



## STATISTICAL ANALYSIS PLAN

---

**Study Title:** A Phase 2b, Dose-Ranging Study of the Effect of GS-5745 on FEV<sub>1</sub> in Adult Subjects with Cystic Fibrosis

**Name of Test Drug:** Andecaliximab (GS-5745)

**Study Number:** GS-US-404-1808

**Protocol Version (Date):** Amendment 2 (May 25, 2016)

**Analysis Type:** Final Analysis

**Analysis Plan Version:** Version 1.0

**Analysis Plan Date:** 05 September 2017

**Analysis Plan Author(s):** PPD

---

**CONFIDENTIAL AND PROPRIETARY INFORMATION**

## TABLE OF CONTENTS

TABLE OF CONTENTS .....	2
LIST OF IN-TEXT FIGURES .....	3
LIST OF ABBREVIATIONS.....	4
1. INTRODUCTION .....	5
1.1. Study Objectives .....	5
1.2. Study Design .....	6
1.3. Sample Size and Power .....	9
2. TYPE OF PLANNED ANALYSIS .....	10
2.1. Interim Analyses .....	10
2.2. Final Analysis .....	10
3. GENERAL CONSIDERATIONS FOR DATA ANALYSES .....	11
3.1. Analysis Sets .....	11
3.1.1. All Randomized Analysis Set.....	11
3.1.2. Full Analysis Set .....	11
3.1.3. Safety Analysis Set.....	11
3.2. Subject Grouping .....	11
3.3. Strata and Covariates.....	12
3.4. Examination of Subject Subgroups .....	12
3.5. Multiple Comparisons .....	12
3.6. Missing Data and Outliers.....	12
3.6.1. Missing Data .....	12
3.6.2. Outliers.....	12
3.7. Data Handling Conventions and Transformations .....	12
3.8. Analysis Visit Windows.....	12
3.8.1. Definition of Study Day .....	12
3.8.2. Analysis Visit Windows.....	13
3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window.....	13
4. SUBJECT DISPOSITION .....	15
4.1. Subject Enrollment and Disposition.....	15
4.2. Extent of Study Drug Exposure and Adherence.....	15
4.2.1. Duration of Exposure to Study Drug.....	15
4.2.2. Adherence to Study Drug .....	16
4.3. Deviations .....	16
5. BASELINE CHARACTERISTICS .....	17
5.1. Demographics .....	17
5.2. Other Baseline Characteristics .....	17
5.3. Medical History.....	17
6. EFFICACY ANALYSES .....	18
6.1. Primary Efficacy Endpoint.....	18
6.1.1. Statistical Hypothesis for the Primary Efficacy Endpoint .....	18
6.1.2. Analysis of the Primary Efficacy Endpoint .....	18
6.2. Secondary Efficacy Endpoints .....	18
6.2.1. Definitions of Key Secondary Efficacy Endpoints.....	18

6.2.2.	Analysis Methods for Secondary Efficacy Endpoints .....	18
6.3.	Other Efficacy Endpoints .....	18
7.	SAFETY ANALYSES.....	19
7.1.	Adverse Events and Deaths.....	19
7.1.1.	Adverse Event Dictionary .....	19
7.1.2.	Adverse Event Severity .....	19
7.1.3.	Relationship of Adverse Events to Study Drug.....	19
7.1.4.	Serious Adverse Events.....	19
7.1.5.	Treatment-Emergent Adverse Events.....	19
7.1.6.	Summaries of Adverse Events and Deaths.....	20
7.2.	Laboratory Evaluations .....	21
7.2.1.	Summaries of Numeric Laboratory Results .....	21
7.2.2.	Graded Laboratory Values .....	21
7.2.3.	Liver-related Laboratory Evaluations.....	22
7.3.	Body Weight and Vital Signs.....	22
7.4.	Prior and Concomitant Medications.....	22
7.5.	Electrocardiogram Results .....	22
7.6.	Other Safety Measures .....	22
7.7.	Changes From Protocol-Specified Safety Analyses.....	22
8.	REFERENCES .....	23
9.	SOFTWARE.....	24
10.	SAP REVISION.....	25
11.	APPENDIX.....	26
Appendix 1.	Schedule of Assessments.....	26

### LIST OF IN-TEXT FIGURES

Figure 1-1.	Study Design Schema.....	6
-------------	--------------------------	---

## LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
BMI	body mass index
CF	cystic fibrosis
CFQ-R	cystic fibrosis questionnaire - revised
CRF	case report form
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DB	double-blind
DMC	data monitoring committee
ECG	electrocardiogram
ET	early termination
FAS	Full Analysis Set
FEV <sub>1</sub>	forced expiratory volume in 1 second
FRI	functional respiratory imaging
GS	Gilead Sciences
HLT	high-level term
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IXRS	interactive Voice/Web Response System
LLT	lower-level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MMP9	matrix metalloproteinase 9
OL	Open-label
PK	pharmacokinetics
PT	preferred term
Q1, Q3	first quartile, third quartile
RSS	Respiratory Symptom Scale
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SE	standard error
SI (units)	international system of units
SOC	system organ class
SNOT-22	Sino-Nasal Outcome Test
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	upper limit of normal
WHO	World Health Organization

## 1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-404-1808. This SAP is based on the study protocol Amendment 2 dated 25 May 2016 and the electronic case report forms (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

The study was terminated early by the sponsor on 08 June 2017 due to business decision. This SAP describes the analyses to support the synoptic CSR.

