Clinical Study Protocol
GBT440-026

Study Number	GBT440-026
Study Title	**A Phase II open label study to evaluate the effect of GBT440 on hypoxemia in subjects with Idiopathic Pulmonary Fibrosis (IPF) who are using supplemental oxygen at rest (ZEPHYR)**
Investigational Product	GBT440
IND Number	128319
EudraCT Number	2017-001276-27
Sponsor	400 East Jamie Court, Suite 101 South San Francisco, CA 94080 United States of America
Sponsor's Medical Director	Nicholas Vlahakis, MD Senior Medical Director 650 741-7730 (Office Telephone No.) nvlahakis@globalbloodtx.com
Medical Monitor (US)	Toni Bransford, MD Senior Medical Director Worldwide Clinical Trials 973-420-6236 toni.bransford@worldwide.com
Medical Monitor (UK)	Ruben Rosoky, MD, PhD, MFPM Medical Director UBC: An Express Scrips company +41 22 596 4410 ruben.ayzinrosoky@ubc.com
Version / Date	Amendment 2 / 05 June 2017

SPONSOR STATEMENT OF APPROVAL AND COMPLIANCE

A Phase II open label study of GBT440 to evaluate the effect on hypoxemia in subjects with Idiopathic Pulmonary Fibrosis (IPF) who are using supplemental oxygen at rest (ZEPHYR)

Protocol Number: GBT440-026, Amendment 2

APPROVAL

The signatures of the Sponsor representative below represent that the above-referenced clinical trial is being conducted under and in accordance with FDA IND 128319, which provides for the clinical study of GBT440. This IND application is held by GBT. The protocol is being conducted in accordance with all applicable federal, state, and local regulations governing the conduct of this research, including DHHS 45 CFR part 46, FDA 21 CFR parts 50, 54, 56, 312 and 812. GBT will provide the Investigator with all IND status updates pertinent to the conduct of the study.

Sponsor Representative: _____

Date: Jun 7th 2017

Title: Medical Director.

INVESTIGATOR STATEMENT OF APPROVAL AND COMPLIANCE

A Phase II open label study of GBT440 to evaluate the effect on hypoxemia in subjects with Idiopathic Pulmonary Fibrosis (IPF) who are using supplemental oxygen at rest (ZEPHYR)

Protocol Number: GBT440-026, Amendment 2

APPROVAL

The signature of the Investigator below constitutes approval of this protocol as written and reflects the Investigator's commitment to conduct the study in accordance with the protocol, the applicable laws and regulations and in compliance with ICH Good Clinical Practice guidelines.

Principal Investigator (signature): _____

Principal Investigator (printed name) _____

Date: _____

Title: _____

SPONSOR CONTACT INFORMATION

Sponsor's Medical Director	Nick Vlahakis, M.D. Senior Medical Director (650) 741-7730 nvlahakis@globalbloodtx.com
Clinical Trial Manager	Aimee Enriquez Clinical Trial Manager (650) 741-7777 aenriquez@globalbloodtx.com
Clinical Operations Oversight	Bella Oguno, MPH Director, Clinical Operations (650) 351-4758 boguno@globalbloodtx.com

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ABG	Arterial blood gases
AE	Adverse event
AESI	Adverse event of special interest
ALAT	Latin American Respiratory Society
ALK	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATAQ	A Tool to Assess Quality of Life
ATS	American Thoracic Society
AUC	Area under the concentration time curve
BUN	Blood Urea Nitrogen
CL	Clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CNS	Central nervous system
CRA	Clinical research associate
CRF	Case report form
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome
DDI	Drug-drug interaction
DL_{CO}	Diffusing capacity of the lung for carbon monoxide
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EPO	Serum erythropoietin
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GBT	Global Blood Therapeutics
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GMP	Good Manufacturing Practices
Hb	Hemoglobin
HbA	Adult hemoglobin
HbS	Hemoglobin S
hCG	Human chorionic gonadotropin
hERG	Human Ether-à-go-go-Related Gene
IB	Investigator's Brochure
ICF	Informed consent form

ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International normalized ratio
IPF	Interstitial pulmonary fibrosis
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
JRS	Japanese Respiratory Society
MedDRA	Medical dictionary for regulatory activities
6MWD	6-minute walk distance
6MWT	6-minute walk test
MTD	Maximum tolerated dose
NAC	N-acetylcysteine
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
ODC	Oxy-hemoglobin dissociation curve
PD	Pharmacodynamic
PK	Pharmacokinetic
PRO	Patient reported outcome
PT	Prothrombin time
PTT	Partial thromboplastin time
QTcF	Corrected QT interval using the Fridericia formula
OTT	Oxygen titration test
RBC	Red blood cell
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SaO_2	Arterial oxygen saturation
SCD	Sickle cell disease
SD	Standard deviation
SGRQ	St George's Respiratory Questionnaire
SpO_2	Peripheral (resting) oxygen saturation
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Apparent terminal half life
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
VS	Vital signs
V_{ss}	Volume at steady state
WHO	World Health Organization
λz	Apparent terminal rate constant

