CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2b, Dose-Ranging Study of the Effect of GS-5745 on FEV_1 in Adult Subjects with Cystic Fibrosis	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	120100 2015-002192-23 NCT02759562	
Indication:	Cystic Fibrosis	
Protocol ID:	GS-US-404-1808	
Clinical Program Manager:	Name: Telephone: Email:	PPD PPD PPD
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Protocol Version/Date:	Original: VHP Amendment 1.1: Amendment 2:	14 January 2016 06 April 2016 25 May 2016

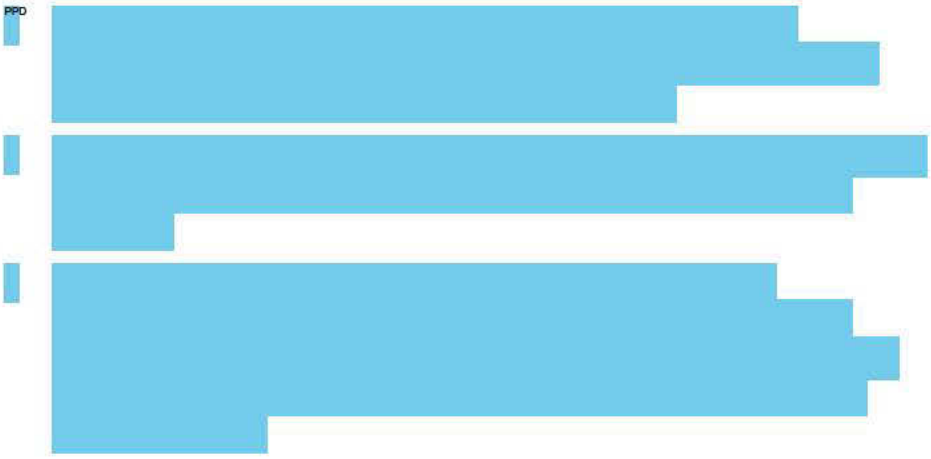
TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Phase 2b, Dose-Ranging Study of the Effect of GS-5745 on FEV_1 in Adult Subjects with Cystic Fibrosis
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	120100 2015-002192-23 NCT02759562
Study Centers Planned:	Up to 75 sites globally
Objectives:	The primary objective of this study is as follows: • To evaluate the effect of GS-5745 on pre-bronchodilator forced expiratory volume in 1 second (FEV_1) % 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 GS-5745 in subjects with CF • To evaluate the effect of GS-5745 on post-bronchodilator forced expiratory volume in 1 second (FEV_1) % predicted in subjects with CF after 8 weeks of treatment Exploratory objectives of this study are as follows: 

Study Design:

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

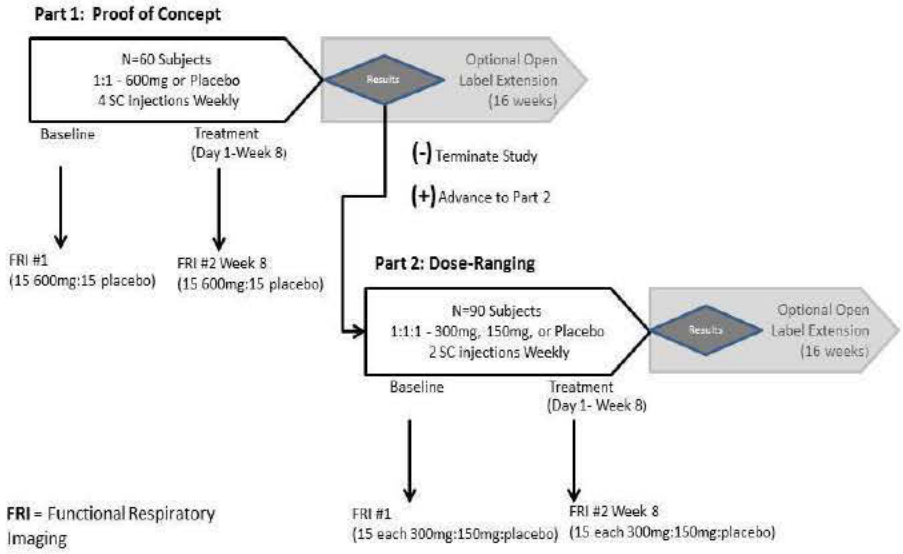
Part 1 will enroll 60 subjects in a 1:1 ratio to receive weekly subcutaneous (SC) injections of either 600 mg GS-5745 or placebo for 8 weeks.

Upon successful completion of Part 1, Part 2 will enroll 90 subjects in a 1:1:1 ratio to receive weekly SC injections of either 300 mg of GS-5745, 150 mg of GS-5745, or placebo for 8 weeks.

Safety and efficacy analyses will be performed for Part 1 after all subjects have completed the Week 8 visit or discontinued from the study. Data monitoring committee (DMC) meetings will occur at multiple times in Part 1 and before completion of Part 2 (see DMC Section 8.11). Visits and procedures for both Part 1 and Part 2 will be the same.

Subjects enrolled into either Part 1 or Part 2 will have the option of participating in an open-label extension (OLE) at the Week 8 visit. The open-label extension will allow an additional 16 weeks of dosing with GS-5745 600 mg SC weekly in Part 1 and 300 mg SC in Part 2.

Study Design Schema



There will be a FRI sub-study for both Part 1 and Part 2 which will require 2 FRI scans (at Baseline and at the Week 8 visit). A subset of study sites will be trained in FRI. All subjects enrolling into the study at those sites will participate in the FRI sub-study up to 35 subjects in Part 1 and up to 52 subjects in Part 2 to account for an attrition rate of 15%.

There will be a sputum cytology sub-study for both Part 1 and Part 2. A subset of select sites will perform sputum cytology slide preparation from induced sputum samples to investigate changes in total cell count and cell count differential in sputum. No additional procedures will be required of subjects participating in the sputum cytology sub-study.

PPD

Number of Subjects Planned:	Up to 150 subjects
Target Population:	Subjects with CF ≥ 18 years of age
Duration of Treatment:	Subjects will receive weekly SC injections for 8 weeks. Subjects completing either Part 1 or Part 2 will be invited to participate in an OLE and will receive an additional 16 weeks of weekly SC injections of GS-5745. All subjects will be followed for 30 days after the last dose of study drug.
Diagnosis and Main Eligibility Criteria:	**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 et al 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_1 ≥ 40% and ≤ 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_1(L), calculated as the absolute value of [(first FEV_1 – second FEV_1) / first FEV_1] x 100 should be < 12% **AND** — The absolute difference in FEV_1 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 transpetidase (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 m2 based on the 4-variable Modification of Diet in Renal Disease (MDRD) formula: GFR = $175 \times [SCr]^{-1.154} \times [age]^{-0.203} \times [1.212$ if patient is African American] × [0.742 if patient is Female] {Levey et al 2006}

Study Procedures/ Frequency:

The following procedures will be performed during the main study and the optional OLE phase. For subjects who do not elect to roll over onto the OLE, they will complete Week 8 study procedures, followed by the 30-day follow up visit. All post Week 8 study visits and assessments are only applicable to subjects participating in the OLE phase.

Vital Signs (VS): Blood pressure, pulse, respiratory rate, temperature, and weight will be captured at each visit with the exceptions of the PK visits (Day 5) and (Day 48).

Height: Height will be measured at Screening.

Physical exam (PE): Complete PE will be performed at Screening and the 30-day Follow-up visit.

Centralized Spirometry: In the screening period 1 pre-bronchodilator spirometry will be conducted.

At all other visits, Baseline through Follow-up, where spirometry is indicated, spirometry will be collected both pre- and post-bronchodilator. Subjects will withhold their standard of care inhaled CF therapies including bronchodilators prior to study specific spirometry.

Peak Expiratory Flow (PEF) Stability: Peak expiratory flow rate (PEFR) measurements will be collected and recorded each morning (AM) by subjects before their AM bronchodilator during the screening period to calculate their PEF stability limit. Subjects will perform and recorded daily PEF values for at least 7 days to determine the mean AM pre bronchodilator PEF value. This value will be used to determine a > 30% drop in PEF prior to study drug administration.

Oxygen Saturation: Oxygen saturation will be measured at Baseline, Week 8, and at the 30 Day Follow-up Visit.

Spontaneous Sputum Collection: Spontaneous sputum will be collected from all subjects for analysis of microbiology (dominant species and CFU). Collection will occur at Screening and at Weeks 2, 6 in the blinded phase of the study, and Week 20 in the OLE of the study.

Induced Sputum: The induced sputum will be processed for Biomarker analysis including, but not limited to, total and free MMP9, and MMP9 activity. Collection will occur at Baseline, Weeks 4, 8, 12, and 24, and at the 30-Day Follow-up Visit. A sub-set of select sites will perform sputum cytology slide preparation from induced sputum samples.

FRI Sub-study Only: Approximately 30 subjects (15 on 600 mg GS-5745 and 15 on placebo) enrolled into Part 1 of the study will have FRI performed once at Baseline and again at Week 8. Subjects will withhold their standard of care inhaled CF therapies the AM of the FRI and receive standardized doses of inhaled albuterol/salbutamol prior to FRI. If the study proceeds to Part 2, approximately 15 subjects in each treatment arm (300 mg GS-5745, 150 mg GS-5745, and placebo) will have FRI performed once at Baseline and again at Week 8.

Cystic Fibrosis Questionnaire-Revised (CFQ-R): The CFQ-R will be performed prior to any other study related procedures at Baseline, Weeks 2, 4, 6, 8, 12, 16, 20, 24, early termination visit, and at the 30-day Follow-Up visit.

Treatment Satisfaction Questionnaire for Medication (TSQM) (If available): The questionnaire will be performed prior to any other study related procedures at Baseline, and on Weeks 4, 8, 12, 16, 20, 24, and at the early termination visit.

Sino-Nasal Outcome Test (SNOT-22) (If available): The questionnaire will be performed prior to any other study related procedures at Baseline and Weeks 8, 24, and at the early termination visit.

Pulmonary Exacerbation Evaluation: A modified version of the Fuchs criteria {Ramsey et al 2011, Wainwright et al 2015} will be used for categorization of pulmonary exacerbations at Baseline, Weeks 1, 2, 4, 6, 8, 9, 10, 12, 16, 20, 24, and at the early termination visit.

PK Blood Draws: Performed 2 hours after study drug administration at Baseline. Pharmacokinetic blood draws will be performed prior to study drug administration on Weeks 1, 2, 4, 6, 8, and at the early termination visit.

PK Sub-study: PPD

Anti-drug Antibodies (ADA): Baseline, Weeks 4, 8, 16, and 24, and at the 30-day Follow-Up Visit.

Safety Laboratory Tests: Complete blood count (CBC) with differential, chemistry panel will be collected at Screening, Baseline, Weeks 2, 4, 8, and 16, and at the Follow-up visit. Urinalysis will be collected at Screening, Baseline, Weeks 2, 8, and 16, and at the Follow-up visit.

Erythrocyte Sedimentation Rate (ESR): Collected at Screening, Week 8 and Week 24, and will be analyzed at the local lab.

Urine Cotinine: Screening and Weeks 4, 8, and 16.

Serum β-HCG (females of childbearing potential only): Screening and at the 30-Day Follow-Up Visit.

Urine Pregnancy Tests (females of childbearing potential only): Urine pregnancy tests will be performed at Baseline and at Weeks 2, 4, 6, 8, 9, 10, 12, 16, 20, and 24.

12-Lead ECG: Screening, Baseline, Week 4, 8, 16, 24, and the 30-day Follow-up visit.

Blood Biomarker Samples: Blood for biomarkers will be collected at Screening, Baseline, Weeks 2, 4, and 8, and at the 30-day Follow-up visit. Biomarker analysis will include but not limited to total and free MMP9, and MMP9 activity. A blood sample will be collected for RNA to study gene expression at Baseline, Weeks 4 and 8, Early Termination visit and at the 30-day Follow-up visit. Blood will also be collected from all subjects at Baseline for CF genotyping for subjects who do not have a historical genotyping available.

	Optional Genomic Testing: PPD [redacted]
Test Product, Dose, and Mode of Administration:	GS-5745 drug product is a sterile, clear, aqueous buffered solution. GS-5745 will be supplied as 150 mg/mL solution in a single-use, pre-filled syringe intended to deliver a 1.0 mL SC injection. Subjects in Part 1 randomized to GS-5745 will receive 600 mg (4 SC injections of GS-5745) per dose. Subjects randomized to GS-5745 in Part 2 will receive either 300 mg (2 SC injections of GS-5745) or 150 mg (1 SC injection of GS-5745 and 1 SC injection of placebo).
Reference Therapy, Dose, and Mode of Administration:	Matched placebo administered by SC injection. Subjects randomized to placebo in Part 1 will receive 4 SC injections per dose. Subjects randomized to placebo in Part 2 will receive 2 SC injections per dose.
Criteria for Evaluation:	
Safety:	Safety evaluation will be assessed by adverse events (AEs), concomitant medications, clinical laboratory tests, vital signs, ECG data, and ADA data.
Efficacy:	The primary endpoint is absolute change in pre-bronchodilator FEV_1 percent predicted from Baseline to Week 8 of the study.
Pharmacokinetics:	Plasma concentrations of GS-5745 will be determined.
Statistical Methods:	**Primary Endpoint:** The primary endpoint, the absolute change in pre-bronchodilator FEV_1 percent predicted from Baseline to Week 8, will be analyzed using a mixed effect model for repeated measure (MMRM) for Part 1 and Part 2 respectively. The model for each part of the study will include treatment, Baseline FEV_1 percent predicted level, visit and treatment-by-visit interaction as fixed effect, and subject as a random effect. Estimated least square means of treatment effects and estimated differences in treatment effects between GS-5745 treatment group and placebo group at Week 8 will be presented with the 90% confidence intervals (CIs) and adjusted p-values. Safety evaluation will be assessed by AEs, concomitant medications, clinical laboratory tests, vital signs, ECGs and ADA data.

GS-5745 concentrations and PK parameters (as applicable) will be listed and summarized using descriptive statistics.

Sample Size Justification:

A sample size of 25 evaluable subjects per arm for Part 1 and Part 2 will provide 80% power to detect a difference of 5% change from Baseline in percent predicted FEV_1 between GS-5745 active treatment and placebo with a 2-sided alpha level of 0.1 assuming a common standard deviation (SD) of 7% {Brouwer et al 2014, Ramsey et al 2011, Retsch-Bogart et al 2009}. To compensate for early drop out, 30 subjects per arm will be enrolled assuming an attrition rate of 15%.

With respect to the sub-study in FRI, a sample size of 15 subjects on GS-5745 and 15 subjects on placebo provides more than 90% power to detect a 6% difference in FRI measurements (approximating an absolute change of 3% in FEV1) between the GS-5745 and the placebo arms in FRI change from Baseline based on a 2-sample t-test at a 2-sided alpha level of 0.1. The calculation assumes the SD of FRI change being 5% for the GS-5745 arm and 2% for placebo arm, as the FRI response is expected to be more heterogeneous in the treatment group. To compensate for early drop out, up to 35 subjects in Part 1 and up to 52 subjects in Part 2 will be enrolled assuming an attrition rate of 15%.