### 1.1. Study Objectives

The primary objective of this study is as follows:

- To evaluate the effect of andecaliximab on pre-bronchodilator forced expiratory volume in 1 second (FEV<sub>1</sub>) % predicted in subjects with cystic fibrosis (CF) after 8 weeks of treatment

The secondary objectives of this study are as follows:

- To assess safety, tolerability, and pharmacokinetics (PK) of andecaliximab in subjects with CF
- To evaluate the effect of andecaliximab on post-bronchodilator FEV<sub>1</sub> % predicted in subjects with CF after 8 weeks of treatment

Exploratory objectives of this study are as follows:

PPD [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## 1.2. Study Design

This was a Phase 2b, randomized, double-blind, placebo-controlled, multiple-center, multiple dose study comprising of 2 parts.

In Part 1, 60 subjects were to be enrolled in a 1:1 ratio to receive weekly subcutaneous (SC) injections of either 600 mg andecaliximab or placebo for 8 weeks.

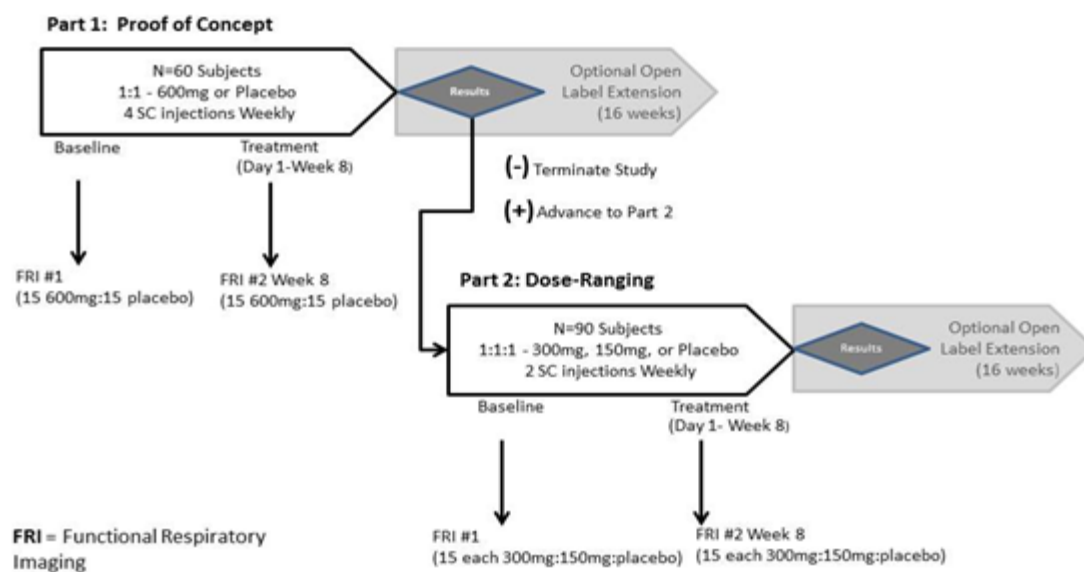
Upon successful completion of Part 1, 90 subjects were to be enrolled in Part 2 in a 1:1:1 ratio to receive weekly SC injections of either 300 mg of andecaliximab, 150 mg of andecaliximab, or placebo for 8 weeks.

An Interactive Voice/Web Response System (IXRS) was employed to manage subject randomization and enrollment into Part 1 and Part 2 of the study, shipping of study drug, and dispensing of study drug.

Safety and efficacy analyses were to be performed for Part 1 after all subjects complete the Week 8 visit or discontinued from the study. There were 3 Data Monitoring Committee (DMC) meetings planned in Part 1 and 1 in Part 2.

Subjects enrolled into either Part 1 or Part 2 had the option of participating in an open-label extension (OLE) starting from the Week 8 visit. The open-label extension would allow an additional 16 weeks of dosing with andecaliximab 600 mg SC weekly in Part 1 and 300 mg SC in Part 2.

**Figure 1-1. Study Design Schema**



There was a FRI sub-study which required 2 FRI scans (at Baseline and at the Week 8 visit).

Up to 150 subjects with CF  $\geq$  18 years of age were planned to be enrolled.

Subjects randomized to placebo in Part 1 received 4 SC injections per dose. Subjects randomized to placebo in Part 2 would receive 2 SC injections per dose.

The study was terminated after 6 subjects were enrolled in Part 1 of the study. Therefore, Part 2 was not initiated.