PROTOCOL SYNOPSIS

Protocol Title	**A Phase II open label study to evaluate the effect of GBT440 on hypoxemia in subjects with Idiopathic Pulmonary Fibrosis (IPF) who are using supplemental oxygen at rest (ZEPHYR)**
Protocol Number	GBT440-026
Sponsor	Global Blood Therapeutics 400 East Jamie Court Suite #101 South San Francisco, CA 94080
Study Drug	GBT440 capsules or tablets: 300 mg strength, administered orally
Objectives	Primary To evaluate the effect of GBT440 on oxygen saturation at rest, breathing room air, on Days 30 and 90 compared to baseline Secondary • To evaluate the effect of GBT440 on the requirement for supplemental oxygen (O_2) at rest and post-exercise at Days 30 and 90 compared to baseline • To evaluate the effect of GBT440 on resting and post-exercise Alveolar-arterial O_2 tension difference [$P(A\text{-}a)O_2$] at Days 30 and 90 compared to baseline • To evaluate the effect of GBT440 on 6-minute walk distance (6MWD) at Days 30 and 90 compared to baseline • To evaluate the effect of GBT440 on IPF-related symptoms, using patient reported outcomes (PROs), at Days 30 and 90 compared to baseline • To evaluate pulmonary function at Day 90 compared to baseline • To evaluate the safety and tolerability of 900 mg and 1500 mg GBT440 dosed daily for 90 days • To evaluate the pharmacokinetics (PK) of GBT440 Exploratory • To evaluate the effect of GBT440 on the need for any O_2 while at rest at Days 30 and 90 compared to baseline • To compare the change in O_2 requirement between the two O_2 flow rate allocation groups • To evaluate the effect of GBT440 on extent of activity during daily living at Days 30 and 90 compared to baseline

Study Design	This is an open label study that will be conducted in two parts. Together, Parts A and B will provide safety and efficacy data across the two GBT440 doses that are expected to improve oxygen saturation in the enrolled subjects. Approximately up to 32 eligible subjects will be enrolled in the study. • In Part A, up to approximately 16 eligible IPF subjects will receive 900 mg of GBT440 administered orally as 3 × 300 mg capsules or tablets once daily for 90 days. • In Part B, up to approximately 16 eligible IPF subjects will receive 1500 mg of GBT440 administered orally as 5 × 300 mg capsules or tablets once daily for 90 days. The screening period for each subject commences when the subject undergoes the first study-specific screening assessment and must be completed and tests evaluated before dosing (Day 1). Subjects may be rescreened up to 2 times, if deemed appropriate by the Principal Investigator. The rescreening visit should not occur sooner than 10 calendar days after the failed screening visit. Subjects on a stable dose of pirfenidone or nintedanib and/or N-acetyl cysteine for the treatment of IPF are eligible for entry into the study. After the screening visit, the study includes the following study periods: • Treatment period (90 days): subjects in Part A will receive 900 mg (3 × 300 mg) and subjects in Part B 1500 mg (5 × 300 mg) capsules or tablets daily • Safety follow up (30 days): safety will be assessed for at least 5 half-lives after the last dose of GBT440 in both Parts A and B
Number of Subjects	Approximately up to 32 subjects will be enrolled in the study.
Replacement of Subjects	Subjects who discontinue for reasons unrelated to toxicity, may be replaced if: • the subject does not take at least 80% of their daily doses of study drug, prior to Day 30 (24 days) or Day 90 (72 days) and/or • the subject does not take study drug for at least 8 consecutive days prior to Days 30 or 90.
Number of Centers	The study will be conducted at up to 10 clinical sites in the United States and the United Kingdom.
Duration of Study Participation	Approximately up to 151 days, including screening, treatment and follow-up periods