DMC Meetings

A total of 4 scheduled DMC meetings will occur throughout Part 1 and prior to the end of Part 2 of the study.

- Part 1: Safety Analysis #1 after 10 subjects have completed Week 2 Visit or early discontinued from the study
- Part 1: Safety Analysis #2 after 30 subjects have completed Week 8 Visit or early discontinued from the study
- Part 1: Safety Analysis #3 and Interim Efficacy Analysis after all randomized subjects have completed Week 8 Visit or early discontinued from the study
- Part 2: Safety Analysis #4 after 45 subjects have completed Week 8 Visit or early discontinued from the study

The detail is outlined in Section 8.11 with the corresponding GO/NO GO decision criteria.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ABPA	allergic bronchopulmonary aspergillosis
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
CBC	complete blood count
CF	cystic fibrosis
CFU	colony forming units
CFQ-R	Cystic Fibrosis Questionnaire – Revised
CFR	Code of Federal Regulations
CFTR	CF transmembrane conductance regulator
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DSPH	Drug Safety and Public Health
DMC	data monitoring committee
EC	ethics committee
eCRF	electronic case report form
ECG	Electrocardiogram
ELISA	enzyme-linked immunosorbent assay
ESR	Erythrocyte Sedimentation Rate
FDA	US Food and Drug Administration
FEF_{25-75}	forced expiratory flow at 25-75%
FEV_1	forced expiratory volume in 1 second
FRC	functional residual capacity
FRI	functional respiratory imaging
FSH	follicle stimulating hormone
FVC	forced vital capacity
GCP	good clinical practice
GGT	gamma-glutamyl transpetidase
GMP	good manufacturing process
hCG	human chorionic gonadotropin

HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
HSP	Hysterosalpingogram
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
IUD	intrauterine device
IV	Intravenous
IWRS	interactive web response system
IXRS	interactive web/voice response system
kDa	kiloDalton
LABA	long acting beta agonist
LLT	lower-level term
MedDRA	Medical Dictionary for Regulatory Activities
MMP9	matrix metalloproteinase 9
MMRM	mixed effect model for repeated measure
MRI	magnetic resonance imaging
mSv	Millisievert
NPD	nasal transepithelial potential difference
NTM	nontuburculosis mycobacterium
PA	*Pseudomonas aeruginosa*
PE	physical exam
PEF	peak expiratory flow
PEFR	peak expiratory flow rate
PFS	pre-filled syringe
PGP	Proline-Glycine-Proline
PK	Pharmacokinetics
PT	Preferred term
RSS	Respiratory Symptom Scale
SAP	Statistical analysis plan
SABA	short-acting beta agonist
SADR	serious adverse drug reaction
SAE	serious adverse event
SAMA	short-acting muscarinic antagonist
SC	Subcutaneous
SD	standard deviation
SNOT-22	Sino-Nasal Outcome Test

SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TLC	total lung capacity
TSQM	Treatment Satisfaction Questionnaire for Medication
UC	ulcerative colitis
ULN	upper limit of normal
US	United States
VS	vital signs

1. INTRODUCTION

1.1. Background

Cystic fibrosis (CF) affects approximately 100,000 people worldwide {Dmitrienko et al 2003}. CF is the most common life-shortening genetic disorder in Caucasians, with a median age of death of 27.5 years in the US {Boyle 2007, Cystic Fibrosis Foundation 2013} and 28.0 years in the EU {European Cystic Fibrosis Society 2010}. CF is an autosomal recessive disorder characterized by progressive, obstructive pulmonary disease. Patients with CF are particularly susceptible to chronic airway infections with opportunistic bacteria such as *Staphylococcus aureus, Haemophilus influenzae, Pseudomonas aeruginosa* (*PA*), *Stenotrophomonas maltophilia, Achromobacter* species, and *Burkholderia* species.

The majority (70%) of patients with CF die of cardiorespiratory failure{Foundation 2010}. This is the end result of a continuous cycle of airway obstruction, inflammation, and infection leading to bronchiectasis, parenchymal destruction, and loss of pulmonary function {Gibson et al 2003}. Patients also experience episodes of acute pulmonary exacerbation, which is characterized by worsening respiratory symptoms and an acute decline in lung function.

The current standard of care in CF includes treatment with inhaled anti-pseudomonal antibiotics (eg, tobramycin and Cayston®) and mucolytics (eg, dornase) {Mogayzel et al 2013}. Recently 2 CF transmembrane conductance regulator (CFTR) modulator therapies have been approved for treatment of CF patients with select genetic mutations. Ivacaftor (Kalydeco®) {Davies et al 2013, Ramsey et al 2011} has been approved for CF patients who carry one of the G551D CFTR gating mutations. The other is a combination product combining ivacaftor with lumacaftor for CF patients who are homozygous with the most common CF mutation, F508del. Both drugs improve lung function and reduced pulmonary exacerbations. While current CTFR modulator therapies provide clinical benefit to almost 50% of the CF population, the therapy does not represent a complete clinical cure.

1.2. GS-5745

1.2.1. General Information

For further information on GS-5745, refer to the Investigator's Brochure (IB) for GS-5745.

1.2.2. Preclinical Pharmacology and Toxicology

GS-5745 is a humanized high-affinity monoclonal IgG4 antibody that is a selective and potent allosteric inhibitor of matrix metalloproteinase 9 (MMP9). In CF patients, sputum MMP9 levels are 13- to 14-fold higher in sputum to 100-fold higher in bronchoalveolar lavage (BAL) than that of healthy controls at Baseline and during CF exacerbations, respectively {Bergin et al 2013, Hahn et al 2012}. Murine surrogates of GS-5745, with similar epitope specificity and inhibitory activity, have demonstrated significant anti-inflammatory and tissue-protective activity in rodent models of ulcerative colitis (UC) and rheumatoid arthritis (RA). Unlike pan-MMP inhibitors,

specific inhibition of MMP9 with a murine surrogate of GS-5745 showed no evidence of inducing musculoskeletal symptoms or pathology in a rat model. In addition, there were no effects on safety pharmacology endpoints (clinical observations, electrocardiograms, respiratory rate) in the 4-week repeat-dose toxicity studies at doses of up to 100 mg/kg/dose.

The toxicology program consists of completed 4-week and 26-week repeat-dose IV toxicity studies in both rats and monkeys and a human tissue cross-reactivity study. To support the transition to a SC formulation, a SC local tolerability study in rats was conducted and the 26-week toxicity studies in rats and cynomolgus monkeys included both IV and SC routes. Rat and rabbit embryo fetal development studies and a rat fertility study have also been completed. As expected, there was no specific GS-5745 staining observed in normal human tissues. At doses of GS-5745 up to 100 mg/kg/dose IV, data indicate no test article-related maternal or fetal effects in rats and rabbits, and no test article-related effects on male or female fertility in rats. Findings associated with GS-5745 treatment in the 4-week repeat-dose toxicity studies have been limited to reversible physeal hypertrophy in rats, an expected response to MMP9 inhibition, and reversible increased adrenal gland weight in female monkeys at all doses, which was associated with slight hypertrophy of the zona fasciculata in a single 100-mg/kg/dose female monkey. In the 26-week studies, there were no findings of toxicological concern in rats or cynomolgus monkeys following weekly IV or SC administration at doses up to 100 mg/kg/dose and 150 mg/kg/dose, respectively. The lack of physeal hypertrophy observed in the rat 26-week study is presumably due to the reversible nature of this finding as longitudinal bone growth and growth plate closure slows/completes. There were no adverse injection site reactions observed in the 26-week studies, and no adverse findings in the local tolerability study.

The NOAEL in the rat and monkey 26-week studies was 100 mg/kg/dose IV and 150 mg/kg/dose SC, the highest doses evaluated by each route of administration in each study. The maximum proposed SC clinical dose of approximately 10 mg/kg [600 mg (4 x 150 mg/ml injections) to a 60 kg patient] is 15-fold lower than the high SC dose in the 26-week toxicity studies.

Therefore, the toxicology studies support the proposed SC dose, dose regimen, and the duration of the clinical study. Overall, the nonclinical program has demonstrated that GS-5745 has the potential to be a safe and effective therapy for controlling the inflammation and tissue damage associated with CF. A more detailed description of the nonclinical program is provided in the IB.

1.2.3. Clinical Trials of GS-5745

In addition to the clinical development program in CF, GS-5745 is being developed for the treatment of solid tumors, UC, RA, and chronic obstructive pulmonary disease (COPD). At least 221 subjects have been enrolled in clinical studies evaluating GS-5745. Details of the clinical studies in these diseases can be found in the IB.

A Phase 1 study of GS-5745 administered IV (up to 5 mg/kg GS-5745 every 2 weeks) or SC (150 mg GS-5745 weekly) in patients with moderately to severely active UC demonstrated clinical activity at Day 36 and low rates of AEs were observed. Additionally, immunohistochemistry and RNA sequencing provided supportive evidence of the biological activity of GS-5745{Bhandari et al 2015}.

In a Phase 1 study of GS-5745 (with doses up to 1800 mg IV every 2 weeks) alone and in combination with chemotherapy in patients with advanced solid tumors, preliminary safety data demonstrated a manageable safety profile. There were no observed responses in the monotherapy escalation phase. However, when combined with chemotherapy in the expansion phase in subjects with measurable target lesions there were objective response rates of 64% (7/11) and 41% (7/17) for esophagogastric and pancreatic cancers respectively {Bendell et al 2015}.

GS-5745 has also been studied in RA. A total of 18 subjects (15 active: 3 placebo) with active RA documented by a mean Screening CRP value of >=8.0 mg/L received 400 mg of GS-5745 or placebo every 2 weeks for a total of 3 infusions. Subjects continued their routine RA medical regimen during the study, but the use of biologics was prohibited. All subjects had baseline moderate to high disease activity assess by Disease Activity Score (DAS28-CRP) and completed the study. At Day 43 the proportion of subjects that achieved either low disease activity or remission in the GS-5745 and placebo groups were 4/15 (27%) and 0/3 (0%) respectively.

Highlighting FEV_1 results of the Phase 1 COPD study (8 active: 3 placebo), of the 6 subjects that received 400 mg IV every 2 weeks for a total of 3 infusions, 2 of 6 subjects demonstrated mean absolute improvement in FEV_1% of 8.6% and 6.6% respectively. Changes in FEV_1 in the 2 placebo subjects that also completed 3 doses over the same time course were <4.0%. Though the sample size is small and study duration brief, it suggests GS-5745 may be able to positively affect FEV_1 in respiratory indications.

To date there has been no study drug-related adverse safety signal observed in any of the completed or active studies in any of the indications under clinical development with GS-5745 (oncology, UC, Crohn's disease, RA, COPD).

1.3. Rationale for this Study

MMP9 is a zinc-dependent endopeptidase that cleaves collagen and gelatin and is involved in neutrophil migration and remodeling of the airway. Neutrophils are a major source of MMP9, but it is also produced by bronchial epithelial cells, endothelial cells, smooth muscle cells, fibroblasts, and other immune cells such as macrophages, lymphocytes, eosinophils, mast cells, NK cells, and dendritic cells {Atkinson et al 2003}. Dysregulated MMP9 in CF has been postulated to contribute to proteolytic damage to lung parenchyma, enhance IL-8 activity, and release chemotactic peptides such as Proline-Glycine-Proline (PGP) {Devereux et al 2014}. Excess airway MMP9 is associated with reduced lung function {Gaggar et al 2007, Sagel et al 2005} and acute exacerbations {Roderfeld et al 2009} in CF patients. Confirmation of the clinical importance of MMP9 in CF has been demonstrated in a recent prospective interventional study in CF subjects hospitalized with a respiratory exacerbation who received an 8-day course

of doxycycline, a non-specific inhibitor of MMP9 or placebo for 8 consecutive days in addition to standard of care medical therapy. Subjects that received doxycycline had significant reductions in 1) sputum MMP9 levels and activity, 2) a clinically meaningful increase in $FEV_{1,}$ and 3) a reduction in hospital stay compared to the placebo group (Amit Gaggar, supporting documentation on file). Gilead's proposed study aims to build upon these positive findings by exploring the effects of a selective MMP9 inhibitor (GS-5745) dosed over a long course on lung function in a cohort of stable CF subjects.

1.3.1. Route of Administration

The highest safe and practical dose of GS-5745 will be administered in Part 1 of the study to maximize the likelihood of observing a clinical effect on the primary endpoint, FEV_1. As of 07 Dec 2015 GS-5745 has been administered to 221 subjects in several Phase 1 studies in oncology, UC, RA, and COPD and in Phase 2 studies in UC and Crohn's disease. The majority of dosing with GS-5745 has been with an IV formulation with up to 1800 mg every 2 weeks as the highest dose safely administered to oncology subjects. While a short-term IV study with GS-5745 may be achievable in CF, feedback from CF experts suggests that long-term chronic IV treatment with GS-5745 would be difficult and the preferred route would be SC. Thus, this proof-of-concept study will use a SC formulation.

1.3.2. Dose Selection

The GS-5745 SC formulation currently available for clinical studies is a pre-filled syringe at a concentration of 150 mg/mL. To investigate the highest, safe and practical SC dose of GS-5745 for this study, single and multiple SC injection regimens were considered. Weekly SC dosing of 600 mg GS-5745 is expected to be safe in CF patients. Taking into consideration that the bioavailability of the SC formulation of GS-5745 is approximately 44%, this CF dosing regimen would translate to a bimonthly dose of approximately 528 mg which is below the proposed Phase 3 oncology study in gastric adenocarcinoma of 800 mg IV Q 2 weeks and similar to the fixed dose IV dosing of 400 mg every 2 weeks in the Phase 1 RA and COPD studies. As of 25 September 2015 review of the safety data of GS-5745 in all current indications (oncology, UC, Crohn's disease, RA, and COPD) no adverse safety signal has been observed. Moreover, no increased risk of infections or sepsis has been noted despite the use of chemotherapy or immunosuppressive agents in the oncology, UC, Crohn's and RA studies. Thus, the body of GS-5745 safety data suggests that dosing 600 mg SC weekly in CF subjects should not pose an unreasonable risk for serious adverse events.

To determine potential range of MMP9 concentrations as well as binding to GS-5745 in sputum of CF subjects, *in vitro* mixing experiments were performed. Sputum samples from six distinct CF patients with stable disease were evaluated. The mean MMP9 concentration was ~2600 ng/ml (~28.3 nM), spanning 570-3700 ng/ml (6--40 nM), across these six sputum samples. After mixing varying concentrations of GS-5745 into each sputum sample, free MMP9 and GS-5745-bound-MMP9 were measured using an enzyme-linked immunosorbent assay (ELISA). On average, 1:1 binding was observed between MMP9 and GS-5745, establishing stoichiometric binding of GS-5745 to MMP9 in sputum. Stoichiometric binding is expected based on the K_D of GS-5745 for MMP9 and the knowledge that MMP9 complex formation (with TIMP, NGAL, etc.) does not interfere with GS-5745 binding.