### **Main Inclusion Criteria**

- Male or female 18 years of age or older
- Confirmed diagnosis of CF as determined by the 2008 Cystic Fibrosis Foundation Consensus Report {Farrell 2008} criteria
- Subjects must be able to perform acceptable and reproducible spirometry as per the American Thoracic Society (ATS) guidelines
- Must have a body weight of  $> 40$  kg (88.2 lb) at study Screening
- Pre-bronchodilator FEV<sub>1</sub>  $\geq 40\%$  and  $\leq 80\%$  of predicted at Screening
- Two pre-bronchodilator spirometry measures taken at least 4 days apart (one during Screening, one at Baseline) using the sponsor provided central spirometry equipment must meet the following 2 criteria:
  - The relative difference of FEV<sub>1</sub>(L), calculated as the absolute value of [(first FEV<sub>1</sub> - second FEV<sub>1</sub>) / first FEV<sub>1</sub>] x 100 should be  $< 12\%$  **AND**
  - The absolute difference in FEV<sub>1</sub> should be  $< 200$  ml
- Negative Investigation/History of Important Bacteria Infections:

#### **Tuberculosis (TB):**

- A negative QuantiFERON-TB Gold test during Screening

#### **Non-Tuberculous Mycobacteria species (NTM):**

- All sputum cultures for **ANY** *Mycobacterium spp.* performed within 24 months prior to Screening must be negative. If only 1 NTM culture was performed within 24 months prior to Screening, that NTM culture and the most recent NTM culture obtained  $> 24$  months prior to Screening both must be negative **AND**

— A negative sputum culture < 12 months **prior to** Screening for any *Mycobacterium spp.*  
**AND**

— No current treatment for active NTM during Screening

***Burkholderia spp.***

— All sputum/throat cultures for ANY *Burkholderia spp.* performed 24 months prior to Screening must be negative. If only 1 *Burkholderia* culture was performed 24 months prior to Screening, that *Burkholderia spp.* culture and the most recent *Burkholderia spp.* culture obtained > 24 months prior to Screening must both be negative **AND**

— A negative culture for *Burkholderia spp.* during Screening **AND**

— No current treatment for *Burkholderia spp.* during Screening

- Clinically stable with no evidence of significant respiratory symptoms that would require administration of IV antibiotics, oxygen supplementation, or hospitalization within 30 days of Baseline.
- A chest radiograph, computed tomography (CT), or magnetic resonance imaging (MRI) within 90 days of Baseline, interpreted as showing no acute findings such as infiltrates (lobar or diffuse interstitial), pleural effusion, or pneumothorax, and no significant intercurrent illness; chronic, stable findings (eg, chronic scarring or atelectasis) are allowed. If not available then a chest radiograph at Screening will be obtained and should be interpreted as above.
- On stable CF chronic medical regimen for at least 30 days prior to Baseline and expected to remain stable through the completion of the study. This includes but is not limited to: chronic azithromycin use, inhaled bronchodilators, inhaled corticosteroids, inhaled dornase alpha, inhaled hypertonic saline, inhaled mannitol, ivacaftor, and/or ivacaftor/lumacaftor.
  - Inhaled antibiotics (ie, tobramycin, aztreonam, colistin) should be stable for 2 “on-treatment cycles” to be considered a stable CF medication (ie, approximately 2 months if they are taken as continuous inhaled antibiotics or approximately 4 months if they are taken as an alternating inhaled antibiotic).
- Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures

**Main Exclusion Criteria**

- Concurrent use of oral antibiotics (excluding the use of chronic oral azithromycin) or IV antibiotics within 30 days of Baseline. Prophylactic and chronic doxycycline use is prohibited during the study.
- Hospitalization for a respiratory event within 30 days of Baseline



- Current use of systemic immunosuppressive drugs including oral corticosteroids within 30 days of Baseline
- Current requirement for daily continuous oxygen supplementation or requirement (medically necessary) of more than 2 L/minute at night (subject would not meet this exclusion criterion if supplemental oxygen is used for comfort only)
- History of solid organ (including lung) or hematologic transplant, or currently on a transplant waiting list
- Laboratory parameters at screening:
  - Abnormal liver function tests defined as > 3 times the upper limit of normal (ULN) of any of the following: serum aspartate transaminase (AST), serum alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT), and serum alkaline phosphatase.
  - Total bilirubin > 2 times the ULN
  - Hemoglobin < 10 g/dL for females and < 11.5 g/dL for males at Screening
  - Estimated glomerular filtration rate (eGFR) <40 mL/1.73 m<sup>2</sup> based on the 4-variable Modification of Diet in Renal Disease (MDRD) formula:  
GFR = 175 × [SCr]<sup>-1.154</sup> × [age]<sup>-0.203</sup> × [1.212 if patient is African American] × [0.742 if patient is Female] {Levey 2007}

The study procedures performed during the main study and the optional OLE phase are presented in the Appendix 1. Subjects who did not elect to roll over into the OLE completed Week 8 study procedures, followed by the 30-day follow up visit.

### 1.3. Sample Size and Power

A sample size of 25 evaluable subjects per arm for Part 1 and Part 2 would provide 80% power to detect a 5% difference between andecaliximab and placebo treatment in change from Baseline in FEV<sub>1</sub> percent predicted with a 2-sided alpha level of 0.1 and a common standard deviation (SD) of 7% {Brouwer 2014, Ramsey 2011, Retsch-Bogart 2009}. Assuming an attrition rate of 15%, 30 subjects per arm were to be enrolled.

With respect to the FRI sub-study, a sample size of 15 subjects on andecaliximab and 15 subjects on placebo would provide more than 90% power to detect a 6% difference in FRI measurements (approximating an absolute change of 3% in FEV<sub>1</sub>) between the andecaliximab and the placebo arms in FRI change from Baseline, based on a 2-sample t-test and 2-sided alpha level of 0.1. The calculation assumes the SD of FRI change being 5% for the andecaliximab arm and 2% for placebo arm, as the FRI response is expected to be more heterogeneous in the treatment group.