Study Population	Inclusion Criteria 1) 45 to 85 years of age inclusive, at randomization 2) Able and willing to provide signed informed consent to participate in this study 3) Documented diagnosis of IPF, as indicated in the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Respiratory Society (ALAT) 2011 Guidelines 4) Receiving supplemental O_2 for use at rest. • Subjects using O_2 only with exercise will not be eligible. 5) Resting oxygen saturation (SpO_2) between 85 and 88% for at least 30 consecutive seconds while breathing room air (refer to Section 5.1 and Section 5.5.2 for details on confirming eligibility) Or Resting SpO_2 <85% for 10 consecutive seconds or, if in the opinion of the site staff, it is not safe or tolerable for the subject to continue without using their supplemental oxygen for 10 consecutive seconds whilst the SpO2 is <85%. Either of these 2 criteria should be met at both screening and Day 1 visits. 6) Able, in the Investigator's opinion, to walk a total of at least 100 meters at completion of the baseline 6-minute walk test (6MWT) 7) Weight ≥40 kg 8) Able, in the Investigator's opinion, to complete the O_2 titration study unassisted at baseline (Day 1) and Days 30, 90, and 120 9) Able, in the Investigator's opinion, to comply with the study procedures, including attending the assessment visits and adhering to study requirements and restrictions 10) Male or female of childbearing potential willing and able to use highly effective methods of contraception from study start to 30 days after the last dose of study drug Exclusion Criteria 1) Forced expiratory volume in 1 second (FEV_1) / forced vital capacity (FVC) <70% 2) History of interstitial lung diseases secondary to other medical conditions (e.g., scleroderma, sarcoidosis, or rheumatoid arthritis) or resulting from clinically significant environmental exposures including but not limited to, drug toxicity, hypersensitivity pneumonitis, or asbestos 3) Hospitalization due to an exacerbation of IPF within 30 days of screening 4) Documented pulmonary hypertension that is severe (World Health Organization [WHO] Functional Class IV) and/or clinically unstable, as determined by the study Investigator

	• Subjects with documented mild to moderate pulmonary hypertension on a stable regimen of therapy for at least 3 months prior to screening will be eligible for the study 5) Subject plans to begin, or has commenced, pulmonary rehabilitation within 30 days of screening • Subject who is on a stable exercise regimen at screening or whose regimen, in the opinion of the Investigator, is not expected to change at any time during the entire study will be considered eligible for the study 6) Corticosteroid therapy for the treatment of IPF, >10 mg per day of prednisone (or an equivalent), administered for 7 days or longer, within 30 days of screening. • Subjects receiving a stable dose of ≤10 mg per day of prednisone (or an equivalent) for at least 14 days prior to screening, and in the opinion of the Investigator not anticipated to require a dose adjustment during the study, are eligible for the study 7) Corticosteroid therapy for treatment of non-IPF diseases, unless: • Receiving a stable dose of prednisone (or an equivalent) for at least 14 days prior to screening, and in the opinion of the Investigator not anticipated to require a dose adjustment during the study 8) Participated in another clinical trial of an investigational drug (or medical device) within 30 days or 5-half-lives, whichever is longer, prior to screening, or is currently participating in another trial of an investigational drug (or medical device). 9) Aspartate aminotransferase (AST), alanine aminotransferase (ALT) or total bilirubin >2 × upper limit of normal (ULN) 10) Serum creatinine >2.0 mg/dL 11) Clinical evidence of active infection, within 14 days of screening, which may include but is not limited to bronchitis, pneumonia, urinary tract infection, or cellulitis. 12) Active viral hepatitis within the last 6 months 13) Active tuberculosis within the last 6 months • Testing for latent tuberculosis is not required 14) Electrocardiogram (ECG) with a corrected QT interval using the Fridericia formula (QTcF) >450 ms (males) or QTcF >470 ms (females) • If ventricular pacing is noted on ECG, then QTcF intervals will not be calculated 15) Family or personal history of congenital long QT syndrome 16) Female who is breast-feeding or pregnant 17) Known current malignancy or current evaluation for a potential malignancy or history of malignancy within the past 2 years prior to screening, except for appropriately treated non-melanoma skin carcinoma, carcinoma in situ of the cervix, Stage 1 uterine cancer 18) Current smoker (including use of eCigarettes or vaporizing) or history of smoking within 3 months from screening

	19) History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within 3 months of screening, including but not limited to, congestive heart failure requiring hospitalization or uncontrolled clinically significant arrhythmias 20) History of mental illness within the last 5 years, unless the subject fulfills one of the following conditions: • The subject has not required or been prescribed any psychiatric medication (including but not limited to antidepressants or anxiolytics) within 12 months before screening and, in the opinion of the Investigator, the subject is able and safe to participate in the study • The subject has been on a fixed regimen of psychiatric medications for at least 6 months before screening and displays no sign of acute mental illness and, in the opinion of the Investigator, the subject is able and safe to participate in the study 21) Other clinically significant medical disease that is uncontrolled despite treatment and is likely, in the study Investigator's opinion, to significantly impact the study's efficacy and safety assessments 22) Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable) 23) Known hypersensitivity to any component of the study drug
Study Evaluations	**Safety Assessments** Subject safety and tolerability will be monitored throughout the study using standard measures, including physical examinations, vital signs (including blood pressure, pulse rate, body temperature, respiratory rate), 12-lead ECGs, safety labs (hematology, serum chemistry, urinalysis, coagulation, and pregnancy tests), concomitant medication usage and adverse event (AE) monitoring. **Clinical Assessments** ***Oxygen Titration Test (OTT)*** The OTT will be used to assess the subjects' O_2 requirements at rest and with exercise, as measured by pulse oximetry and arterial blood gases (ABG). Subjects will exercise by walking along a 6MWT or equivalent course. *Refer to the separate OTT manual for complete instructions on the conduct of the OTT*. The flow of O_2 will be titrated to maintain a stable SpO_2 of 89 to 92%. ***Oxygen Saturation Measurement*** The measurement of peripheral oxygen saturation (SpO_2) will be performed using the pulse oximeter provided by the Sponsor. Screening and Day 1 Visit SpO_2 measured at these visits are to determine eligibility for inclusion into the study, and will be performed at rest, breathing room air.