To best predict a dose that achieves a GS-5745 concentration in molar excess of sputum MMP9, we considered both the previously-observed GS-5745 pharmacokinetics and CF-specific factors that may influence pharmacokinetics. Subcutaneous dosing of GS-5745 has been studied in UC using a 150 mg/ml formulation in a prefilled syringe. Weekly dosing of one 150 mg SC injection for 4 weeks has demonstrated clinical efficacy in a Phase 1 study, and Phase 2 studies are underway in UC and Crohn's disease using the SC formulation. Baseline mean total plasma MMP9 concentrations in the Phase 1 UC studies were found to be 143.09 ng/ml with the maximum value being 1279.40 ng/ml (N=50 (Gilead, data on file). In contrast, total plasma MMP9 concentrations in CF appear to be much higher with a mean of approximately 670 ng/ml and a maximum value of > 1500 ng/ml (N=19) {Hahn et al 2012} using the same ELISA. These findings suggest that the total body MMP9 load is greater in CF than in UC. The relative increase of MMP9 in CF to UC may be 4 to 5-fold. Thus, to account for a potentially larger MMP9 antigen sink in CF, subjects will receive a 4.0-fold higher dose in CF, or 600 mg (4 SC injections [1 mL/injection] of GS-5745 [150 mg/ml] weekly) in Part 1 of this study.

Pharmacokinetic modeling provides further rationale for weekly SC dosing of 600 mg GS-5745. Plasma PK of GS-5745 in CF subjects was predicted based on preliminary population PK modeling results in UC patients, assuming a 5-fold higher target-mediated drug clearance in CF than in UC subjects base on higher plasma MMP9. GS-5745 levels in sputum were assumed to be 10% of plasma concentrations in CF subjects, based upon an approximate 1 log reduction between serum and sputum IgG_4 in patients with non-CF bronchiectatsis {Hill et al 1998}, a surrogate for CF. The projected C_{max} and C_{min} of GS-5745 in sputum are 2.4 μg/mL (16.3 nM) and 0.02 μg/mL (0.14 nM) after the 1st 600 mg injection, and 7.1 μg/mL (48.4 nM) and 3.1 μg/mL (21.1 nM) after the last injection, respectively, in majority of CF subjects. Based on the approximately 1:1 binding observed in the *in vitro* sputum mixing studies, the 600 mg SC weekly dosing is expected to achieve consistent binding to MMP9 in the sputum in the >75% of CF patients. Correspondingly, 300 mg and 150 mg SC weekly dosing are expected to achieve lower fractional binding of MMP9 in sputum for shorter durations than the 600 mg SC weekly dosing.

1.3.3. Study Duration

Clinical improvement has been observed within 5 weeks of weekly SC dosing of GS-5745 in Phase 1 UC studies. A possible mechanism for this rapid response is that GS-5745 is a high affinity antibody with picomolar potency that targets MMP9 directly at the site of inflammation/tissue damage. The rapid clinical improvement may be due to the inhibition of upregulated MMP9 in affected regions of the colon. It is hypothesized that an 8-week period of treatment with GS-5745 may lead to further clinical improvement than the 5-week endpoint in the Phase 1 UC studies.

It is uncertain if the clinical response timeframe seen in the UC Phase 1 studies can be extrapolated to CF. A study employing the anti-inflammatory ibuprofen, known to improve FEV_1 in CF with chronic therapy {Konstan et al 1995} failed to demonstrate a clinical improvement in FEV_1 after only a 4 week treatment course {Chmiel et al 2015}. To increase the likelihood of observing an improvement in FEV_1 in this study, an 8-week dosing period will be

used paralleling the 8-week induction regimen planned for the Phase 2 UC study. If the results of Part 1 of this study are positive, then 2 lower doses, 300 mg and 150 mg, will be studied in Part 2 of the study.

1.4. Risk/Benefit Assessment for the Study

GS-5745 is currently being evaluated in 5 ongoing clinical studies for the treatment of solid tumors, UC, Crohn's Disease, RA, and COPD. From the adverse events reported in these trials none have been identified as adverse drug reactions causally related to the drug. Also, no drug interactions or contraindications have been reported.

Potential risks may include local injection site reactions and the rare possibility of hypersensitivity or allergic reactions which have been reported with the use of biologics. A single hypersensitivity reaction was observed after a second infusion in a UC subject. The subject was evaluated at the local emergency room and was discharged home in satisfactory condition. Despite this single hypersensitivity reaction after an IV infusion of GS-5745, it should be noted that GS-5745 is not considered to be a 'high risk' agonist as it acts by antagonism and targets MMP9. However, to mitigate the potential risk associated with SC administration of GS-5745, subjects will be monitored for 120 minutes after first SC injection and for 30 minutes after all subsequent SC injections of each dose during the blinded phases of Part 1 and Part 2 of the study. To be prepared for a theoretical risk of a systemic injection site reaction, study sites will be required to have on site and readily available, injectable epinephrine. Home health provider's administering the at home injections will also have readily available an auto-injectable form of epinephrine. Prior to administering drug, clinic staff and the home health provider will review the clinical manifestations of anaphylaxis and the proper use of the auto-injectable epinephrine. Unless there is an adverse event safety signal of concern observed with SC injections in the blinded phases of Part 1 and Part 2, within OLE study subjects will be monitored for 120 minutes after the first SC injection and for 30 minutes after the second SC injection. For subsequent SC injections in the OLE, subjects will be monitored for at least 15 minutes after each injection.

Only patients who are on stable CF medication regimens from 30 days prior to Baseline and throughout the duration of the study will be eligible to enroll therefore the impact on the patients' habitual standard of care should be negligible.

Despite many advances in CF therapies, the majority of CF patients experience progressive loss of lung function and recurrent exacerbations. Compared with healthy controls, patients with CF have MMP9 concentrations 13- to 14-fold higher in sputum and 100-fold higher in bronchoalveolar lavage (BAL) samples {Bergin et al 2013, Devereux et al 2014, Hahn et al 2012}. Dysregulated MMP9 in CF has been postulated to augment proteolytic damage to lung parenchyma, enhance IL-8 activity, and release chemotactic peptides such as PGP {Gaggar et al 2007}. Excess airway MMP9 is associated with reduced lung function {Sagel et al 2005} and acute exacerbations in CF patients {Roderfeld et al 2009}. Therefore, treatment with GS-5745 may reduce airway MMP9 activity in patients with CF and result in reduced airway inflammation and stabilization and/or improvement in lung function.

This clinical study will provide information about the benefits GS-5745 may have in the CF population and potentially provide an additional therapy to improve the health and life-expectancy of patients living with this life-limiting condition. These benefits are believed to outweigh any potential risks, particularly in the context of this clinical trial.

1.5. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is as follows:

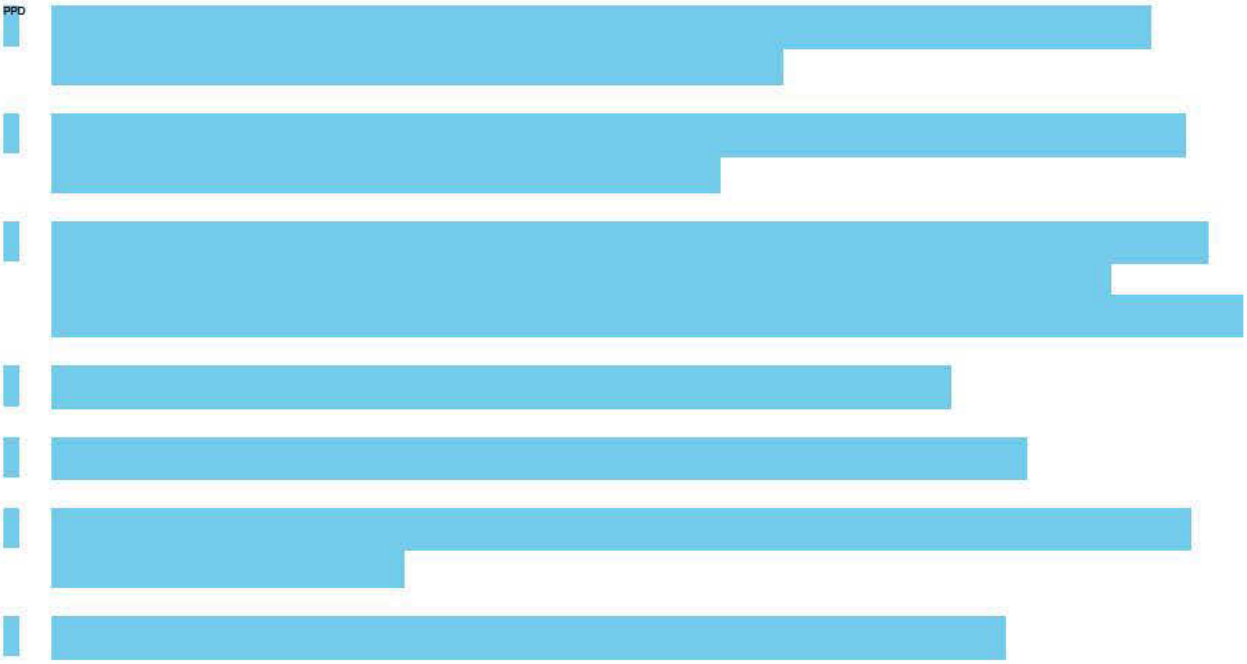
- To evaluate the effect of GS-5745 on pre-bronchodilator FEV_1 % predicted in subjects with CF after 8 weeks of treatment

The secondary objectives of this study are as follows:

- To assess safety, tolerability, and PK of GS-5745 in subjects with CF
- To evaluate the effect of GS-5745 on post-bronchodilator FEV_1 % predicted in subjects with CF after 8 weeks of treatment

Exploratory objectives of this study are as follows:

PPD



3. STUDY DESIGN

3.1. Endpoints

The primary efficacy endpoint of this study is:

- The absolute change in pre-bronchodilator FEV_1 percent predicted from Baseline to Week 8

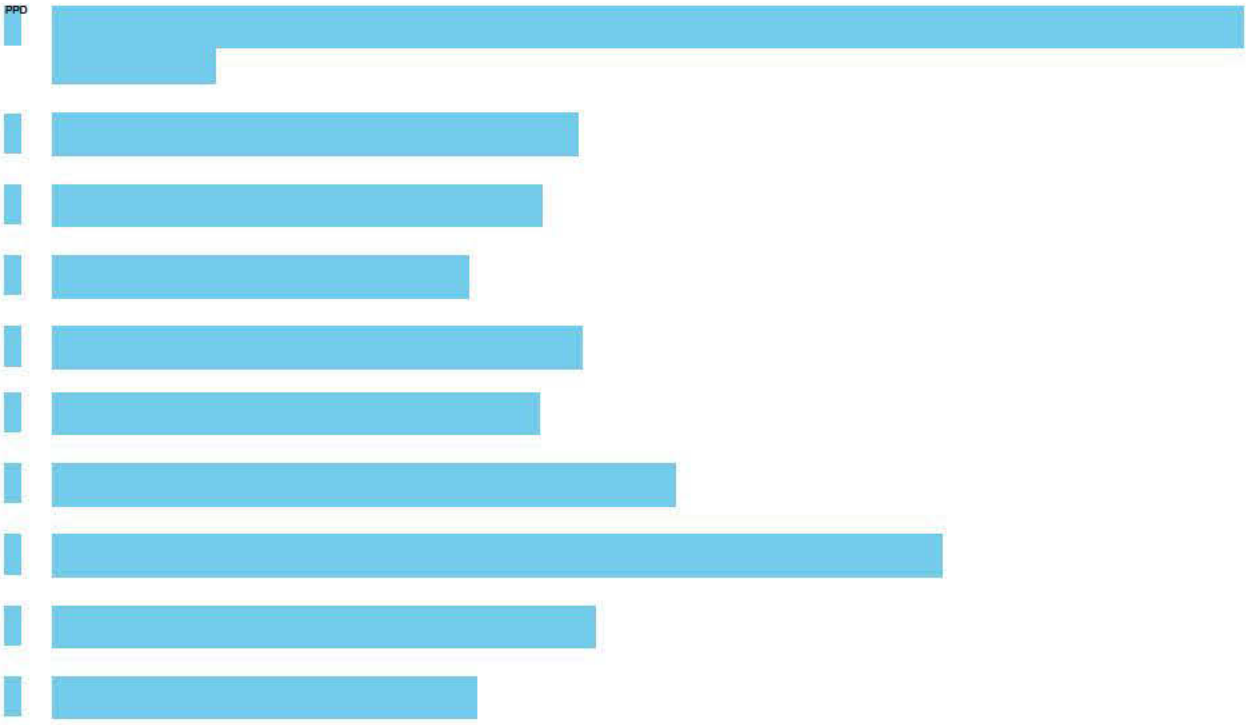
The secondary efficacy endpoints of this study are:

- The absolute change in post-bronchodilator FEV_1 percent predicted from Baseline to Week 8
- The relative change in pre-bronchodilator FEV_1 percent predicted from Baseline to Week 8
- The relative change in post-bronchodilator FEV_1 percent predicted from Baseline to Week 8

The safety of GS-5845 will be assessed by AEs, concomitant medications, clinical laboratory test, vital signs, and ADA data.

Primary PK parameters will include C_{max}, T_{max}, C_{last}, T_{last}, and AUC_{last} (as applicable).

Exploratory endpoints of this study are:



3.2. Study Design

This is a phase 2b, randomized, double-blind, placebo-controlled, multiple-center, multiple dose study.

The study is comprised of 2 parts. Part 1 will enroll 60 subjects in a 1:1 ratio to receive either 600 mg GS-5745 SC or placebo in a blinded manner for 8 weeks. Safety and efficacy analyses will be performed for Part 1 after all subjects have completed the Week 8 visit or discontinued from the study. If the FEV_1 percent predicted change combined with other endpoints indicate positive signals and the DMC determines there are no significant safety signals, then advancement to Part 2 will occur. Refer to Section 8.11 for more information.

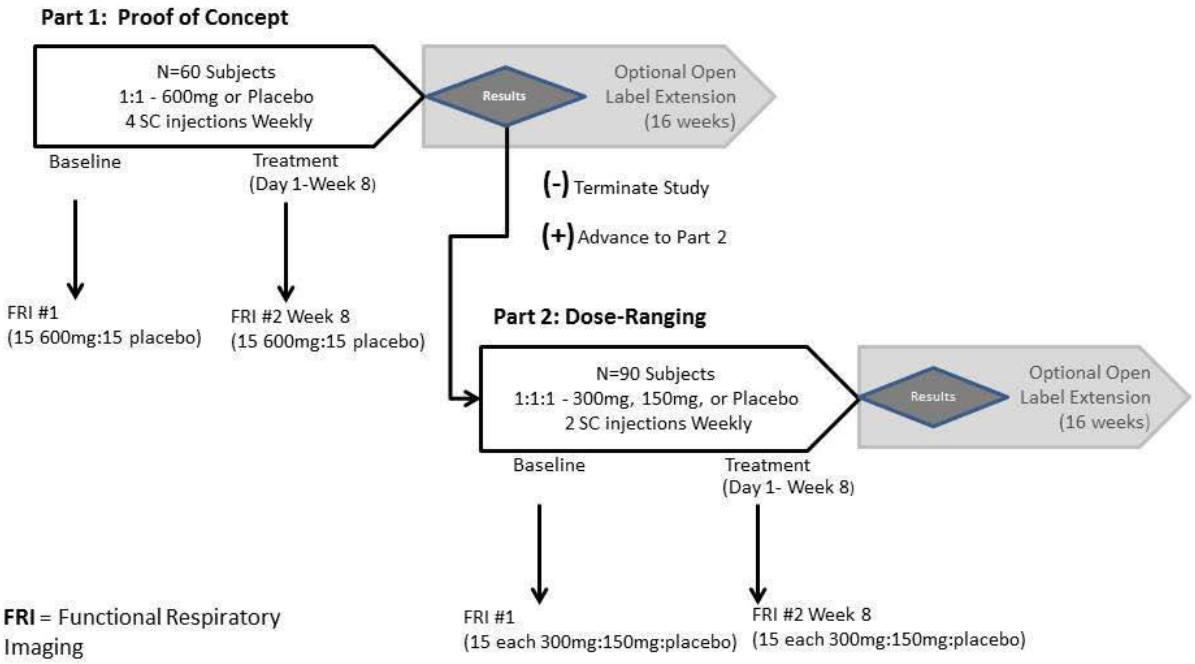
Part 2 will enroll 90 subjects in a 1:1:1 ratio to receive SC injections of either 300 mg GS-5745, 150 mg GS-5745, or placebo for 8 weeks in a blinded manner. Visits and procedures for both Part 1 and Part 2 will be the same.