The study was terminated after 6 subjects had been enrolled. Therefore, no inferential analyses will be performed.

## **2. TYPE OF PLANNED ANALYSIS**

### **2.1. Interim Analyses**

The first DMC safety review was planned when 10 subjects completed the Week 2 visit or discontinued early.

Due to the early study closure, the required number of subjects for the first planned DMC was not reached. Therefore, no DMC interim analyses were performed.

### **2.2. Final Analysis**

After all subjects have completed the study or discontinued early, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the study blind will be broken and the final analysis of the data will be performed.

### **3. GENERAL CONSIDERATIONS FOR DATA ANALYSES**

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listings will be presented for all subjects in the All Randomized Analysis Set and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the subject. The treatment group to which subjects were randomized will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

#### **3.1. Analysis Sets**

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of subjects eligible for inclusion will be summarized by treatment group.

##### **3.1.1. All Randomized Analysis Set**

The All Randomized Analysis Set includes all subjects who were randomized in the study.

##### **3.1.2. Full Analysis Set**

The Full Analysis Set (FAS) includes all subjects who were randomized into the study and took at least 1 dose of study drug. This is the primary analysis set for efficacy analyses.

##### **3.1.3. Safety Analysis Set**

The Safety Analysis Set includes all subjects who took at least 1 dose of study drug. This is the primary analysis set for safety analyses.

#### **3.2. Subject Grouping**

For analyses based on the FAS, subjects will be grouped according to the treatment to which they were randomized.

For analyses based on the Safety Analysis Set, subjects will be grouped according to the randomized treatment except when their actual treatment differs from randomized treatment for the entire treatment duration. In this case, subjects will be grouped based on actual treatment received.

### **3.3. Strata and Covariates**

No stratification factors or covariates will be used in the analyses supporting synoptic CSR.

### **3.4. Examination of Subject Subgroups**

There will be no subgroup analyses.

### **3.5. Multiple Comparisons**

Adjustments for multiplicity will not be applied, as no inferential analyses will be performed.

### **3.6. Missing Data and Outliers**

#### **3.6.1. Missing Data**

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For missing last dosing date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2.

#### **3.6.2. Outliers**

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

### **3.7. Data Handling Conventions and Transformations**

In general, age (in years) on the date of the first dose of study drug will be used for analyses and presentation in listings. If an enrolled subject was not dosed with any study drug, the randomization date will be used instead of the first dosing date of study drug. If only the birth year is collected on the CRF, “01 July” will be used for the unknown birth day and month for the purpose of age calculation. If only birth year and month are collected, “01” will be used for the unknown birth day.

### **3.8. Analysis Visit Windows**

#### **3.8.1. Definition of Study Day**

Study Day will be calculated from the first dosing date of study drug and derived as follows:

- For postdose study days: Assessment Date – First Dosing Date + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, study Day 1 is the day of first dose of study drug administration.

For the outputs based on the study period (double-blind and open-label), the following rule will be applied:

- If subject continues into open-label (OL) period then the double-blind period reports will include the data collected until the date of the first dose of study drug in OL period (Week 8) – 1 day. The open-label period summaries will include the data from the date of the first dose of OL treatment, inclusive.
- If subject does not continue into OL period then all data collected starting from Day 1 will be included in the double-blind period summaries.

### **3.8.2. Analysis Visit Windows**

The nominal visit as recorded on the CRF will be used when data are summarized by visit. Any data relating to unscheduled visits will not be assigned to a particular visit or time point. However, the following exceptions will be made:

- An unscheduled visit prior to the first dosing of study drug may be included in the calculation of the baseline value, if applicable.
- For subjects who prematurely discontinue from the study, early termination (ET) data will be assigned to what would have been the next scheduled visit where the respective data were scheduled to be collected.
- Data collected on 30-day follow-up visit will be summarized as a separate visit, and labeled as “Follow-up Visit”.

### **3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window**

Pre-bronchodilator FEV<sub>1</sub> and post-bronchodilator FEV<sub>1</sub> are considered as 2 separate measurements.

If multiple, valid nonmissing, continuous measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- In general, the baseline value will be the last nonmissing value on or prior to the first dosing date of study drug, unless specified differently. If multiple measurements occur on the same day, the last nonmissing value prior to the time of first dosing of study drug will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements (for continuous data) will be considered the baseline value.

If multiple, valid nonmissing, categorical measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected.
- For postbaseline visits, if there are multiple records with the same time or no time recorded on the same day, the value with the worst severity within the window will be selected.

## **4. SUBJECT DISPOSITION**

### **4.1. Subject Enrollment and Disposition**

A summary of subject disposition will be provided by treatment group and overall. This summary will present the number of subjects screened, the number of subjects randomized, and the number of subjects in each of the categories listed below, for overall and each study phase (double-blind and open-label):

- Safety Analysis Set
- Completed study drug
- Did not complete study drug with reasons for premature discontinuation of study drug
- Completed study
- Did not complete study with reasons for premature discontinuation

For the status of study drug and study completion, and reasons for premature discontinuation, the number and percentage of subjects in each category will be provided. The denominator for the percentage calculation will be the total number of subjects in the All Randomized Analysis Set corresponding to that column.

### **4.2. Extent of Study Drug Exposure and Adherence**

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug.