	Prior to measuring SpO_2 breathing room air, subjects must be rested for at least 10 minutes breathing their usually prescribed flow rate of O_2. Then the subject's supplemental O_2 should be turned off to measure resting, room air SpO_2 as noted below. • Resting oxygen saturation (SpO_2) between 85 and 88% for at least 30 consecutive seconds while breathing room air (refer to Section 4.1 Inclusion Criteria) Or • Resting SpO_2 <85% for 10 consecutive seconds or, if in the opinion of the site staff, it is not safe or tolerable for the subject to continue without using their supplemental oxygen for 10 consecutive seconds whilst the SpO_2 is <85%. Either of these 2 criteria should be met at both screening and Day 1 visits. ***Arterial Blood Gases (ABG)*** Arterial blood samples will be taken at each scheduled OTT: Day 1 (baseline), Days 30, 90, and 120. Two samples will be drawn at each test: • Prior to the beginning of the test (i.e., prior to beginning to walk) while resting and **breathing room air** (i.e., with no oxygen being delivered to the subject) and • Immediately after completion of the OTT while receiving oxygen at the flow rate being delivered at the end of the test An Allen's test should be performed prior to the resting ABG at each OTT. The necessary equipment for performing the ABG should be prepared prior to beginning the OTT and readily available for both samples. Likewise, the necessary materials and equipment to transport the ABG samples for analysis should be readily available to ensure the integrity of the samples is not compromised. ***6-Minute Walk Test (6MWT) and Borg Scale of Perceived Exertion*** Functional exercise capacity will be evaluated at Day 1 (baseline) and Days 30, 90, and 120 using the 6MWT. *Refer to the 6MWT manual for complete instructions.* Guidelines developed by the ERS/ATS will be used for conducting the test and interpreting the results (ATS 2002 and Holland 2014). Instructions for the conduct of the 6MWT will be provided in a separate manual. ***Spirometry and Diffusing Capacity of the Lung for Carbon Monoxide (DLco) Measurements*** All equipment, procedures, and personnel qualifications for the assessment of lung function should be based on the recommendations of the American Thoracic Society (ATS 2003) and will be performed at each site using local equipment and procedures.

	Spirometry measurements will include FVC, FEV_1, DL_{CO} and other measures per the site's local practices. Post-bronchodilator assessments will not be performed. DL_{CO} will be measured at each site by determining the diffusing/transfer capacity of the lung for carbon monoxide. DL_{CO} adjusted for Hb will also be measured. ***Patient Reported Outcome (PRO)Measures*** PRO assessments should be self-administered by the subject, using the paper questionnaires provided by the Sponsor, at the investigational site prior to all other non-PRO assessments and before the subject receives any disease-status information during that assessment. They will be administered as indicated in the Schedules of Assessments in Appendix A (Table 15-1 for Part A; Table 15-2 for Part B). ***A Tool to Assess Quality of Life (ATAQ) in IPF – Symptoms Questionnaire*** The ATAQ-IPF Symptoms Questionnaire is an IPF-specific, self-administered questionnaire that assesses the subject's disease symptoms across three domains (physical activity, cough, and energy level) and a set of questions pertaining to O_2 use. Items are assessed using a Likert scale with a 24-hour recall period. ***A Tool to Assess Quality of Life (ATAQ) in IPF – Impacts Questionnaire*** The ATAQ-IPF Impact Questionnaire is an IPF-specific, self-administered questionnaire that assesses how IPF affects the subjects' quality of life. Items are assessed using a Likert scale with a 1-week recall period. ***St George's Respiratory Questionnaire (SGRQ)*** The SGRQ is a symptom-specific 2-part, patient self-administered questionnaire that assesses shortness of breath while doing a variety of activities of daily living. This questionnaire is comprised of three domains: symptoms, activity and impact. Items are assessed on various response scales, including a 5-point Likert scale and True/False scale. The SGRQ has a recall period of 4 weeks. ***Borg Dyspnea Scale*** The Borg Dyspnea Scale is a 1-item assessment, self-administered by the subject as part of the 6MWT. The instrument will be used during the 6MWT to assess dyspnea from the subject's perspective. The Scale ranges from 0 (Nothing at all) to 10 (Absolute maximum/Highest possible. ***End of Treatment Questionnaire*** The End of Treatment Questionnaire is survey to evaluate the subjects' experience while on the study including symptoms, changes in oxygen saturation and use. This is a self-administered survey to be completed during the Day-90 visit. A paper version of the End of Treatment Questionnaire will be provided to the sites. Subject responses will be entered in the eCRF by the site.