The FRI sub-study will require 2 FRI scans, one at Baseline and 1 at the Week 8 visit. A sub-set of study sites will be trained in FRI. All subjects enrolling into the study at those sites will participate in the FRI sub-study until approximately 30 subjects in Part 1 and up to 52 subjects in Part 2 have enrolled into the sub-study and completed Week 8. See Section 6.3.10 for additional information on FRI.

There will be a sputum cytology sub-study for both Part 1 and Part 2. A select sub-set of sites will perform sputum cytology from induced sputum samples to investigate changes in total cell count and cell count differential in sputum. No additional procedures will be required of subjects participating in the sputum cytology sub-study.

Blood samples for PK will be obtained at select scheduled study visits. PPD

Figure 3-1. Study Design



3.3. Study Treatments

3.3.1. Part 1

Subjects who meet the eligibility criteria at screening will be randomized in a blinded fashion in a 1:1 ratio as follows:

- Treatment arm (n=30): 600 mg GS-5745 (4 SC injections of 150 mg as 1 dose given weekly for 8 doses).
- Placebo arm (n=30): matching placebo (4 SC injections as 1 dose given weekly for 8 doses).

3.3.2. Part 2

Subjects who meet eligibility criteria at screening will be randomized in a blinded fashion in a 1:1:1 ratio as follows:

- Treatment arm 300 mg (n=30): 300 mg GS-5745 (2 SC injections of 150 mg as 1 dose given weekly for 8 doses).
- Treatment arm 150mg (n=30): 150 mg GS-5745 (1 SC injection of 150 mg and 1 SC injection of placebo as 1 dose given weekly for 8 doses).
- Placebo arm (n=30): matching placebo (2 SC injections as 1 dose given weekly for 8 doses).

3.3.3. Open-Label Extension (OLE)

On the Week 8 visit (-3 to + 4 days) of both Part 1 and Part 2, subjects (active and placebo) will be invited to participate in an OLE treatment period.

- Subjects choosing to participate from Part 1 will receive open-label 600 mg of GS-5745 weekly for 16 additional weeks.
- All subjects choosing to participate from Part 2 will receive open-label 300 mg of GS-5745 weekly for 16 additional weeks.

3.3.3.1. Home Administration of Study drug

Weekly clinic visits during the study may pose a significant burden to study subjects. This burden must be balanced against the need to closely monitor these potentially vulnerable subjects during the early doses of study drug. Therefore all subjects will receive at least the first 2 SC study drug injections at the study site. Thereafter, subjects who experienced no major AEs associated with the SC injections will have the option of utilizing a home health provider organization (where available) to complete select visit procedures and study drug dosing during the blinded and OLE portions of this study (see Section 6.1.6).

3.4. Duration of Treatment

Randomized subjects in both Part 1 and Part 2 will complete 8 weeks of weekly dosing. Subjects that choose to participate in the OLE will receive an additional 16 weeks of weekly dosing of GS-5745 for a total of 24 weeks of dosing. Subjects will have their final visit 30 days after the last dose of study drug.

3.5. Protocol Discontinuation Criteria

Study drug administration will be suspended in all subjects if any one of the following criteria are met:

1) The Principal Investigator (or his/her deputy) and the Sponsor consider the number and/or severity of AEs justify discontinuation of the study

2) The Sponsor makes a unilateral request to do so

3) An SAE or a confirmed Grade 4 laboratory finding in the same system organ class and determined to be related to study drug occurs in 2 or more subjects in a cohort.

4) Laboratory results that meet Hy's Law criteria {U.S. Department of Health & Human Services (DHHS) et al 2009}

Decisions to reinitiate dosing will be made by the DMC and Sponsor upon review of all available safety and tolerability data generated by subjects dosed to date.

3.6. Source Data

The subject identification number and randomization number captured by the interactive web response system (IWRS) are considered source data. All other information entered into the electronic data capture (EDC) requires source documentation to be available for verification.

3.7. Biomarker Testing

3.7.1. Biomarker Samples to Address the Study Objectives

Blood and sputum will be collected in this study and will be used to evaluate the association of exploratory systemic and/or tissue specific biomarkers with study drug response, including efficacy and/or AEs and to increase knowledge and understanding of the biology of MMPs and CF or related diseases such as bronchiectasis, asthma, COPD, idiopathic pulmonary fibrosis, and sarcoidosis and/or the validation of a companion diagnostic for GS-5745. The specific analyses will include, but will not be limited to, total and free MMP9 and MMP9 activity. A blood sample will be collected for RNA to study gene expression changes from Baseline in response to GS-5745 with particular emphasis on MMP9 pathway related transcript changes. Blood samples will also be collected for CF genotyping at Baseline for subjects who do not have a historical genotype on file. Since biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it is not possible to specify prospectively all tests that will be done on the specimens provided. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of art knowledge.

3.7.2. Biomarker Samples and Imaging for Optional Future Research

PPD

3.7.3. Biomarker Samples for Optional Genomic Research

PPD

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Up to 150 subjects who meet the eligibility criteria at screening will be randomized to receive GS-5745 or placebo in Part 1 (60 subjects) and Part 2 (90 subjects). The sub-study for FRI will enroll up to 35 subjects in Part 1 and up to 52 subjects in Part 2 to account for an attrition rate of 15%.

Subjects who fail to meet all the inclusion criteria or who meet any of the exclusion criteria will not be randomized in this study. No waivers for any study entry criteria will be granted.

In order to manage the total study enrollment, Gilead Sciences, Inc. (Gilead), at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1) Male or female 18 years of age or older

2) Confirmed diagnosis of CF as determined by the 2008 Cystic Fibrosis Foundation Consensus Report {Farrell et al 2008} criteria

3) Subjects must be able to perform acceptable and reproducible spirometry as per the American Thoracic Society (ATS) Guidelines

4) Must have a body weight of > 40 kg (88.2 lbs) at study Screening

5) Subjects must be a never-smoker or an ex-smoker with < 5 pack-year history of smoking and be smoke-free (including marijuana or e-cigarettes/vaping) for 12 months prior to Screening

6) Pre-bronchodilator $FEV_1 \geq 40\%$ and $\leq 80\%$ of predicted at Screening

7) 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_1(L), calculated as the absolute value of [(first FEV_1 – second FEV_1) / first FEV_1] x 100 should be < 12% **AND**

   — The absolute difference in FEV_1 should be < 200 ml

8) 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 24 months prior to Screening must be negative. If only 1 NTM culture was performed 24 months prior to Screening, that NTM culture and the most recent NTM culture obtained >24 months prior to Visit 1 must both 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 were both negative **AND**

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

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

9) 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.

10) 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.

11) 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 about 4 months if they are taken as an alternating inhaled antibiotic).

12) A negative serum pregnancy test is required for women of childbearing potential (as defined in Appendix 3)

13) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception (as described in Appendix 3)

14) Lactating females must agree to discontinue nursing before administration of study drug and during the course of the study

15) Male subjects must agree to refrain from sperm donation for 90 days after the last dose of study drug is administered

16) Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures

17) Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) Concurrent use of oral antibiotics (excluding the use of chronic azithromycin) or IV antibiotics within 30 days of Baseline. Prophylactic and chronic doxycycline use is prohibited during the study.

2) Hospitalization for a respiratory event within 30 days of Baseline

3) Active allergic bronchopulmonary aspergillosis (ABPA) requiring treatment; previous history of ABPA without current ABPA anti-fungal prophylaxis is acceptable

4) Any acute “non-CF related” illness within 2 weeks prior to Baseline (eg, gastroenteritis)

5) Current use of systemic immunosuppressive drugs including oral corticosteroids within 30 days of Baseline

6) 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)

7) History of anaphylaxis requiring the use of epinephrine

8) History of solid organ (including lung) or hematologic transplant, or currently on a transplant waiting list

9) History of lung resection

10) History of HIV, hepatitis B, or hepatitis C

11) History of malignancy in the last 5 years except for subjects who have been successfully treated for non-melanoma skin cancer or cervical cancer

12) History of alcohol or drug abuse in the past year, including but not limited to cannabis, cocaine, opiates, as determined by the investigator

13) 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 transpetidase (GGT), 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 m2 based on the 4-variable Modification of Diet in Renal Disease (MDRD) formula: GFR = $175 \times [SCr]^{-1.154} \times [age]^{-0.203} \times [1.212$ if patient is African American$] \times [0.742$ if patient is Female$]$ {Levey et al 2006}

14) Clinically significant abnormal ECG at Screening; abnormalities considered not clinically significant, per investigator, are not exclusionary

15) Known hypersensitivity to the investigational medicinal product or formulation excipient

16) Presence of any condition or abnormality that would compromise subject safety or the quality of data, or any serious or active medical or psychiatric illness, which in the opinion of the investigator, would interfere with subject treatment, assessment, or compliance with the protocol

17) Receipt of any investigational non-biological drug therapy within 30 days of enrollment **OR** receipt of any marketed or investigational biologic within 4 months prior to enrollment

18) Females who are pregnant or breastfeeding

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

An interactive Voice/Web Response System (IVRS + IWRS = IXRS) will be 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.

5.1.1. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IXRS system for that subject. Directions for obtaining treatment assignment can be found in the IXRS User Guide. Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the case report form/ electronic case report form (CRF/eCRF), along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator during the blinded phase of the study, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

Gilead Drug Safety and Public Health (DSPH) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description and Handling of GS-5745 and Placebo

5.2.1. Formulation

GS-5745 for SC injection is formulated as a sterile, aqueous buffered solution in a single-use pre-filled syringe (PFS) with a plunger stopper. The buffered solution contains acetate at pH 5.0, sucrose and polysorbate 20 added for stabilization. Each 1 mL PFS contains 150 mg GS-5745 at a concentration of 150 mg/mL.

Placebo for SC injection is formulated as a sterile, aqueous buffered solution in a single-use PFS with plunger stopper. Each 1 mL PFS contains acetate buffer at pH 5.0, sucrose and polysorbate 20.

5.2.2. Packaging and Labeling

GS-5745 SC injection and placebo will be supplied in 1 mL glass pre-filled syringes with gray butyl coated stoppers.

Study drug(s) to be distributed to centers in the United States (US) and other participating countries shall be labeled to meet applicable requirements of the US Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

Gilead or designated distribution depots will distribute study drug to centers as per Good Manufacturing Practice (GMP) requirements.

5.2.3. Storage and Handling

GS-5745 and placebo for SC injection will be shipped and stored under refrigeration between 2 to 8 °C (36 to 46 °F). Storage conditions are specified on the label.

Upon arrival at the clinical center, the study drug products must be stored in a secure area, accessible only to authorized study site personnel. To ensure drug stability and proper product identification, the drug products should be stored in the kits in which they are supplied until needed.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body.

5.3. Dosage and Administration of GS-5745 and Placebo

GS-5745 or placebo for SC injection will be administered to subjects on the thighs, the stomach area (abdomen), or the deltoid area of the upper arms in the blinded phase of the study. In the OLE if self-injection at home is determined to be safe, deltoid injections will not be allowed. If the abdomen area is chosen, the area 5 cm (2 inches) around the umbilicus should be avoided. GS-5745 or placebo will be administered SC at the research center at study visits during the blinded phase of the study. If the dose requires multiple SC injections, all injections should be delivered within 1 hour. The investigator or a qualified designee must be present during the administration during the blinded phase of the study.

In the blinded phase of the study, if the subject has a body temperature of > 38ºC (100.4ºF) , his/her FEV_1 % predicted is less than 40% or his/her FEV_1 % predicted decreases by > 30% from Baseline on study site visits requiring spirometry, AM pre-bronchodilator PEF decreases by >30% from the mean PEFR obtained during Screening during non-spirometry visits, or in the medical opinion of the investigator or home health provider the subject is unfit to receive study drug at a given visit, the subject should not be administered study drug. In consultation with the medical monitor, the Investigator may delay dosing until the parameters above are met. See Section 6.3.6 for additional information on the spirometry measures.

During the OLE portion of the study subjects will have the option to continue to receive study drug SC injections at their respective study clinic receive SC injections by a qualified home health provider (where available) at their residence in the short-term with the long-term plan to eventually self-administer the study drug without supervision at home after the DMC and Gilead have reviewed safety data and agree home administration appears safe. At the beginning of the

OLE subjects will be instructed by clinic staff how to self-administer the SC injections using the thigh and stomach areas only. After successful training and sign-off by the study clinic and/or home health provider (where available) that the subject can correctly self-administered study drug, subjects will self-administer doses at home weekly (±3 days) between study visits and record the doses when they are administered. Subjects who find it difficult to self-administer the study drug SC injections at home may receive assistance with the administration from the home health care service (where available) to ensure proper dosing and adherence or receive their SC injections at their local study sites. All injections should be delivered within 1 hour. Subjects will also be instructed in the safe storage and transport of the study drugs as well as safe disposal of used syringes.

Similar to the blinded phase of the study, in OLE if the subject has a body temperature of > 38ºC (100.4ºF), PEF decreases by > 30 % from the mean obtained during Screening during non-spirometry visits, or in the medical opinion of the investigator or home health provider the subject is unfit to receive study drug at a given visit, the subject should not be administered study drug. In consultation with the medical monitor, the Investigator may delay dosing until the parameters above are met.

If a subject fails to come to their respective study site for a scheduled study visit that includes SC administration of study drug, the investigator should contact the Gilead medical monitor to discuss if a late dose is acceptable or if the dose should be skipped.

If a subject misses 2 doses defined as the series of study drug SC injections associated with 2 study visits (clinic or home visits), the Gilead medical monitor should be contacted to discuss if the study drug should be withdrawn for that subject.

5.4. Prior and Concomitant Medications and Excluded Therapies

At each study visit, the study center will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription medications, non-prescription medications, therapies, and dietary supplements. The use of all inhaled and/or IV antibiotics for respiratory exacerbations during the 12 months prior to Screening will be recorded.