#### **4.2.1. Duration of Exposure to Study Drug**

Total duration of exposure to study drug will be defined as last dosing date minus first dosing date plus 7, regardless of any temporary interruptions in study drug administration, and will be expressed in days. If the last study drug dosing date is missing, the latest study drug end date, clinical visit date, laboratory sample collection date, or vital signs assessment date that occurred during the on-treatment period will be used.

The total duration of exposure to study drug will be summarized using descriptive statistics and using the number (ie, cumulative counts) and percentage of subjects exposed through the following time periods: baseline (Day 1), Week 1 (Day 8), Week 4 (Day 29), Week 8 (Day 57), Week 12 (Day 85), Week 16 (Day 113), Week 20 (Day 141), and Week 24 (Day 169). Summaries will be provided by treatment group for the Safety Analysis Set. No formal statistical testing is planned.

#### **4.2.2. Adherence to Study Drug**

A summary of adherence to study drug will not be provided.

A by-subject listing of study drug administration will be provided by subject ID number (in ascending order) and visit (in chronological order).

#### **4.3. Deviations**

A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected.



## **5. BASELINE CHARACTERISTICS**

### **5.1. Demographics**

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized by treatment group and overall using descriptive statistics for age, and using number and percentage of subjects for sex, race, and ethnicity. The summary of demographic data will be provided for the All Randomized Analysis Set.

A by-subject listing of demographics, including the informed consent date, will be provided by subject ID number in ascending order.

### **5.2. Other Baseline Characteristics**

Other baseline characteristics include body weight (in kg), height (in cm), body mass index (BMI; in  $\text{kg}/\text{m}^2$ ), genotype, and pre-bronchodilator and post-bronchodilator spirometry measurements. These baseline characteristics will be summarized by treatment group and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of baseline characteristics will be provided for the All Randomized Analysis Set. No formal statistical testing is planned.

A by-subject listing of other baseline characteristics will be provided by subject ID number in ascending order.

### **5.3. Medical History**

The summaries of medical history will not be provided.

## **6. EFFICACY ANALYSES**

### **6.1. Primary Efficacy Endpoint**

The primary endpoint is the absolute change in pre-bronchodilator FEV<sub>1</sub> percent predicted from Baseline to Week 8.

The NHANES III {Hankinson 1999} method will be used to calculate the FEV<sub>1</sub> percent predicted value.

#### **6.1.1. Statistical Hypothesis for the Primary Efficacy Endpoint**

No statistical hypotheses will be tested.

#### **6.1.2. Analysis of the Primary Efficacy Endpoint**

The descriptive statistics (n, mean, standard deviation [SD], median, Q1, Q3, minimum, and maximum) for the absolute values and absolute change in pre-bronchodilator FEV<sub>1</sub> percent predicted will be presented for each post-baseline time point including open-label period.

### **6.2. Secondary Efficacy Endpoints**

#### **6.2.1. Definitions of Key Secondary Efficacy Endpoints**

The secondary efficacy endpoints include:

- The absolute change in post-bronchodilator FEV<sub>1</sub> percent predicted from Baseline to Week 8
- The relative change in pre-bronchodilator FEV<sub>1</sub> percent predicted from Baseline to Week 8
- The relative change in post-bronchodilator FEV<sub>1</sub> percent predicted from Baseline to Week 8.

The relative change of FEV<sub>1</sub> % predicted from baseline to Week 8 is calculated as the [absolute change from baseline to Week 8 / baseline FEV<sub>1</sub> % predicted value] x 100.

#### **6.2.2. Analysis Methods for Secondary Efficacy Endpoints**

Descriptive statistics (n, mean, standard deviation [SD], median, Q1, Q3, minimum, and maximum) for absolute change and relative change in post-bronchodilator FEV<sub>1</sub> percent predicted from baseline, as well as relative change in pre-bronchodilator FEV<sub>1</sub> percent predicted from baseline, will be provided for each post-baseline time point including open-label period.

### **6.3. Other Efficacy Endpoints**

Other efficacy endpoints will not be analyzed.

## **7. SAFETY ANALYSES**

### **7.1. Adverse Events and Deaths**

#### **7.1.1. Adverse Event Dictionary**

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

#### **7.1.2. Adverse Event Severity**

Adverse events are graded by the investigator as Grade 1, 2, 3, or 4 according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings. The missing category will be listed last in summary presentation.

#### **7.1.3. Relationship of Adverse Events to Study Drug**

Related AEs are those for which the investigator selected “Related” on the AE CRF to the question of “Related to Study Treatment.” Relatedness will always default to the investigator’s choice, not that of the medical monitor. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

#### **7.1.4. Serious Adverse Events**

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definitions of SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Drug Safety and Public Health Department before data finalization.

#### **7.1.5. Treatment-Emergent Adverse Events**

##### **7.1.5.1. Definition of Treatment-Emergent Adverse Events**

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug.

#### 7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset date is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

#### 7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent (TE) AEs will be summarized based on the Safety Analysis Set.

The AEs will be reported by the treatment period. If subject does not continue into the open-label period then all TEAEs will be reported in the double-blind period summaries. For subjects who continue into the open-label phase, all TEAEs during the double-blind treatment phase are the AEs started prior to the first dose of open-label treatment. The AEs with the onset date on or after the first dose of the open-label treatment and no later than 30 days after permanent discontinuation of study drug will be reported in the open-label summaries.