	Pharmacokinetic Assessments Plasma and whole blood concentrations of GBT440 will be determined using validated assays and collected pre and post drug administration (refer to Table 5-1 and Appendix A).
Restricted Therapies	Subjects should not take the following medications within 14 days prior to screening and during the entire study: • Strong inducers of CYP3A4/CYP3A5, CYP2B6, CYP2C9 and CYP2C19 (refer to Appendix B; these medications may decrease the blood concentration of GBT440) • Herbal medications (e.g., St. John's Wort) The following medications should be used with caution: CYP3A4 substrates with a narrow therapeutic index (refer to Table 8-1; GBT440 may increase the plasma concentration of these medications). Note: based on results from the drug-drug interaction studies, co-administration of GBT440 with pirfenidone or nintedanib is considered to be acceptable and they are allowed in this study.
Statistical Methods	Sample Size The study will enroll up to approximately 32 subjects; up to approximately 16 subjects in Part A and up to approximately 16 subjects in Part B. Study Endpoints The primary endpoint is change and % change from baseline in oxygen saturation at rest (SpO_2 or SaO_2), measured while breathing room air, at Days 30 and 90. Secondary Endpoints • Change and % change from baseline in O_2 flow rate (L/min), measured at rest, to maintain a target oxygen saturation (SpO_2) of 89 to 92%, at Days 30 and 90. • Change and % change from baseline in O_2 flow rate (L/min), measured post-exercise to maintain a target oxygen saturation (SpO_2 or SaO_2) of 89 to 92%, at Days 30 and 90 • Change and % change from baseline in resting P(A-a) O_2 at Days 30 and 90 • Change and % change from baseline in post-exercise P(A-a) O_2 at Days 30 and 90 • Change and % change from baseline in 6MWD, at Days 30 and 90 • Change in patient-reported IPF-related symptoms from baseline, measured by ATAQ and SGRQ, at Days 30 and 90 • Change from baseline in FVC and DLco at Day 90 Exploratory Endpoints • Number and % of total subjects no longer requiring O_2 at rest, at Days 30 or 90

	• Difference between the two O_2 allocation groups, in the change from baseline in resting O_2 flow rate (L/min), to maintain a target oxygen saturation (SpO_2 or SaO_2) of 89 to 92%, at Days 30 and 90 • Change from baseline in daily activity, measured by a pedometer, at Days 30 and 90 <u>Safety Endpoint</u> The frequency and severity of treatment-emergent adverse events (TEAEs) and tolerability of GBT440 administered daily orally for 90 days. <u>Pharmacokinetic Endpoints</u> PK parameters of GBT440 administered daily orally for 90 days in plasma and whole blood, including but not limited to, minimum concentration (C_{min}), at steady state.

1 INTRODUCTION

1.1 Disease Background

Idiopathic Pulmonary Fibrosis (IPF) is a chronic disease of unknown etiology that is characterized by progressive fibrotic destruction of the lung, resulting in worsening dyspnea and progressive loss of lung function (Raghu 2011). IPF is the most common type of interstitial lung disease with a high mortality rate (Michaelson 2000). While the course of the disease is variable, the prognosis is uniformly poor, with a median survival of about 3 to 5 years after diagnosis (Raghu 2006, King 2001, Nicholson 2000). In the United States, it is estimated to affect up to 200,000 people with approximately 50,000 new cases diagnosed each year (Raghu 2006) and approximately 40,000 dying each year (Olson 2012). IPF is typically seen in older adults, more commonly in men than women, usually occurring between the ages of 50 to 80 years, with a median age of 65 at diagnosis (Raghu 2006). Nintedanib and pirfenidone were approved for the treatment of IPF (Raghu 2015) in 2015, specifically targeting the fibrotic process; demonstrating a reduction in the annual decrease in forced vital capacity. However, there was no observed effect on survival, nor an improvement in hypoxemia or a clear and consistent improvement in disease symptoms such as dyspnea (Richeldi 2014, King 2014). As the interstitial fibrosis and architectural distortion advance, the lung becomes increasingly non-compliant and diffusing capacity decreases ultimately leading to hypoxemia, tissue hypoxia, and end-organ dysfunction.