The following medications are excluded from use during the study:

- Systemic immunosuppressive drugs including
- An oral corticosteroid burst of > 7 days duration
- Any investigational drug therapy
- Prophylactic and chronic doxycycline

Effective current therapies should not be discontinued for the sole purpose of participating in this study. Subjects may receive medications as supportive care or to treat AEs as deemed necessary by the investigator or the subject's physician. Should subjects have a need to initiate treatment with any excluded concomitant medication, the Medical Monitor must be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the Sponsor, the investigator must notify Gilead Sciences as soon as he/she is aware of the use of the excluded medication. The allowed concomitant medication(s) for CF must be maintained at a stable dose throughout the duration of the study.

5.5. Concomitant Medication Management

Subjects must remain on stable CF medication regimens from 30 days prior to Baseline, and it is recommended they remain on those medications through the Follow-up visit. If a change in CF medication regimen is required during the course of the study, please contact the medical monitor prior to initiation of therapy.

Specific requirements apply to inhaled CF medications:

- At the time of study entry, subjects who are on a stable regimen of inhaled antibiotics that are continuously administered should remain on those antibiotics throughout the study.
  - A stable regimen of continuous or continuous alternating antibiotics is at least 2 "on-treatment" cycles (about 2 months) prior to Baseline.
- At the time of study entry, subjects who are on a stable regimen of inhaled cycling antibiotics (e.g. aztreonam for inhalation [Cayston], inhaled tobramycin [TOBI and TIP], inhaled colistin) should remain on these antibiotics throughout the study. Inhaled cycling antibiotics should be administered in 28-day-on/28-day-off cycles.
  - A stable regimen of cycling antibiotics is at least 2 "on/off" cycles (about 4 months) prior to Baseline.
- Standard of care inhaled CF therapies (eg, bronchodilators, dornase alpha, inhaled antibiotics, hypertonic saline, inhaled mannitol, inhaled corticosteroids) will be withheld prior to study specified spirometry according to Section 6.3.6

5.6. Accountability for Study drug

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgement of receipt of each shipment of study drug (quantity and condition).

Study drug accountability records will be provided to each study site to:

- Record the date received and quantity of study drug
- Record the date, subject number, the study drug kit number dispensed
- Record the date, quantity of used and unused study drug.

For additional information about study drug accountability and return, refer to Section 9.1.7.

5.7. Rescreening of Study Subjects

Subjects may be rescreened only once if they meet no more than 1 of the criteria below. A request for rescreening form must be completed and approved by the medical monitor prior to a subject rescreen.

If a subject is randomized but not dosed due to a safety concern after the FRI has occurred, the subject may be rescreened with Medical Monitor approval, and may opt to not participate in the FRI sub-study at that site.

1) A subject is unable to produce adequate sputum during the first attempt during screening for any required inclusion/exclusion criteria related to sputum bacteriology.

2) A subject that requires a new course of oral or IV antibiotics, systemic corticosteroids or is hospitalized during screening, may rescreen 30 days after hospital discharge or at least 30 days after the last course of antibiotics/corticosteroids

3) Any acute "non-CF related" illness within 2 weeks prior to Baseline (eg, gastroenteritis).

4) An investigator may petition the medical monitor for a rescreen of subject for a single criterion that is not mentioned above providing details and rationale for the rescreen and completing a request for rescreening form.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Table 6-1 and described in the text that follows. Additional information is provided in the study procedures manual.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Details of Study Visits

6.1.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the Investigator to ensure that subjects are eligible to participate in the study prior to randomization or enrollment and throughout the study.

Once consent has been obtained, all screening tests and procedures have been assessed, and study eligibility has been confirmed, eligible subjects will be randomized to study treatment as described in Section 3.3.

The study center will not be released to initiate dosing until:

- The Institutional Review Board (IRB) or Ethics Committee (EC) reviewed and approved the study and the informed consent document;
- All required regulatory documents have been submitted to and approved by Gilead or the CRO;
- A master services agreement and/or study agreement is executed;
- The site initiation meeting has been conducted by the Gilead clinical monitor (or designee). The initiation meeting will include a review of the protocol, the IB, and investigator responsibilities.

Table 6-1. 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
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**[l]	**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**						
Withhold all inhaled CF therapies morning of study visit	X[q]	X		X			X		X			X		X			X		X	X	
Written Informed Consent	X																				
CFQ-R[a]		X			X		X		X			X				X	X	X	X	X	X
TSQM (if available)[a]		X					X					X				X	X	X	X		
SNOT-22 (if available)[a]		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[b]	X																			X	X
Symptom Driven Physical Exam[b]		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
Blood for Safety Labs[c]	X	X			X		X					X					X			X	X
ESR[r]	X											X							X		
Urine Cotinine	X						X					X					X				
Urinalysis	X	X			X							X					X			X	X
Serum Pregnancy Test[d]	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[m]																				

	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[l]**	**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**						
Pre- and post-bronchodilator Spirometry[e]		X			X		X		X			X		X			X		X	X	X
PEFR	X	X[p]		X		X		X			X		X			X		X			
Chest X-ray[f]	X																				
ECG	X	X					X					X					X		X	X	
Induced sputum for biomarkers		X					X					X				X			X	X	X
Spontaneous sputum for microbiology[g]	X, X				X				X									X			
FRI Scan[h]		X										X									
Blood for PK[i]		X		X	X		X		X			X									X
PK sub-study			X							X											
Anti-drug Antibodies		X					X					X					X		X	X	X
Blood for Biomarkers	X	X			X		X					X								X	X
Blood for RNA Biomarkers		X					X					X								X	X
Blood for CF genotyping[j]		X																			
Optional blood sample for genomic research[j]		X																			
Randomization		X																			
Study drug administration[k]		X		X	X	X	X	X	X		X	X[n]	X-weekly through week 23-X								
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X[o]		X[o]	X[o]	X[o]	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 (±1) and Day 48 (±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 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.

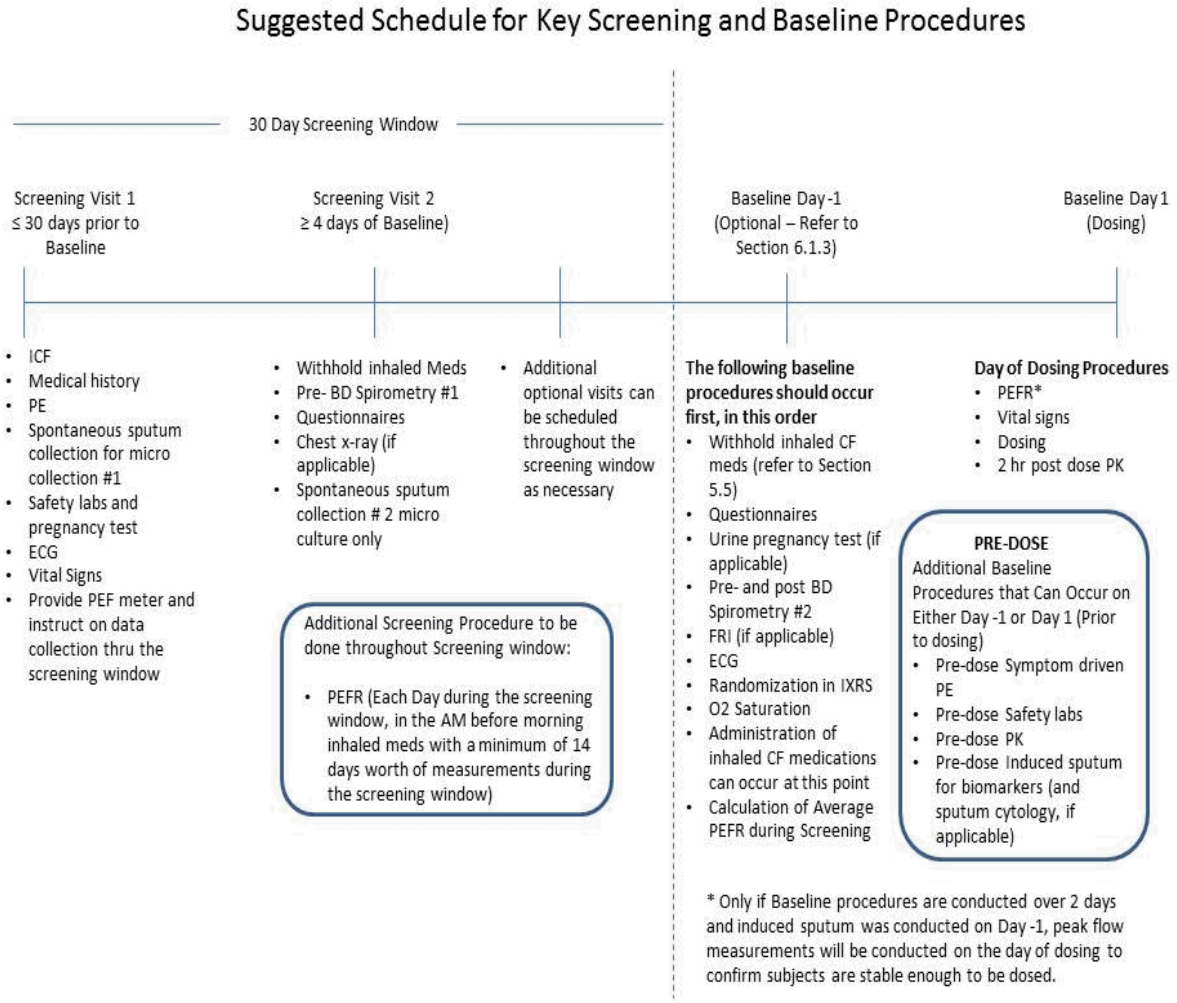
o Subjects enrolled into the open-label extension may request assistance administering the SC injections either by returning to the clinic or utilizing a home health care service provided by the Sponsor to ensure proper dosing and adherence. If determined acceptable by the DMC, home self-administration 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.

Figure 6-1. Suggested Schedule for Key Screening and Baseline Procedures



6.1.2. Screening Period (Day -30 to -1)

Subjects will be screened up to 30 days prior to randomization/enrollment to determine eligibility for participation in the study. Written informed consent must be obtained from each subject before initiation of any Screening procedures. After informed consent is obtained, screening procedures outlined in Table 6-1 and described in the following text will be initiated.

The screening procedures may require multiple visits. Medical history taken during Screening will also include a 1-year history of hospitalizations and IV, inhaled, and oral antibiotic therapy for pulmonary exacerbations.

Two pre-bronchodilator screening spirometry measures taken at least 4 days apart (one during Screening, one at Baseline) must be taken to meet Inclusion Criterion 7 (see Section 6.3.6).

Subjects meeting all of the inclusion criteria and none of the exclusion criteria are eligible for Randomization (Baseline). Subjects who do not meet the eligibility criteria will be excluded from randomization and may be considered for rescreening for the study in consultation with the medical monitor.

From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any AEs related to protocol-mandated procedures on the AE case report form (CRF/eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history CRF/eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.1.3. Baseline/Randomization (Day 1)

All Baseline tests and procedures must be completed prior to randomization and dosing on Day 1 as indicated in Table 6-1.

If subjects are unable to complete all Baseline assessments in a single day, the baseline/randomization visit may be split over 2 consecutive days as needed. If the visit is to be split over 2 days, the following procedures may be done on the first day and should be done prior to standard of care inhaled CF therapies as indicated in Section 5.5:

- Refer to Figure 6-1 for recommended visit schedule and order of procedures for Screening and Baseline visits.
- Sputum induction and blood draws for safety and pre-dose PK can be performed on either day of the baseline/randomization visit, but must be performed prior to study drug dosing.
- At the Baseline/Randomization visit, subjects who meet the eligibility criteria will be randomized into the study. Study drug should be administered after randomization. Subjects will be observed for 2 hours after the last injection. Blood for PK will also be obtained 2 hours after the last injection of study drug. Day 1 will be the day on which the subject receives the first dose of study drug.

6.1.4. Blinded Treatment Period: Day 5 through Week 7

At visits in the blinded treatment period, subjects should complete the CFQ-R, SNOT-22, and the TSQM prior to all other procedures when indicated in Table 6-1. At visits where study drug dosing is indicated, the subject should be observed for 30 minutes after the last injection. Subjects who provide separate consent for the PK sub-study will provide a Day 5 plasma PK sample. At the Day 48 visit blood for PK will be obtained.

For sites and subjects utilizing home health services for at home dosing of study drug, site staff should instruct the subject on the packaging, storage, self-administration, and safe needle disposal for GS-5745. Following 2 successful doses in clinic within the blinded period, the subjects and the site may choose to utilize the home health service (See Section 6.1.6 for further information). If the home health option is utilized, subjects will be dispensed GS-5745 at the visit prior to the scheduled home health visit for Weeks 3, 5, and 7 within the blinded period.

Subjects will perform peak expiratory flow rate measurements prior to study drug administration on days when study spirometry is not performed. Doses should be administered at 1 week intervals (±3 days), all injections for a single dose should be delivered within 1 hour, and the date/time of administration will be recorded. Please refer to the Pharmacy Manual for additional information.

6.1.5. Week 8 (-3 to + 4): Primary Endpoint and Open-Label Extension

All Week 8 tests and procedures must be completed prior to participating in the OLE and dosing as indicated in Table 6-1.

Subjects who agree to participate in the OLE portion of the study will be entered into the IXRS to confirm enrollment into the open-label extension after all other procedures as indicated in Table 6-1. The first dose of open-label GS-5745 should be dispensed as directed by IXRS and administered to the subject at Week 8. Sites should train the subject on administration of the study drug at this visit. Subjects will be observed for 30 minutes after the last injection for the first 2 doses.

If the home health option is utilized during OLE, subjects will be dispensed GS-5745 at the visit prior to the scheduled home health visit for Weeks 11, 13 to 15, 17 to 19 and 21 to 23.

Subjects who do not agree to participate in the OLE portion of the study will be discontinued from the study and will be asked to return to the clinic in 30 days for their 30-day Follow-up visit as indicated in Table 6-1.

6.1.6. Utilization of Home Health Services

Weekly clinic visits during the study may pose a significant burden to study subjects. This burden must be balanced against the need to closely monitor these potentially vulnerable subjects during the early doses of study drug. Therefore, sites and subjects will have the option of utilizing a home health nursing organization provided by the Sponsor to complete visit procedures and study drug dosing during selected visits during the blinded and OLE portions of this study. Should the subject and site choose to utilize the home health service, blinded study visits at Weeks 3, 5, 7 and OLE visits at Weeks 11, 13 to 15, 17 to 19 and 21 to 23 may occur at the subject's home. The DMC and Gilead will be closely monitoring SC injection safety throughout the study. If it is judged in the OLE phase of the study that home self-administration without a home health provider present does not pose an unacceptable safety risk, then subjects may be trained for SC self-injection. Once the subject has successfully completed the self-administration training and is judged as capable of home SC self-administration of study drug by the trainer, the subject may begin self-administration of study drug at home without supervision at any of the remaining OLE visits mentioned above.

6.1.7. Open-Label Extension: Week 9 through 24

All OLE tests and procedures should be completed as indicated in Table 6-1 for subjects participating in the OLE only.

At Week 9 and 10 site staff should instruct the subject on the packaging, storage, self-administration, and safe needle disposal for GS-5745. Following 2 successful doses in clinic within the OLE, subjects will be dispensed GS-5745 to administer Weeks 11, 13 to 15, 17 to 19, and 21 to 23 doses at home by a qualified home health service selected by the Sponsor to ensure proper dosing and adherence. In the OLE subjects will perform peak expiratory flow rate measurements prior to study drug administration on days when study spirometry is not performed. Doses should be administered at one week intervals (±3 days), all injections for a single dose should be delivered within 1 hour, and the date/time of administration will be recorded. Please refer to the Pharmacy Manual for additional information.