##### 7.1.6.1. Summaries of AE incidence in Combined Severity Grade Subsets

For TEAEs described below, summaries will be provided by SOC, PT, treatment group, and study phase:

- All TE treatment-related AEs
- All TE SAEs
- All TEAEs leading to premature discontinuation of study drug
- TEAEs of Interest:
  - injection site reactions (based on Gilead medical search terms provided by DSPH)

A brief, high-level summary of AEs described above will also be provided by treatment group and study phase.

In addition to the above summary tables, all TEAEs will be summarized by PT only, in descending order of total frequency. Summaries of all TEAEs by SOC, PT and maximum severity will also be provided.

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and PT in descending order of total frequency within each SOC. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual subject during the study.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent
- SAEs
- Deaths
- AEs leading to premature discontinuation of study drug

## **7.2. Laboratory Evaluations**

A by-subject listing for laboratory test results will be provided by subject ID number and visit in chronological order for hematology and serum chemistry separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities [CTCAE severity grade] will be flagged in the data listings, as appropriate

No formal statistical testing is planned.

### **7.2.1. Summaries of Numeric Laboratory Results**

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

Descriptive statistics for laboratory tests will not be presented.

### **7.2.2. Graded Laboratory Values**

The Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.03 will be used for assigning toxicity grades to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

#### 7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values within the reference range at baseline, but which become lower or higher than the reference range or values had a directional change in abnormality from baseline (eg, the value low at baseline became high at postbaseline visit) at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days. If the relevant baseline laboratory value is missing, any postbaseline laboratory value that is lower or higher than the reference range will be considered treatment emergent.

#### 7.2.2.2. Summaries of Laboratory Abnormalities

The summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by lab test, treatment group and study phase; subjects will be categorized according to the most severe postbaseline abnormality grade for a given lab test.

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values within study period.

A by-subject listing of treatment-emergent laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

#### 7.2.3. Liver-related Laboratory Evaluations

Liver-related laboratory evaluations will be presented as part of serum chemistry results.

#### 7.3. Body Weight and Vital Signs

Body weight and vital signs will not be summarized or listed.

#### 7.4. Prior and Concomitant Medications

Prior and concomitant medications will not be summarized or listed.

#### 7.5. Electrocardiogram Results

Electrocardiogram (ECG) data will not be summarized or listed.

#### 7.6. Other Safety Measures

A data listing will be provided for subjects experiencing pregnancy during the study.

#### 7.7. Changes From Protocol-Specified Safety Analyses

The limited efficacy and safety summaries are provided due to low number of subjects enrolled prior to the study termination.

## 8. REFERENCES

- Brouwer ES, Napravnik S, Eron JJ, Jr., Stalzer B, Floris-Moore M, Simpson RJ, Jr., et al. Effects of combination antiretroviral therapies on the risk of myocardial infarction among HIV patients. *Epidemiology* 2014;25 (3):406-17.
- Farrell PM, Rosenstein BJ, White TB, Accurso FJ, Castellani C, Cutting GR, et al. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. *J Pediatr* 2008;153 (2):S4-S14.
- Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159 (1):179-87.
- Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 2007;53 (4):766-72.
- Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med* 2011;365 (18):1663-72.
- Retsch-Bogart GZ, Quittner AL, Gibson RL, Oermann CM, McCoy KS, Montgomery AB, et al. Efficacy and safety of inhaled aztreonam lysine for airway *Pseudomonas* in cystic fibrosis. *Chest* 2009;135 (5):1223-32.

## **9. SOFTWARE**

SAS<sup>®</sup> Software Version 9.4. SAS Institute Inc., Cary, NC, USA.



## 10. SAP REVISION

<b>Revision Date (DD MMM YYYY)</b>	<b>Section</b>	<b>Summary of Revision</b>	<b>Reason for Revision</b>

## 11. APPENDIX

### Appendix 1. Schedule of Assessments

	Screening	Baseline Randomization	Optional PK	Study Drug Administration Visits						Optional PK	Study Drug Administration Visit	Primary Endpoint	Optional Open-Label Extension						30-Day Follow-Up Visit	Early Termination Visit	
				1	2	3	4	5	6				7	8	9	10	11, 13-15, 17-19, 21-23	12			16
<b>Week</b>		<b>Baseline</b>		<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>10</b>	<b>11, 13-15, 17-19, 21-23</b>	<b>12</b>	<b>16</b>	<b>20</b>	<b>24</b>			
<b>Day</b>	<b>-30 to -1</b>	<b>1<sup>l</sup></b>	<b>5</b>	<b>8</b>	<b>15</b>	<b>22</b>	<b>29</b>	<b>36</b>	<b>43</b>	<b>48</b>	<b>50</b>	<b>57</b>	<b>64</b>	<b>71</b>		<b>85</b>	<b>113</b>	<b>141</b>	<b>169</b>		
<b>Window in days</b>			<b>±1</b>	<b>±3</b>	<b>±3</b>	<b>±3</b>	<b>±3</b>	<b>±3</b>	<b>±3</b>	<b>±1</b>	<b>±3</b>	<b>-3 to +4</b>	<b>±3</b>	<b>±3</b>	<b>±3</b>	<b>±3</b>	<b>±3</b>	<b>±3</b>	<b>±3</b>	<b>±7</b>	
<b>Home Health Visit Option</b>						<b>X</b>		<b>X</b>		<b>X</b>	<b>X</b>			<b>X</b>							
Withhold all inhaled CF therapies morning of study visit	X <sup>q</sup>	X		X			X		X			X		X			X		X	X	
Written Informed Consent	X																				
CFQ-R <sup>a</sup>		X			X		X		X			X				X	X	X	X	X	X