Treatment of hypoxemia using supplemental oxygen (O_2) remains an important part of IPF management with the therapeutic goal of increasing blood oxygenation and in turn reducing the potential detrimental effects of hypoxic tissue injury and dysfunction and patient symptoms. Supplemental oxygen relieves dyspnea and improves functional status, but requires burdensome equipment for oxygen administration. Although minimal data are available specifically for IPF, the clinical benefit of improved oxygenation, is based on strong physiologic rationale and ethical considerations (Raghu 2011). Increased oxygenation as a therapeutic goal in patients with IPF-associated pulmonary hypertension and/or sleep disordered breathing is inferred from the clinical benefit demonstrated in other hypoxemic pulmonary diseases. In addition, studies have shown that dyspnea can be reduced and 6-minute walk distance (6MWD) increased with improved oxygenation from supplemental O_2 (Visca 2011). However, the use of supplemental O_2 comes with a cost to the patient who has to take on the physical burden of the oxygen delivery equipment, which can severely limit patient mobility and quality of life (FDA: The Voice of the Patient).

IPF remains a disease with high-unmet medical need requiring novel therapies that address not only the underlying fibrosis but also the associated hypoxemia and patients' quality of life.

1.2 GBT440

Global Blood Therapeutics (GBT) has developed GBT440, a novel small molecule allosteric modulator of hemoglobin (Hb) oxygen affinity that is currently being investigated for the treatment of sickle cell disease (SCD). GBT440 binds to the N-terminal valine of a Hb α chain, and increases the affinity of Hb for oxygen resulting in a left shift in the

oxy-hemoglobin dissociation curve (ODC). It has the same pharmacodynamic effect on both mutated hemoglobin (HbS) and normal adult hemoglobin (HbA). Preliminary data from Phase 2 SCD trials (Lehrer-Graiwer 2015) showed reduction in red blood cell (RBC) sickling consistent with GBT440's effect on maintaining more Hb in an oxygenated state. Based on GBT440's similar effect on HbA it is expected, in IPF patients, to increase oxygen uptake in the lungs, improving hypoxemia and oxygen delivery to tissues.

1.3 Rationale for Study

IPF is a severely debilitating disease characterized by progressive fibrosis, worsening hypoxemia, dyspnea and poor quality of life. Despite the recent approval of pirfenidone and nintedanib to treat IPF, these and other therapies have not demonstrated significant improvement in oxygenation, patient symptoms, functional status, or survival [Richeldi 2014, King 2014].

GBT440, a hemoglobin modifier that causes a left-shift in the oxy-hemoglobin dissociation curve (ODC) has the potential to enable increased oxygen uptake in the lungs and oxygen saturation, resulting in improved oxygen delivery to tissues. In support of this hypothesis, individuals with naturally occurring high affinity Hb mutations are physiologically adapted to the low oxygen tensions present at high altitude and are able to load and deliver more oxygen than normal controls (Hebbel 1978). Furthermore, numerous animal models have shown that increasing Hb oxygen affinity during acute and chronic hypoxia improves arterial oxygenation, cardiovascular function and survival (Xin 2016, Eaton 1974, Eaton 2004, Yalcin and Cabrales 2012).

Based on these observations and its ability to safely increase Hb oxygen affinity in humans (including IPF patients in the ongoing GBT440-006 study, healthy subjects and patients with SCD in the ongoing GBT440-001 study), study GBT440-026 was initiated in IPF patients. Study GBT440-006 is investigating the effect of GBT440 on oxygen saturation in a sub-population of IPF patients who demonstrate exercise-induced oxygen desaturation. In the current study (GBT440-026 Zephyr), the efficacy and safety of GBT440 is being studied in a broader IPF population who have more severe hypoxemia and require supplemental O_2 at rest. It is expected that GBT440 may demonstrate significant oxygenation improvement in these particular patients since a left shift in the ODC will provide a relatively large improvement in oxygenation since their room air SpO_2 is on the steep segment of the ODC.

Although supplemental O_2 can successfully treat hypoxemia, it does have significant disadvantages which negatively impact patient quality of life including the burden and decreased mobility from the required oxygen delivery devices and local complications (FDA: The Voice of the Patient) which in turn leads to poor compliance. GBT440 therapy may be able to provide the clinical benefits of oxygen therapy without the burden of oxygen supplementation and avoiding the negative effects of poor patient compliance and associated intermittent hypoxemia. In some patients, GBT440 may obviate the need for oxygen therapy and in others may facilitate the use of lower flow O_2 allowing patients to use more convenient oxygen equipment for the same clinical benefit. GBT440 could also be useful as an adjunct to oxygen therapy in more severe subjects who are not adequately oxygenated despite noninvasive oxygen therapy.

1.4 Nonclinical Data

An overview of the key nonclinical data is provided below. For additional details regarding the nonclinical pharmacology, pharmacokinetic (PK) and toxicology studies conducted to date, refer to the GBT440 Investigator's Brochure (IB).