6.1.8. 30-Day Follow-Up Visit

Thirty days after the last dose of study drug, subjects will return to the clinic for a follow-up visit. Procedures should be completed as indicated in Table 6-1.

6.1.9. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 6.1.10, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study. If the subject is withdrawn from the study, the following Early Termination procedures should be performed if possible:

- Administer CFQ-R (prior to any procedures), SNOT-22 and TSQM
- Review of AEs and concomitant medications
- Complete physical examination including body weight
- Obtain vital signs
- Obtain serum pregnancy test (for females of child-bearing potential only)
- Obtain blood for PK, ADA analysis, and biomarkers
- Obtain blood and urine for safety lab
- Obtain oxygen saturation
- Obtain pre- and post-bronchodilator spirometry
- Obtain induced sputum

6.1.10. Criteria for Discontinuation of Study Treatment

Study medication may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree. Following resolution of intercurrent illness and/or fever, and in collaboration with the medical monitor, the investigator may decide to allow the subject to resume study dosing.
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 3
- Discontinuation of the study at the request of Gilead, a regulatory agency or an IRB/IEC

6.2. End of Study

The end of this study is defined as the date of the last study visit of the last study subject.

6.3. Details of Scheduled Assessments

6.3.1. Physical Exam

A complete physical exam will be performed at Screening and the 30-day Follow-up Visit. A symptom-driven physical exam will be performed at Baseline, Weeks 4, 8, 12, 16, 20, and 24, and can be performed as needed at other study visits.

All physical exams will include a body weight measurement. Height will be captured at Screening only.

A musculoskeletal symptom assessment will be conducted at Screening, Baseline, and at Weeks 4, 8, 12, 16, 20, 24, and 30-day follow-up visit.

6.3.2. Vital Signs

Vital signs to be collected include resting blood pressure, pulse, respiratory rate and temperature.

6.3.3. CFQ-R, TSQM, and SNOT-22 Questionnaires

The CFQ-R is a CF-specific quality of life measure encompassing both generic and CF-specific domains for a 2-week recall period. Because all study subjects will be 18 years of age or older, only the self-administered version of the questionnaire will be used in this study.
The questionnaire takes approximately 15 minutes to complete and will be administered before any other study procedures at study visits indicated in Table 6-1. This questionnaire will be in electronic form and accessed on a secure website using a PC or laptop computer, where available.

The TSQM questionnaire is a generic medication acceptance measure designed to assess effectiveness, side effects, convenience, and global satisfaction. It is self-administered questionnaire that takes approximately 15 minutes to complete and will be administered before any other study procedures at study visits indicated in Table 6-1. This questionnaire will be in electronic form and accessed on a secure website using a PC or laptop computer.

The Sino-nasal Outcome Test (SNOT-22) is a symptom-based rhinosinusitis outcome measure. The questionnaire is self-administered with 22 questions that takes approximately 15 minutes to complete. It will be administered before any other study procedures at study visits as indicated in Table 6-1. This questionnaire will be in paper form.

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.

6.3.4. Pulmonary Exacerbation Evaluation

A modified version of the Fuchs criteria {Ramsey et al 2011, Wainwright et al 2015} will be used for categorization of pulmonary exacerbations during the course of the study. A pulmonary exacerbation is defined as a change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the following 12 signs/symptoms. New or changed antibiotic therapy from the previous visit for the following sinopulmonary signs/symptoms will be determined at all visits and documented in the source documents:

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature above 38ºC

- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination of the chest
- Decrease in pulmonary function by 10 percent or more from a previously recorded value
- Radiographic changes indicative of pulmonary infection

6.3.5. Oxygen Saturation

Oxygen saturation by pulse oximetry will be performed as indicated in in Table 6-1. Sites should follow their institutional guidelines for pulse oximetry. If a subject is on oxygen this should be measured after they have been off oxygen for at least 5 minutes.

6.3.6. Spirometry

All sites will be provided with centralized spirometry equipment to be used for spirometry assessments throughout the study. Spirometry data will be transmitted to a centralized spirometry vendor for quality review. In the Screening period, spirometry will be collected pre and post-bronchodilator, subjects are required to withhold their inhaled CF therapies including all bronchodilators. Two pre-bronchodilator spirometry measures are required using the study provided central spirometry equipment to meet the inclusion criteria. If a subject's Screening pre-bronchodilator FEV_1 % is 38-39.9% or 80.1-82% the upper limit FEV_1 % inclusion, baseline spirometry may be repeated one time assuming all other inclusion/exclusion criteria have been met. If a subject's relative change in FEV_1 % at Baseline from Screening is 12.1-14% the upper limit FEV_1 % inclusion, baseline spirometry may be repeated one time assuming all other inclusion/exclusion criteria have been met.

At all visits after Screening, including Baseline, spirometry should be performed at approximately the same time of the morning on designated study-specific days in Table 6-1. ATS guidelines should be followed for all PFT maneuvers as well as for selecting specific PFT efforts to report {American Thoracic Society Committee on Diagnostic Standards for Non-Tuberculous Respiratory Diseases 1995}. Spirometry collected at Baseline and Week 8 visits will be reviewed for quality by the central spirometry vendor in real time to ensure that acceptable measurements are selected and to reduce variabliltiy at the Baseline visit. Additional study-specific PFT guidelines are outlined below.

Standard of care inhaled CF therapies (eg, bronchodilators, dornase alpha, inhaled antibiotics, hypertonic saline, inhaled corticosteroids) will be withheld prior to study specified spirometry in the treatment and follow-up period as follows:

Pre-bronchodilator spirometry is defined as occurring after a subject has:

- Withheld their short-acting beta-agonist (eg, albuterol/salbutamol) or anticholinergic (eg, ipratropium bromide) for more than 4 hours before the spirometry assessment; AND
- Withheld their long-acting bronchodilator (eg, salmeterol) for more than 12 hours before the spirometry assessment; AND
- Withheld their once-daily, long-acting bronchodilator for more than 24 hours before the spirometry assessment.

See Appendix 5 for specific inhaled washout details.

Doses of bronchodilators taken within the previous 24 hours of spirometry will be recorded for each spirometry assessment.

Post-bronchodilator is defined according to ATS guidelines, occurring approximately 15 minutes after 4 puffs of a bronchodilator (ie, albuterol, salbuterol, or levalbuterol).

With the exception of the screening period, at all visits at which spirometry is indicated, both a pre-bronchodilator and a post-bronchodilator spirometry will be performed. In the event that a subject forgets to withhold their inhaled CF medications at Baseline or Week 8, the visit should be rescheduled to another date within the screening window. At all other visits, if a subject forgets to withhold their inhaled CF medications, spirometry should be performed post-bronchodilator only and recorded as such.

On days of study drug administration at the study site the post-bronchodilator FEV_1% predicted will be utilized as a safety measurement. If an individual subjects post-bronchodilator FEV_1% predicted is either 1) <40% predicted, 2) >30% below the Baseline FEV_1% predicted, or 3) PEF decreases by >30% from the mean obtained during Screening during non-spirometry visits, study drug dosing should be postponed and rescheduled during the study visit window.

Subjects should not be informed of their study-related spirometry results during the Blinded Treatment Period (Baseline through Week 8) regardless if the subject prematurely discontinues treatment. In addition, subjects should not be informed of their study drug allocation (active:placebo) until after all subjects have completed Part 1 of the protocol.

Refer to the Central Spirometry Study Manual for additional information about spirometry.

6.3.6.1. Real-Time Central Spirometry Over-Read

At Baseline and at Week 8, critical FEV_1 data points for the primary endpoint of the study, spirometry may be reviewed in real-time by the central spirometry reader. This real-time review should eliminate randomizing subjects that have unacceptable spirometry, exceed the FEV_1 reversibility inclusion criterion, or at Week 8 have unacceptable spirometry and may prevent unnecessary radiation exposure for subjects performing FRIs at these visits.

In the event that a real-time central spirometry over-read is not available at a given Baseline or Week 8 visit, the preferred option is to reschedule the subject for repeat spirometry (and FRI if applicable) within the study visit window. If this is not possible, the alternative will be to allow the study investigator to review the spirometry and if judged to be acceptable and meets the FEV_1 reversibility criterion for Baseline, the subject may proceed to Randomization or Week 8 Visit FRI (if applicable).

6.3.7. Peak Expiratory Flow Rate (PEFR)

PEFR measurements are a simple and useful objective measure to assess current lung function. At Screening subjects will be given a peak flow meter and be instructed in its proper use. Daily serial AM assessments prior to morning CF inhaled medications and inhaled bronchodilators will be captured during Screening to obtain a target of at least 7 days or more of data. A mean AM pre-bronchodilator PEFR will be calculated. PEFR should be taken around the same time each morning. The mean AM PEFR value calculated at Baseline will be utilized as an anchor to assess an individual subject's current lung function throughout the study.

On days of study drug administration that do not require study site spirometry (at study site or at subject's home) an AM pre-bronchodilator PEFR will be obtained. If the best of 3 PEFR measurements is >30% below the mean PEFR Baseline value, a subject may administer 2-4 puffs of a short-acting bronchodilator and repeat the PEFR 15-20 minutes later. If post-bronchodilator PEFR remains >30% below the mean PEFR value then dosing of study drug should be postponed and rescheduled within the study window.

Investigators may request subjects to perform additional unscheduled PEFR measurements throughout the study as judged by local clinical practice. These values should also be recorded.

6.3.8. Induced Sputum

Induced sputum will be collected from subjects for analysis of biomarkers including, but not limited to, total and free-MMP9 and MMP9 activity. Refer to the Sputum Induction manual for details on the induced sputum procedure.

6.3.9. Spontaneous Sputum Collection for Bacterial Microbiology

Spontaneous sputum will be collected for analysis of microbiology (dominant species and CFU) only. In the event that the subject cannot spontaneously expectorate sputum, a throat swab will be acceptable. Spontaneous sputum collected for microbiology will be sent to a central lab for analysis.

A minimum of 0.5 mL or 0.5 g of sputum should be collected. Every effort should be made to obtain an expectorated sputum sample. If spontaneous sputum in not able to be collected at a scheduled spontaneous sputum visit, a throat swab for microbiology should be collected. Refer to Laboratory Manual for collection and shipping instructions.

Obtaining spontaneous sputum for microbiology prior to microbiology lab holidays or days the lab is closed is discouraged.

The first spontaneous sputum sample culture results will be used to satisfy the negative *Burkholderia spp.* inclusion criterion.

Sputum and throat swabs for microbiology should be collected 4 hours or more after any inhaled antibiotics.

6.3.10. Functional Respiratory Imaging – Sub-study only

Approximately 30 subjects (15 on 600 mg GS-5745, 15 on placebo) in Part 1 of the study and approximately 45 (15 on 300 mg GS-5745, 15 on 150 mg GS-5745, and 15 on placebo) subjects in Part 2 of the study will have FRI performed at a sub set of study sites as indicated in Table 6-1.

Standard of care inhaled CF therapies (eg, bronchodilators, dornase alpha, inhaled antibiotics, hypertonic saline, inhaled mannitol, inhaled corticosteroids) will be withheld prior to spirometry and FRI. FRI should be performed after the bronchodilator is administered for spirometry, but prior to the standard of care inhaled CF medications. In the event that a subject forgets to withhold their inhaled CF medications at Baseline or Week 8, the visit should be rescheduled to another date within the screening window.

Every effort should be made to perform each FRI scan in the AM to avoid known potential diurnal variation in FEV_1 values. In addition, every effort should be made to have the Week 8 FRI scan performed at the same time of day as the Baseline FRI +/- 3 hours. If the timing of the Week 8 FRI is > 4 hours the time of the Baseline FRI, then the Week 8 spirometry and FRI should be rescheduled within the study visit window. If this is not possible and the Week 8 spirometry are acceptable the subject may continue in the study, the Week 8 FRI study will be lost, and that FRI subject will need to be replaced. Refer to the Fluidda FRI imaging manual for more information.

FRI imaging will be performed as described previously {De Backer et al 2010}. Briefly, a low dose multislice CT scan of the chest is taken at total lung capacity (TLC) and functional residual capacity (FRC). The radiation dose per scan is estimated to be on the order of 1 to 2 millisievert (mSv). A 2015 estimate for annual radiation exposure from natural sources from the U.S. Nuclear Regulatory Commission is 3.1 millisieverts. (ref) http://www.nrc.gov/reading-rm/doc-collections/fact-sheets/bio-effects-radiation.html {United States Nuclear Regulatory Commission (USNRC) 2016}. Segmentation principles allow for quantification and visualization of the lung, lobar and airway volumes. Computational fluid dynamics is used to calculate airway resistance. FRI outcome parameters include: image-based lobar volume at FRC (iLobes_FRC), image-based airway volume at TLC (iV*aw*) and image-based airway resistance at TLC (aRaw). See the Fluidda FRI imaging manual for more details.

6.3.11. 12-Lead ECG

A standard 12-lead ECG will be performed at screening, baseline, Week 4, 8, 16, 24 and the 30-day follow-up visit as indicated in Table 6-1. Sites should follow their institutional guidelines when performing the 12-lead ECG.

6.3.12. Laboratory Assessments

6.3.12.1. Safety Laboratory Tests

Blood and urine will be collected for safety laboratory tests at time points indicated in Table 6-1. The tests will include complete blood count (CBC) with differential, chemistry panel, and urinalysis.

6.3.12.2. Urine Cotinine

Urine will be collected for a urine cotinine test at time points indicated in Table 6-1.

6.3.12.3. Serum and Urine Pregnancy Tests

For females of childbearing potential, serum pregnancy tests will be done at Screening and at the 30-day Follow-up Visit. Urine pregnancy tests will be performed for females of childbearing potential as indicated in Table 6-1, prior to FRI scans or any study drug administration at those visits. For additional information about the definition of childbearing potential, see Appendix 3 Section 2.

6.3.12.4. Erythrocyte Sedimentation Rate

Erythrocyte Sedimentation Rate (ESR): Collected at Screening, Week 8 and Week 24, and will be analyzed at the local lab.

6.3.13. Pharmacokinetic Assessments

6.3.13.1. PK Blood Draws

Blood for PK analysis will be collected at time points as indicated in Table 6-1. See Section 8.7 for additional information.

6.3.13.2. Serum Anti-Drug Antibodies

Blood will be collected for anti-drug antibodies at time points indicated in Table 6-1.

6.3.13.3. Blood Biomarker Samples

Blood for biomarkers will be collected at time points as indicated in Table 6-1. The analysis includes but is not limited to total and free MMP9, MMP9 activity and breakdown neo-epitopes of MMPs. Blood will also be collected at Baseline for CF genotyping for subjects who do not have a historical genotype on file.