	Screening	Baseline Randomization	Optional PK	Study Drug Administration Visits						Optional PK	Study Drug Administration Visit	Primary Endpoint	Optional Open-Label Extension						30-Day Follow-Up Visit	Early Termination Visit	
Week		Baseline	1	2	3	4	5	6	7	8	9	10	11, 13-15, 17-19, 21-23	12	16	20	24				
Day	-30 to -1	1 <sup>1</sup>	5	8	15	22	29	36	43	48	50	57	64	71		85	113	141	169		
Window in days			±1	±3	±3	±3	±3	±3	±3	±1	±3	-3 to +4	±3	±3	±3	±3	±3	±3	±3	±7	
Home Health Visit Option						X		X		X	X				X						
TSQM (if available) <sup>a</sup>		X				X						X			X	X	X	X			
SNOT-22 (if available) <sup>a</sup>		X										X						X			
Medical History	X																				
Concomitant Medications	X	X	X	X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X
Pulmonary Exacerbation Evaluation		X		X	X		X		X			X	X	X		X	X	X	X	X	
Complete Physical Exam <sup>b</sup>	X																		X	X	

	Screening	Baseline Randomization	Optional PK	Study Drug Administration Visits						Optional PK	Study Drug Administration Visit	Primary Endpoint	Optional Open-Label Extension						30-Day Follow-Up Visit	Early Termination Visit	
Week		Baseline		1	2	3	4	5	6	7	8	9	10	11, 13-15, 17-19, 21-23	12	16	20	24			
Day	-30 to -1	1 <sup>l</sup>	5	8	15	22	29	36	43	48	50	57	64	71		85	113	141	169		
Window in days			±1	±3	±3	±3	±3	±3	±3	±1	±3	-3 to +4	±3	±3	±3	±3	±3	±3	±3	±7	
Home Health Visit Option						X		X		X	X			X							
Symptom Driven Physical Exam <sup>b</sup>		X					X					X			X	X	X	X			
Vital Signs	X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Blood for Safety Labs <sup>c</sup>	X	X			X		X					X				X			X	X	
ESR <sup>f</sup>	X											X							X		
Urine Cotinine	X						X					X				X					
Urinalysis	X	X			X							X				X			X	X	
Serum Pregnancy Test <sup>d</sup>	X																		X	X	

	Screening	Baseline Randomization	Optional PK	Study Drug Administration Visits						Optional PK	Study Drug Administration Visit	Primary Endpoint	Optional Open-Label Extension						30-Day Follow-Up Visit	Early Termination Visit	
Week		Baseline		1	2	3	4	5	6	7	8	9	10	11, 13-15, 17-19, 21-23	12	16	20	24			
Day	-30 to -1	1 <sup>l</sup>	5	8	15	22	29	36	43	48	50	57	64	71		85	113	141	169		
Window in days			±1	±3	±3	±3	±3	±3	±3	±1	±3	-3 to +4	±3	±3	±3	±3	±3	±3	±3	±7	
Home Health Visit Option						X		X		X	X				X						
Urine Pregnancy Test		X			X		X		X			X	X	X		X	X	X	X		
Oxygen Saturation		X										X								X	X
Screening Spirometry	X <sup>m</sup>																				
Pre- and post-bronchodilator Spirometry <sup>e</sup>		X			X		X		X			X		X			X		X	X	X
PEFR	X	X <sup>p</sup>		X		X		X			X		X		X		X				
Chest X-ray <sup>f</sup>	X																				
ECG	X	X					X					X				X		X	X		

	Screening	Baseline Randomization	Optional PK	Study Drug Administration Visits						Optional PK	Study Drug Administration Visit	Primary Endpoint	Optional Open-Label Extension						30-Day Follow-Up Visit	Early Termination Visit
Week		Baseline	1	2	3	4	5	6	7	8	9	10	11, 13-15, 17-19, 21-23	12	16	20	24			
Day	-30 to -1	1 <sup>l</sup>	5	8	15	22	29	36	43	48	50	57	64	71	85	113	141	169		
Window in days			±1	±3	±3	±3	±3	±3	±3	±1	±3	-3 to +4	±3	±3	±3	±3	±3	±3	±3	±7
Home Health Visit Option					X		X		X	X			X							
Induced sputum for biomarkers		X				X						X		X			X	X	X	
Spontaneous sputum for microbiology <sup>g</sup>	X, X				X			X								X				
FRI Scan <sup>h</sup>		X										X								
Blood for PK <sup>i</sup>		X		X	X	X		X				X								X
PK sub-study			X						X											
Anti-drug Antibodies		X				X						X			X		X	X	X	X
Blood for Biomarkers	X	X			X	X						X							X	X