1.4.1 Nonclinical Pharmacology

In vitro pharmacology studies were conducted to characterize the pharmacodynamic (PD) effects of GBT440. These studies demonstrated that GBT440 binds to Hb, modulates Hb-O_2 affinity and maintains the oxyHb state during deoxygenation. In addition, these studies showed that GBT440-modified Hb retains the Bohr Effect, which is the ability to augment oxygen delivery in metabolically active (low pH) tissues. This should preserve the ability of GBT440-modified Hb to off-load oxygen to metabolically active tissues, despite its increased affinity for oxygen.

In vivo pharmacology studies were performed in murine models of acute hypoxia challenge and pulmonary hypoxemia (lipopolysaccharide [LPS]-induced acute lung injury [ALI] and bleomycin induced lung fibrosis and hypoxemia (Xin 2016). These in vivo studies demonstrated that pharmacologically increasing Hb-O_2 affinity in these murine models of pulmonary hypoxemia resulted in improved O_2 saturation, translating into improved physiologic endpoints and survival.

1.4.2 Nonclinical Pharmacology

The safety pharmacology studies conducted with GBT440 are summarized in the GBT440 Investigator's Brochure. Safety assessments of GBT440 in 3 in vivo studies did not identify any biologically significant effects in the central nervous system (CNS) and respiratory system. There were minor effects in the cardiovascular (CV) safety pharmacology studies, with a mild increase in systolic BP at higher doses (1000 mg/kg) and a small decrease (15.3%) in hERG channel current at 10µM. Based on these results, there appears to be a low risk to humans for adverse effects on CNS, respiratory, or CV function.

1.4.3 Nonclinical Pharmacokinetics

The PK studies conducted with GBT440 are summarized in the GBT440 Investigator's Brochure. PK evaluations showed that GBT440 had low blood clearance (CL), low blood V_{ss}, and long terminal $t_{½}$ and was well absorbed in all animal species tested. GBT440 whole blood concentrations were much higher than plasma concentrations (calculated RBC: plasma ratio ~150:1), consistent with a high affinity and specificity of GBT440 for Hb. The PK properties of GBT440 in animals suggest that it will preferentially bind to Hb and be slowly, but completely eliminated from the body. With increasing doses in rats and dogs, the exposure with GBT440 is less than dose-proportional.

1.4.4 Metabolism and Potential Drug Interactions

Metabolism was the major route of elimination of GBT440 in humans. Renal excretion was a minor elimination pathway.

In vitro metabolism studies indicate that GBT440 could be metabolized by several CYP enzymes, i.e., CYP1A1, 1B1, 2B6, 2C9, 2C19, 3A4, and 3A5. However, in total, the data show that the exposure of GBT440 is unlikely to dramatically increase (<1.7-fold) when coadministered with a CYP inhibitor. Refer to Section 8.5.2 for restricted therapies in this study.

GBT440 has also been evaluated as a potential inhibitor/substrate of various membrane transporters. Refer to the GBT440 IB for further details of these studies.

1.4.5 Toxicology

The toxicity of GBT440 has been evaluated in single dose, repeat dose and reproductive toxicity studies. The genotoxic potential of GBT440 has been evaluated in a battery of in vitro and in vivo assays. The details of the nonclinical toxicology program, including toxicokinetics, are provided in the GBT440 IB.

1.5 Clinical Development of GBT440

Clinical studies have been conducted in healthy subjects (including 10 Phase I clinical pharmacology studies) and in patients with SCD and IPF.

The Phase II IPF study (GBT440-006) is a randomized, controlled trial evaluating the safety and PK of GBT440 and its effects on oxygen saturation in IPF subjects who are hypoxemic with exercise. GBT440 is being dosed at 600 mg, 900 mg and 1500 mg orally daily for 28 days.

The Phase I/II study (GBT440-001) is a randomized, placebo-controlled, ascending dose study evaluating the safety, tolerability, PK, and PD effects of single and multiple doses of orally administered GBT440 in healthy subjects and subjects with SCD. Healthy subjects have received multiple doses of 300 mg to 900 mg/day for up to 15 days. SCD subjects have received multiple doses of 500 mg to 1000 mg/day for up to 28 days, and 700 mg or 900 mg/day for up to 90 days; some subjects (900 mg) are continuing treatment for up to 6 months under a separate protocol (GBT440-024).

The Phase III study (GBT440-031) is a randomized, double-blind placebo-controlled study evaluating the efficacy and safety in SCD patients at GBT440 doses of 900 mg or 1500 mg for up to 72 weeks

The Phase II study in adolescent subjects with SCD (GBT440-007) is an open label, single dose and multiple dose PK study of GBT440 in pediatric subjects, ages 12 to 17 years.