6.3.13.4. Biomarker Samples for Optional Genomic Research

PPD

6.3.14. Sample Storage

PPD The stored blood and sputum samples may be used by the Sponsor or its research partner for future clinical laboratory testing to provide additional clinical data. At the conclusion of this study, these samples may be retained in storage by Gilead at its research partner facility for a period of up to 15 years.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

A SAE is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity

- A congenital anomaly/birth defect

- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin). For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.
- **Yes:** The adverse event occurred as a result of protocol procedures, (eg., venipuncture)

7.2.2. Assessment of Severity

The severity grading of AEs will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. See Section 7.5.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (CRF/eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study drug. These AEs must be reported to the CRF/eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow-up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the CRF/eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of study drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period; however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drug, he/she should promptly document and report the event to Gilead DSPH.

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead Sciences DSPH	Fax: +1 (650) 522-5477 Email: Safety_fc@gilead.com

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF/eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs),

or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

To minimize the possibility of exposing study subjects to unusual risk, the safety information from this study will also be reviewed periodically by an independent DMC (as described in Section 8.11). The DMC may have access to partially blinded or unblinded data and will make recommendations regarding the study according to the DMC charter.

7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For AEs or SAEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality, see Section 7.1.3.

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Severity should be recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-0614_QuickReference_8.5x11.pdf.

7.6. Toxicity Management

- All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Section 7.5 and Appendix 3.
- Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before investigational medicinal product discontinuation, unless such a delay is not consistent with good medical practice.

- When restarting investigational medicinal product following resolution of the adverse event, the investigational medicinal product should be restarted at full dose or modified dose that is dependent upon discussion with the Gilead Sciences Medical Monitor.

- Any recurrence of the investigational medicinal product-related Grade 3 or 4 clinical or clinically significant laboratory adverse event following dose interruption mandates permanent discontinuation of investigational medicinal product.

- Any questions regarding toxicity management should be directed to the Gilead Sciences Medical Monitor.

7.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

- Continue investigational medicinal product at the discretion of the investigator.

7.6.2. Grades 3 Laboratory Abnormality or Clinical Event

- For Grade 3 clinically significant laboratory abnormality or clinical event, investigational medicinal product may be continued if the event is considered to be unrelated to investigational medicinal product.

- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to investigational medicinal product, investigational medicinal product should be withheld until the toxicity returns to ≤ Grade 2.

- If a laboratory abnormality recurs to ≥ Grade 3 following re-challenge with investigational medicinal product and is considered related to investigational medicinal product, then investigational medicinal product should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to investigational medicinal product may not require permanent discontinuation.

7.6.3. Grade 4 Laboratory Abnormality or Clinical Event

- For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to investigational medicinal product, investigational medicinal product should be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to Baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

- Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (eg, Grade 4 CK after strenuous exercise or triglyceride elevation that is nonfasting or that can be medically managed) or a clinical event considered unrelated to investigational medicinal product.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the CRF/eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows: Email: Safety_FC@gilead.com and Fax: +1 (650) 522-5477.

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH, fax number +1 650 522-5477 or email Safety_FC@gilead.com. Refer to Appendix 3 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

Refer to Appendix 3 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

Refer to Section 7.3 and the CRF/eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

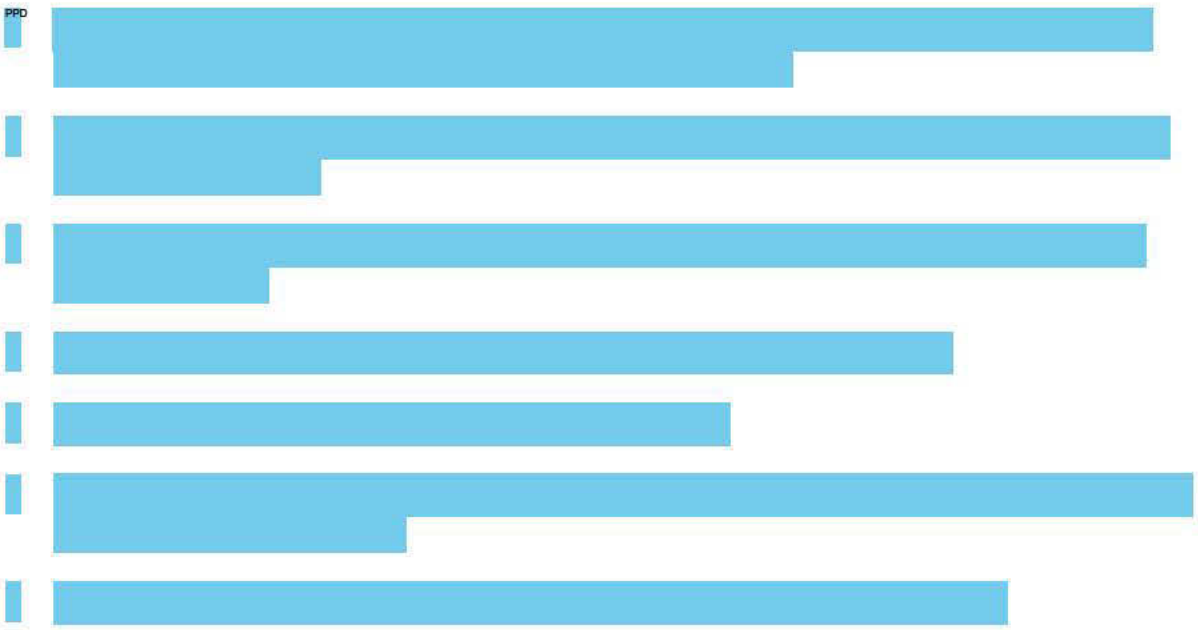
The primary objective of this study is as follows:

- To evaluate the effect of GS-5745 on pre-bronchodilator FEV_1 % predicted in subjects with CF after 8 weeks of treatment

The secondary objectives of this study are as follows:

- To assess safety, tolerability, and PK of GS-5745 in subjects with CF
- To evaluate the effect of GS-5745 on post-bronchodilator FEV_1 % predicted in subjects with CF after 8 weeks of treatment

Exploratory objectives of this study are as follows:



8.1.2. Primary Endpoint

- The absolute change in pre-bronchodilator FEV_1 percent predicted from Baseline to Week 8

8.1.3. Secondary Endpoints

8.1.3.1. Efficacy Endpoints

- The absolute change in post-bronchodilator FEV_1 percent predicted from Baseline to Week 8
- The relative change in pre-bronchodilator FEV_1 percent predicted from Baseline to Week 8
- The relative change in post-bronchodilator FEV_1 percent predicted from Baseline to Week 8

8.1.3.2. Safety Endpoints

The safety evaluation will be assessed by AEs, concomitant medications, clinical laboratory tests, vital signs and ADA data.

8.1.3.3. Pharmacokinetic Endpoints

Primary PK parameters will include C_{max}, T_{max}, C_{last}, T_{last}, and AUC_{last} (as applicable)

8.1.4. Other Endpoints of Interest

- Changes from Baseline in total and free MMP9 concentration and enzyme activity in sputum and/or blood
- Change from Baseline in FRI
- Change from Baseline in CFQ-R-RSS
- Change from Baseline in TSQM
- Change from Baseline in SNOT-22 score
- Change from Baseline in body weight
- Change from Baseline in sputum bacterial CFUs
- Change from Baseline in other biomarkers related to MMP9 pathway
- Change from Baseline in sputum cytology
- Rate of pulmonary exacerbations

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The primary analysis set for efficacy analysis is defined as the Full Analysis Set (FAS), which includes all subjects who were randomized into the study and received at least 1 dose of study drug.

Subjects will be analyzed according to the treatment group to which they are randomized.

8.2.1.2. Safety

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

Subjects will be analyzed according to the treatment they actually receive.

8.2.1.3. Pharmacokinetics

The PK Analysis Set includes all subjects who were randomized and have received at least 1 dose of study drug and for whom concentration data of GS-5745 are available.

Subjects will be analyzed according to the treatment they actually receive.

8.2.1.4. Biomarkers

The Biomarker Analysis Set includes all subjects who were randomized and have received at least 1 dose of study drug and for whom biomarker data are available.

Subjects will be analyzed according to the treatment they actually receive.

8.3. Data Handling Conventions

Values for missing safety laboratory data will not be imputed. However, a missing Baseline result will be replaced with a screening result, if available. If no pre-treatment laboratory value is available, the Baseline value will be assumed to be normal (ie, no grade [Grade 0]) for the summary of graded laboratory abnormalities. If safety laboratory results for a subject are missing for any reason at a time point, the subject will be excluded from the calculation of summary statistics for that time point.

Values for missing vital signs data will not be imputed. However, a missing Baseline result will be replaced with a screening result, if available.

8.4. Demographic Data and Baseline Characteristics

Demographic and Baseline measurements will be summarized using standard descriptive methods for continuous variables and number and percentage of subjects for categorical variables.

Demographic summaries will include sex, race/ethnicity, and age. Baseline data will include a summary of body weight, height, BMI, spirometry measurements, patient-reported outcome scores. Additional Baseline characteristic variables may be added if necessary.

8.5. Efficacy Analysis

The primary endpoint, the absolute change in pre-bronchodilator FEV_1 percent predicted from Baseline to Week 8, will be analyzed using a mixed effect model for repeated measure (MMRM) for Part 1 and Part 2 respectively. The model for each part of the study will include treatment, Baseline FEV_1 percent predicted level, visit and treatment-by-visit interaction as fixed effect, and subject as a random effect. Estimated least square means of treatment effects and estimated differences in treatment effects between GS-5745 treatment group and placebo group at Week 8 will be presented with the 90% confidence intervals (CIs) and adjusted p-values.

Analyses of absolute change in post-bronchodilator percent predicted FEV_1, relative change in pre and post -bronchodilator percent predicted FEV_1 and other endpoints listed in Section 8.1.4 will be discussed in the statistical analysis plan (SAP). In general, continuous endpoints with repeated measures will be analyzed using the MMRM model. For change in FRI and SNOT-22, an ANCOVA model with corresponding baseline values as covariate will be used. Categorical endpoints will be analyzed using MMRM and non-parametric tests. All endpoints will be summarized using descriptive statistics (n, mean, standard deviation [SD], median, Q1, Q3, minimum, and maximum) for continuous data and by the number and percent of subjects for categorical data.

8.6. Safety Analysis

Safety endpoints will be analyzed by the number and percentage of subjects for categorical variables or 8-number summary (n, mean, standard deviation, median, first quartile [Q1], third quartile [Q3], minimum, and maximum) for continuous variables.

All data collected during the course of study will be included in data listings. Additional details will be provided in the SAP.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug will be generated from the study drug administration and study drug accountability eCRF pages. The number of doses administered and the level of adherence will be summarized.

8.6.2. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

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.

Summaries (number and percentage of subjects) of TEAEs by SOC and PT will be provided. Treatment-emergent AEs will also be summarized by relationship to study drug and severity. In addition, TEAEs leading to premature discontinuation of study drug and study will be summarized and listed.

8.6.3. Laboratory Evaluations

Selected laboratory data (using conventional units) will be summarized using only observed data. Data and change from Baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme in Section 7.5.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from Baseline at any time post Baseline will be summarized. If Baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment emergent.

8.6.4. Other Safety Evaluations

Individual data for physical examination findings, prior and concomitant medications and medical history will be provided. Vital signs measurements will be listed by subject and summarized by incidence of events/abnormalities or descriptive statistics as appropriate.

8.7. Pharmacokinetic Analysis

The plasma concentration data of GS-5745 will be summarized by nominal sampling time and treatment using descriptive statistics (ie, n, arithmetic mean, geometric mean, coefficient of variation (%) standard deviation, median, minimum, and maximum). For the PK substudy, PK parameters (C_{max}, T_{max}, C_{last}, T_{last}, and AUC_{last}, as applicable) may be listed and summarized using descriptive statistics. Plasma concentrations over time may also be plotted in semi-logarithmic and linear formats as mean ± standard deviation, and median (Q1, Q3) for PK sub-study. Exposure-response analysis may be performed.

8.8. Immunogenicity Analysis

Immunogenicity of GS-5745 will be evaluated based upon the incidence of anti-drug (GS-5745) antibody (ADA) formation. The number and percentage of subjects exhibiting positive ADA results at each specified time point will be summarized. ADA results with supporting data will be included in a listing as well. Impact of ADA on GS-5745 PK, safety, and efficacy will also be evaluated as applicable.

8.9. Biomarker Analysis

The changes from Baseline at Week 8 in total and free MMP9 and MMP9 activity in sputum and blood will be analyzed using an analysis of variance model or a mixed effect model for repeated measure for comparing GS-5745 to placebo cohorts. Estimated least square means and 90% confidence intervals (CI) of the changes from baseline will also be reported for each cohort as well as for difference between GS-5745 and placebo cohorts.

Analysis for other biomarkers and additional exploratory analyses will be discussed in Biomarker Analysis Plan (BAP).

8.10. Sample Size

A sample size of 25 evaluable subjects per arm for Part 1 and Part 2 will provide 80% power to detect a difference of 5% in percent predicted FEV_1 absolute change from Baseline between GS-5745 active treatment and placebo with a 2-side alpha level of 0.1 assuming a common SD of 7% {Brouwer et al 2014, Ramsey et al 2011, Retsch-Bogart et al 2009}. To compensate for early drop out, 30 subjects per arm will be enrolled assuming an attrition rate of 15%.

With respect to the sub-study in FRI, a sample size of 15 subjects on GS-5745 and 15 subjects on placebo provides more than 90% power to detect a 6% difference between the GS-5745 and placebo arms in FRI change from Baseline based on a 2 sample t-test at a 2-sided alpha level of 0.1. The calculation assumes SD of FRI change being 5% for the GS-5745 arm and 2% for the placebo arm as the FRI response is expected to be more heterogeneous in the treatment group.

8.11. Data Monitoring Committee

An independent multidisciplinary DMC will review the progress of the study and perform interim reviews of safety data. A total of 4 scheduled DMC meetings will occur throughout Part 1 and prior to the end of Part 2 of the study as outlined below.

Part 1: Safety Analysis #1

Because GS-5745 has not been administered previously to CF subjects, the DMC will review the unblinded safety data after 10 subjects (~5 active and ~5 placebo) have completed the Week 2 Visit or have prematurely discontinued from the study. Enrollment will continue during the DMC review process.

Part 1: Safety Analyses #2

The DMC will review the unblinded safety data after 30 subjects (~15 active and ~15 placebo) have completed the Week 8 Visit or have prematurely discontinued from the study. Enrollment will continue during the DMC review process.

Part 1: Safety Analyses #3 and Interim Efficacy Analysis

An interim efficacy and safety analysis will be performed when all 60 subjects (~30 active and ~30 placebo) have completed the Week 8 Visit or have prematurely discontinued from the study. The DMC and a select number of Gilead employees not directly involved in the study conduct will review the unblinded data.

With no safety concern, an estimated mean difference in absolute FEV_1% predicted between GS-5745 and placebo being ≥ 5% may trigger the initiation of Part 2. If the mean difference is < 2%, Part 2 may not be initiated. A comprehensive review of safety, FEV1, FRI and other efficacy data including sputum MMP-9, CFQ-R, SNOT-22, TSQM, and CF exacerbation will be conducted before the decision is made to advance to Part 2 of the study. Enrollment of subjects into Part 2 of the study will be postponed until after the completion of the third DMC and unblinded Gilead review of the data.

Part 2: Safety Analysis #4

The DMC will review the unblinded safety data after 45 subjects (~ 15 in each treatment group) have completed the Week 8 Visit or have prematurely discontinued from the study. Enrollment will continue during the DMC review process.

