	<50 bpm and decrease from baseline ≥10 bpm	
	<50 bpm and decrease from baseline ≥20 bpm	
	Tachycardia	Per HV grade 1, 2, 3, plus shift change
	>100 bpm	
	>115 bpm	
	>130 bpm	
	Increase from baseline ≥10 bpm	
	Increase from baseline ≥20 bpm	
	>100 bpm and increase from baseline ≥10 bpm	
	>100 bpm and increase from baseline ≥20 bpm	
PR	≥240 ms	
	≥300 ms	
	≥200 ms and increase from baseline ≥40 ms	
	≥200 ms and increase from baseline ≥100 ms	
QRS	>110 ms	
	>160 ms	
	Increase from baseline ≥20 ms	
	Increase from baseline ≥40 ms	
QTc	>450 ms (Male)	
	>470 ms (Female)	
	≥500 ms	
	Increase from baseline >10 ms	
	Increase from baseline >20 ms	
	Increase from baseline >40 ms	
	Increase from baseline >60 ms	

Table 12-10 Threshold Criteria for Vital Signs

Parameter	Threshold Criteria	Comments
HR	Same PCS as above in ECG category	
SBP	SBP increased	809/770 analyses
	>140 mmHg	
	>160 mmHg	
	>10 mmHg increase from baseline	
	>20 mmHg increase from baseline	
	>140 mmHg & >10 mmHg increase from baseline	
	>140 mmHg & >20 mmHg increase from baseline	
	>160 mmHg & >10 mmHg increase from baseline	
	>160 mmHg & >20 mmHg increase from baseline	
	SBP decrease	Per HV grade 1, 3, plus shift change
	<90 mmHg	
	<80 mmHg	
	>10 mmHg decrease from baseline	
	>20 mmHg decrease from baseline	
	<90 mmHg and >10 mmHg decrease from baseline	
	<90 mmHg and >20 mmHg decrease from baseline	
	<80 mmHg and >10 mmHg decrease from baseline	
	<80 mmHg and >20 mmHg decrease from baseline	
DBP	DBP increased	809/770 analyses
	>90 mmHg	
	>100 mmHg	
	>5 mmHg increase from baseline	
	>10 mmHg increase from baseline	
	>90 mmHg and >5 mmHg increase from baseline	
	>90 mmHg and >10 mmHg increase from baseline	
	>100 mmHg and >5 mmHg increase from baseline	
	>100 mmHg and >10 mmHg increase from baseline	
	DBP decreased	
	<60 mmHg	
	<45 mmHg	
	>5 mmHg decrease from baseline	
	>10 mmHg decrease from baseline	
	<60 mmHg and >5 mmHg decrease from baseline	
	<60 mmHg and >10 mmHg decrease from baseline	
	<45 mmHg and >5 mmHg decrease from baseline	
	<45 mmHg and >10 mmHg decrease from baseline	
Weight	Weight gain	CTCAE grade 1-3
	≥5 % increase from baseline	
	≥10 % increase from baseline	
	≥ 20% increase from baseline	

Weight loss ≥5 % decrease from baseline ≥10 % decrease from baseline ≥ 20% decrease from baseline	CTCAE grade 1-3



12.7 Standards for Efficacy and Safety Variable Display in TFLs

Continuous Variables

The precision for continuous variables has been specified in the Vertex Standard Programming Rules document (Version 1.0, December 2015):

[redacted]

The precision of the measurement in raw values for other continuous variables will be used to determine the number of decimal places to present in tables, figures, and derived listings. Minimum and maximum values will be reported with the same precision as the units of measure. The mean, median, and SD will be reported to 1 greater decimal place.

Categorical Variables: Percentages will be presented to 1 decimal place.