	Screening	Baseline Randomization	Optional PK	Study Drug Administration Visits						Optional PK	Study Drug Administration Visit	Primary Endpoint	Optional Open-Label Extension						30-Day Follow-Up Visit	Early Termination Visit	
Week		Baseline		1	2	3	4	5	6	7	8	9	10	11, 13-15, 17-19, 21-23	12	16	20	24			
Day	-30 to -1	1 <sup>l</sup>	5	8	15	22	29	36	43	48	50	57	64	71		85	113	141	169		
Window in days			±1	±3	±3	±3	±3	±3	±3	±1	±3	-3 to +4	±3	±3	±3	±3	±3	±3	±3	±3	±7
Home Health Visit Option						X		X		X	X			X							
Blood for RNA Biomarkers		X					X					X								X	X
Blood for CF genotyping <sup>j</sup>		X																			
Optional blood sample for genomic research <sup>j</sup>		X																			
Randomization		X																			
Study drug administration <sup>k</sup>		X		X	X	X	X	X	X		X	X <sup>n</sup>	X-weekly through week 23-X								
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>o</sup>		X <sup>o</sup>	X <sup>o</sup>	X <sup>o</sup>	X	X	X

	Screening	Baseline Randomization	Optional PK	Study Drug Administration Visits						Optional PK	Study Drug Administration Visit	Primary Endpoint	Optional Open-Label Extension						30-Day Follow-Up Visit	Early Termination Visit	
Week		Baseline		1	2	3	4	5	6	7	8	9	10	11, 13-15, 17-19, 21-23	12	16	20	24			
Day	-30 to -1	1 <sup>l</sup>	5	8	15	22	29	36	43	48	50	57	64	71		85	113	141	169		
Window in days			±1	±3	±3	±3	±3	±3	±3	±1	±3	-3 to +4	±3	±3	±3	±3	±3	±3	±3	±7	
Home Health Visit Option						X		X		X	X				X						
Musculoskeletal Symptom Assessment	X	X					X					X				X	X	X	X	X	

- a Questionnaires should be obtained prior to any other procedures. At visits where there are multiple questionnaires, the CFQR should be completed first, then SNOT-22 and then TSQM. If on a given visit SNOT-22 is not done then the CFQ-R is completed first and then the TSQM.
- b Includes height at screening visit and weight at all visits and to be conducted prior to dosing. A complete physical examination will be performed at screening and the 30-day Follow-up Visit. A symptom-driven physical examination will be performed at the Baseline, Week 4, 8, 12, 16, 20, and 24, and can be performed as needed at other study visits.
- c Safety labs include CBC with differential, chemistry panel.
- d For female subject post-menopausal for less than 2 years, if FSH < 40 mIU/ mL a serum pregnancy test will be required.
- e Subjects will withhold their standard of care inhaled CF therapies prior to study specific spirometry
- f Chest x-ray will be obtained during the screening period if subject does not have a CT scan, MRI or chest x-ray obtained in the 90 days prior to Baseline.
- g Spontaneous and induced sputum should be obtained AFTER spirometry and FRI (if applicable) have been completed. If spontaneous sputum cannot be obtained, a throat swab may be used for microbiology culture. A second spontaneous sputum microbiology for culture will be collected in the screening period.
- h For subjects enrolled in the FRI sub-study only. Subjects will withhold their standard of care inhaled CF therapies prior to FRI.



- i At Baseline, PK should be obtained prior to and 2 hours after study drug administration. At all other visits with study drug dosing, PK should be performed prior to study drug administration. Subjects who consent to the optional PK sub-study will have one additional single PK sample collected at Day 5 ( $\pm 1$ ) and Day 48 ( $\pm 1$ ). Optional Day 5 PK and Day 8 should occur at least 1 day apart.
- j Blood for CF genotyping should be taken at baseline for subjects who do not have a historical genotype on file, but may be collected at any time during the study, if necessary. Blood for optional genomic research should only be taken from subjects who consented to this optional procedure. It should be taken at baseline, but may be collected at any time during the study, if necessary.
- k Observe subject for 2 hours after study drug administration on Day 1, and for 30 minutes after study drug administration at all other visits during the blinded phase of the study.
- l The baseline/randomization visit may be split over 2 days as needed. If the visit is split over 2 days, the following procedures should be done on the first day prior to standard of care inhaled CF therapies as indicated in protocol Section 5.5: questionnaires, urine pregnancy test (for women of childbearing potential only), oxygen saturation, pre- and post-bronchodilator spirometry, and FRI. Subjects must withhold their standard of care inhaled CF therapies again the next morning and perform spirometry prior to any remaining study procedures and study dosing. The day on which the first dose of study drug is administered is Baseline.
- m Two spirometry measures (pre-bronchodilator) taken at least 4 days apart (one during Screening, one at Baseline) must be taken to meet inclusion criterion 7.
- n Study drug dosing will occur at Week 8 only for subjects who elect to enroll in the open-label extension and only after all other procedures have been completed.
- o Subjects enrolled into the open-label extension may request assistance administering the SC injections either by returning to the clinic or utilizing a home health care service provided by the Sponsor to ensure proper dosing and adherence. If determined acceptable by the DMC, home self-administration may be conducted in the OLE.
- p PEFR will be performed at Baseline only if baseline procedures are conducted over 2 days and induced sputum was conducted on Day -1 to confirm subjects are stable enough to be dosed.
- q As screening will occur over at least two different days, subjects should only be asked to withhold these medications the morning of their screening spirometry assessment and only after they have been properly consented.
- r To be conducted at the site's local lab.