8.12. Interim Analyses

To determine if Part 2 of the study should be initiated, an interim analysis will be conducted when all the randomized subjects from Part 1 have completed the Week 8 visit or discontinued from the study. Unblinded data from Part 1 will be used to evaluate drug safety and efficacy, which may result in a study amendment before the initiation of Part 2 of the study.

A Gilead internal unblinded team independent of the blinded study team will be assembled at the beginning of the study, which consists of medical monitor, statistical programmer, biostatistician and other personnel if necessary. The Gilead internal unblinded team will be granted the access to unblinded clinical data including treatment assignment to closely monitor study progress and drug safety. To mitigate the risks of inadvertently releasing the treatment information to the sites and subjects, the internal team will keep the unblinded information confidential and will not communicate the information to blinded study team, site staff or subjects. Data unblinding due to medical emergency will follow standard Gilead procedures.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures.

The investigator must use the most current IRB or IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB or IEC or local requirements. The consent form will inform subjects about genomic testing and sample retention, and their right to receive clinically relevant genomic analysis results.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions.
NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, CRF/eCRF, the IMP, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB/IEC, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);

- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. Subsequent to data entry, a study monitor will perform source data verification

within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Where possible, study drug should be destroyed at the site. At the start of the study, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for disposal or return of unused study drug supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead Sciences, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. This can occur only after the study monitor has performed drug accountability during an on-site monitoring visit.

A copy of the site's study drug disposal SOP or written procedure (signed and dated by the PI or designee) will be obtained for Gilead site files. If the site does not have acceptable procedures in place, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of unused study drug supplies.

If study drug is destroyed on site, the investigator must maintain accurate records for all study drug destroyed. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review study drug supplies and associated records at periodic intervals.

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agencies. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, e.g. attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the CRF/eCRF.

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

American Thoracic Society Committee on Diagnostic Standards for Non-Tuberculous Respiratory Diseases. Standardization of spirometry 1994 update. American journal of respiratory and critical care medicine. 152: 1107-36. 1995:

Atkinson JJ, Senior RM. Matrix metalloproteinase-9 in lung remodeling. Am J Respir Cell Mol Biol 2003;28 (1):12-24.

Bendell J, Starodub A, Sharma S, Wainberg Z, Shah M, Thai D. Phase I study of GS-5745 alone and in combination with chemotherapy in patients with advanced solid tumors [Abstract 4030] [Pre-Press]. American Society of Clinical Oncology (ASCO) Annual Meeting; 2015 29 May - 02 June; Chicago, IL. J Clin Oncol.

Bergin DA, Hurley K, Mehta A, Cox S, Ryan D, O'Neill SJ, et al. Airway inflammatory markers in individuals with cystic fibrosis and non-cystic fibrosis bronchiectasis. Journal of inflammation research 2013;6:1-11.

Bhandari BR, Fogel R, Onken J, Yen EH, Kanwar B, Subramanian GM, et al. Safety and Efficacy of GS-5745 an Anti-Matrix Metalloproteinase 9 (MMP) Monoclonal Antibody in Patients With Moderately to Severely Active Ulcerative Colitis [Poster Tu2056]. Digestive Disease Week (DDW); 2015 17-19 May; Washinton, D. C.

Boyle MP. Adult cystic fibrosis. JAMA 2007;298 (15):1787-93.

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.

Chmiel JF, Konstan MW, Accurso FJ, Lymp J, Mayer-Hamblett N, VanDevanter DR, et al. Use of ibuprofen to assess inflammatory biomarkers in induced sputum: Implications for clinical trials in cystic fibrosis. J Cyst Fibros 2015.

Cystic Fibrosis Foundation. Patient Registry Annual Data Report to the Center Directors 2013.

Davies JC, Wainwright CE, Canny GJ, Chilvers MA, Howenstine MS, Munck A, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. Am J Respir Crit Care Med 2013;187 (11):1219-25.

De Backer JW, Vos WG, Vinchurkar SC, Claes R, Drollmann A, Wulfrank D, et al. Validation of computational fluid dynamics in CT-based airway models with SPECT/CT. Radiology 2010;257 (3):854-62.

Devereux G, Steele S, Jagelman T, Fielding S, Muirhead R, Brady J, et al. An observational study of matrix metalloproteinase (MMP)-9 in cystic fibrosis. J Cyst Fibros 2014;13 (5):557-63.

Dmitrienko A, Offen WW, Westfall PH. Gatekeeping strategies for clinical trials that do not require all primary effects to be significant. Statist Med 2003;22 (15):2387-400.

European Cystic Fibrosis Society. ECFS Patient Registry: Annual Data Report (Version 01.2014). 2010.

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.

Foundation CF. Patient Registry. Annual Data Report to the Center Directors, 2009. Cystic Fibrosis Foundation 2010.

Gaggar A, Li Y, Weathington N, Winkler M, Kong M, Jackson P, et al. Matrix metalloprotease-9 dysregulation in lower airway secretions of cystic fibrosis patients. American journal of physiology. Lung cellular and molecular physiology 2007;293 (1):L96-L104.

Gibson RL, Burns JL, Ramsey BW. Pathophysiology and management of pulmonary infections in cystic fibrosis. Am J Respir Crit Care Med 2003;168 (8):918-51.

Hahn C, Xu X, Gaggar A. Relationship Between Matrix Metalloprotease-9 Levels And Activity In Systemic And Pulmonary Compartments In Cystic Fibrosis Lung Disease. Am J Respir Crit Care Med. 2012;185 (2012):A2802.

Hill SL, Mitchell JL, Burnett D, Stockley RA. IgG subclasses in the serum and sputum from patients with bronchiectasis. Thorax 1998;53 (6):463-8.

Konstan MW, Byard PJ, Hoppel CL, Davis PB. Effect of high-dose ibuprofen in patients with cystic fibrosis. N Engl J Med 1995;332 (13):848-54.

Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145 (4):247-54.

Mogayzel PJ, Jr., Naureckas ET, Robinson KA, Mueller G, Hadjiliadis D, Hoag JB, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med 2013;187 (7):680-9.

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.

Roderfeld M, Rath T, Schulz R, Seeger W, Tschuschner A, Graf J, et al. Serum matrix metalloproteinases in adult CF patients: Relation to pulmonary exacerbation. J Cyst Fibros 2009;8 (5):338-47.

Sagel SD, Kapsner RK, Osberg I. Induced sputum matrix metalloproteinase-9 correlates with lung function and airway inflammation in children with cystic fibrosis. Pediatr Pulmonol 2005;39 (3):224-32.

U.S. Department of Health & Human Services (DHHS), Food & Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July, 2009.

United States Nuclear Regulatory Commission (USNRC). Biological Effects of Radiation. Available at: http://www.nrc.gov/reading-rm/doc-collections/fact-sheets/bio-effects-radiation.html. Accessed May. 2016.

Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. N Engl J Med 2015.

11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404, USA

STUDY ACKNOWLEDGEMENT

A Phase 2b, Dose-Ranging Study of the Effect of GS-5745 on FEV_1 in Adult Subjects with Cystic Fibrosis

GS-US-404-1808, Amendment 2, 25 May 2016

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

DAVID GOSSETT, MD
Name (Printed)
Author

PPD
Signature

31 MAY 2016
Date

INVESTIGATOR STATEMENT

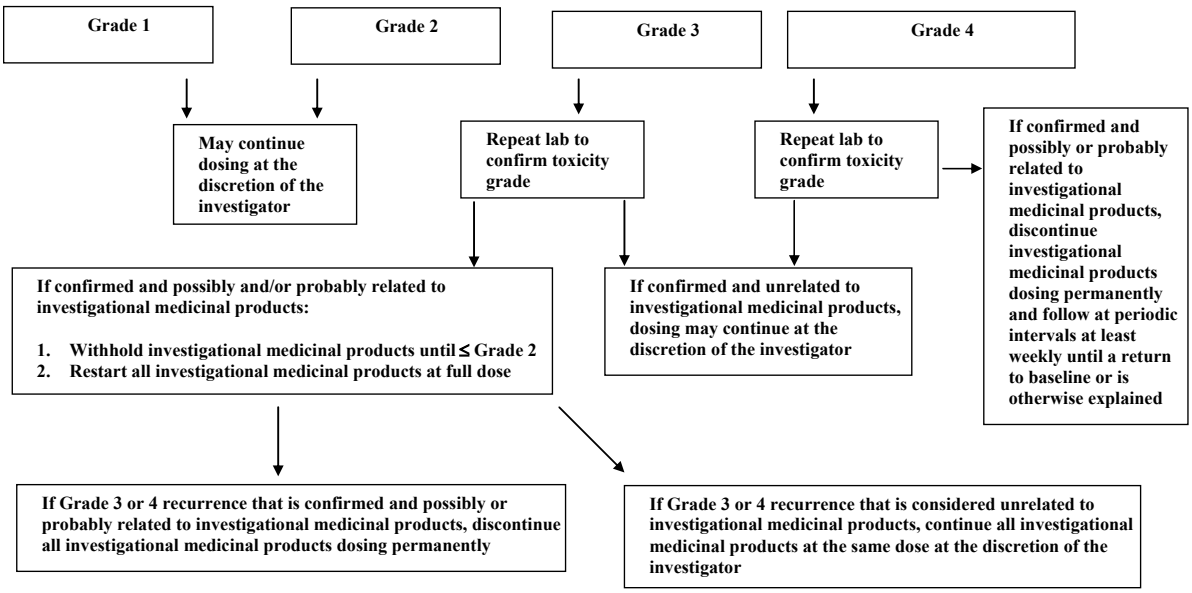
I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed) | Signature

Date | Site Number

Appendix 2. Management of Clinical and Laboratory Adverse Events



Appendix 3. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born subject is considered fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study drug Effects on Pregnancy and Hormonal Contraception

The risks of treatment with GS-5745 during pregnancy have not been evaluated in humans. The potential for genotoxicity is not expected given that GS-5745 is a monoclonal antibody and embryofetal toxicity is suspected based on nonclinical toxicological studies. Women of childbearing potential should be informed of the potential risk and use highly effective methods of birth control during treatment with GS-5745 from screening until 30 days after the end of relevant systemic exposure. Given that GS-5745 is a monoclonal antibody, a clinically relevant interaction between GS-5745 and contraceptive steroids is not suspected and therefore, hormonal contraception may be used as part of the birth control methods. Please refer to the latest version of the investigator's brochure for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline visit prior to randomization. At minimum, a pregnancy test will be performed at the end of relevant systemic exposure. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed

to rule out pregnancy. This is even true for women of childbearing potential with infrequent or irregular periods. Female subjects must also agree to one of the following from Screening until 30 days following the end of relevant systemic exposure.

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.
  - Intrauterine device (IUD) with a failure rate of <1% per year
  - Intrauterine hormone-releasing system (IUS) with a failure rate of <1% per year
  - Tubal sterilization
  - Essure micro-insert system (provided confirmation of success 3 months after procedure)
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Or

- Consistent and correct use of one hormonal method and one barrier method
  - Barrier methods
    - Diaphragm with spermicide
    - Cervical cap with spermicide
    - Male condom (with or without spermicide)
  - Hormonal methods
    - Oral contraceptives (either combined or progesterone only)
    - Injectable progesterone
    - Implants of levonorgestrel
    - Transdermal contraceptive patch
    - Contraceptive vaginal ring

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the end of relevant systemic exposure.

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment until at least 90 days after the end of relevant systemic exposure.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator and discontinue study drug immediately if they become pregnant or if they suspect that they are pregnant at any time during the study or within 30 days of last study drug dose. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.

Appendix 4. Recommended General Process for Diagnosing CF {Farrell et al 2008}

In individuals presenting with symptoms of CF or a positive family history, the following diagnostic process is recommended:

1) A diagnosis of CF can be made if the sweat chloride value is ≥ 60 mmol/L. A second, confirmatory sweat chloride test is recommended unless mutation analysis identifies the presence of 2 CF-causing mutations. These patients, who may present at any age, are likely to develop CF lung disease.

2) A sweat chloride value ≤ 39 mmol/L in individuals over age 6 months is not consistent with a diagnosis of CF. CF is unlikely in this group. However, 2 identified CF-causing mutations can occur in this group; these individuals have CF and should be followed in a CF care center.

3) Individuals with sweat chloride values in the intermediate range (30 to 59 mmol/L for infants under age 6 months; 40 to 59 mmol/L for older individuals) should undergo extensive CFTR mutation analysis (ie, expanded panel of CFTR mutations, evaluation for deletions, or gene sequencing):

    a) In the presence of 2 CF-causing mutations, a diagnosis of CF can be made.

    b) Individuals with no or 1 CF-causing mutation and clinical findings suggestive of CFTR dysfunction (ie, obstructive azoospermia, bronchiectasis, or acute, recurrent, or chronic pancreatitis) may be diagnosed with a CFTR-related disorder, depending on their clinical picture or family history, and are at risk for CF. Sweat chloride testing should be repeated in infants by age 2 to 6 months and immediately in older individuals. If sweat chloride values remain in the intermediate range on repeat testing, then further assessment should be performed at a CF care center that can provide basic and ancillary testing to clarify the diagnosis, including:

- Clinical assessment
- Expanded genetic testing
- Exocrine pancreatic function tests
- Respiratory tract culture for CF-associated pathogens, especially *P aeruginosa*.

Depending on clinical presentation, assessment also may include ancillary tests, such as:

- Genital evaluation in males (ie, genital examination, rectal ultrasound, semen analysis)
- Pancreatic imaging
- High-resolution chest CT

- Bronchoalveolar lavage, including microbiology assessment
- Pulmonary function testing (not routinely recommended in infants at this time)
- NPD testing
- Exclusionary testing for ciliary dyskinesia and immune deficiency.

Significant clinical signs or symptoms of CF, laboratory indication of PI, or a positive culture for a CF-associated pathogen (especially P aeruginosa), should be considered strongly suggestive of CF. Individuals who have sweat chloride values in the intermediate range and exhibit no significant signs of CF should be monitored periodically for the appearance of symptoms until the diagnosis can be ruled in or out.

Appendix 5. Medications Washouts

Inhaled Bronchodilators	Minimum Time Interval from Last Medication to Complete Lung Function Testing
Short-acting *B2* agonists (salbutamol, albuterol, levalbuterol)	4 hours
Long-acting *B2* agonists Q12hrs (salmeterol, fomoterol, arformoterol)	12 hours
Long-acting *B2* agonists Q24hrs (indacaterol)	24 hours
Short-acting *B2* anticholinergics (ipratropium bromide)	4 hours
Long-acting anticholinergics Q24 hrs (tiotropium bromide)	24 hours
Short-acting bronchodilator combos (albuterol/ipratropium bromide)	4 hours
Long-acting bronchodilator combos (vilanterol and umeclidinium)	24 hours
Long-acting bronchodilator & corticosteroid 12 hrs (fomoterol/budesonide, salmeterol/fluticasone propionate)	12 hours
Long-acting bronchodilator & corticosteroid 24 hrs (vilanterol/fluticasone furoate)	24 hours
Oral Bronchodilators	
Standard *B2* agonist tablets	12 hours
Long-acting *B2* agonist tablets	24 hours
Theophylline	24 hours
Roflumilast	24 hours