Refer to the GBT440 IB for additional details regarding GBT440 development and all clinical studies.

1.5.1 Safety Findings

To date, GBT440 has been well tolerated over a range of doses administered to healthy and SCD subjects, for up to 90 days.

As of 30 September 2016, a total of 259 subjects have received at least 1 dose of GBT440: 205 healthy subjects, 47 adult SCD subjects and 7 pediatric SCD subjects.

In Study GBT440-001, the majority of the adverse events (AEs) were mild or moderate (Grade 1 or Grade 2), most commonly headache or diarrhea, and no clinically significant findings in vital signs, 12-lead electrocardiograms (ECGs), or laboratory safety values were identified.

In the SCD subjects dosed for 90 days, the majority of the AEs were also mild or moderate (Grade 1 or Grade 2). The most common AEs, occurring in ≥2 subjects and at a similar frequency in GBT440 and placebo-treated subjects, were headache, back pain, fatigue, and rhinitis.

The AEs that occurred at a higher rate in subjects receiving GBT440 included cough, diarrhea, and rash, of which diarrhea and rash were considered treatment-related by the Investigator. No episodes of anaphylaxis, anaphylactoid, or hypersensitivity reactions were reported.

Rashes were morbilliform in nature, typically involved the trunk or extremities, associated with mild pruritus, resolving within 2 to 5 days (in one case with continued dosing), and were not associated with any systemic features.

Overall, 10 serious adverse events (SAEs) have been reported as of 30 September 2016, in 10 subjects with SCD, considered by the Investigator to be not related to the study drug. There were 7 events of sickle cell crisis (Grade 3), all occurring off treatment during follow-up (1 placebo; 6 GBT440); 1 event of presumed infection with hemolysis (Grade 2) (GBT440); 1 event of an ovarian cyst (Grade 3), occurring after the last dose of study drug (GBT440) and 1 event of Grade 2 upper respiratory tract infection requiring hospitalization (GBT440).

Please refer to the GBT440 IB for additional details on GBT440 safety findings.

1.5.2 Pharmacokinetic Parameters

The mean PK results of GBT440 from analyzed samples to date derived from whole blood concentration-time profiles, shows that both maximum blood concentration (C_{max}) and area under the curve (AUC) increases proportionally with study drug dose for both single or multiple doses in Study GBT440-001. The exposure of GBT440 at steady-state was consistent with accumulation predicted based on the single dose data.

For the same dose, GBT440 exposure was lower and the $T_{1/2}$ was significantly shorter in subjects with SCD compared with healthy subjects. At steady-state, the exposure in subjects with SCD was also lower than that observed in healthy subjects. Since IPF patients will most likely have hematocrit values within the normal range, PK of GBT440 in these patients are expected to be similar to that of healthy volunteers.

Please refer to the GBT440 IB for additional details of GBT440 PK parameters.

1.5.3 Dose Rationale

The selection of the GBT440 doses for this study are based on a benefit risk profile that supports studying the potential efficacy and safety of GBT440 in a population of IPF subjects who have a high unmet medical need.

Based on data from in vivo studies of hypoxemia (Section 1.4.1) demonstrating a dose-dependent increase in Hb-O_2 affinity (PD effect of GBT440) and PK/PD data from study GBT440-001 the selected doses are expected to increase Hb-O_2 affinity to an extent that will result in a clinically significant increase in oxygen saturation.

The safety of the proposed doses is based on the overall favorable safety profile of GBT440 in studies to date:

- Study GBT440-006 in IPF subjects who desaturate with exercise. The safety findings from 16 subjects in Part A of the study who completed 28 days of dosing (900 mg and 600 mg GBT440) were reviewed by the study's Safety Monitoring Committee who endorsed continuing the study with the addition of a 1500 mg dose arm.
- Safety findings from healthy volunteers, SCD patients and IPF patients have not demonstrated that a daily, oral 900 mg dose of GBT440 represents a maximum tolerated dose (MTD).
- Continued favorable safety profile in ongoing studies evaluating GBT440 in subjects with SCD (refer to Section 1.5), including continued dosing for up to 6 months.

The safety of the proposed doses is based on the totality of available nonclinical and clinical safety data from IPF and SCD patients.

1.5.4 Potential Risk of GBT440 Treatment

Tissue Hypoxia

There is a theoretical risk of tissue hypoxia in subjects treated with GBT440 based on the mechanism of action and the potential for impairment in O_2 offloading at the tissues. However, in vitro data show that GBT440-modified Hb remains sensitive to the Bohr effect, and in vivo data from animal models of pulmonary hypoxemia are consistent with increased oxygen extraction and consumption by tissues. Furthermore, clinical data from subjects receiving study drug and those participating in maximal cardio-pulmonary exercise tests in the ongoing Phase I/II study, GBT440-001, have not identified a concern with tissue hypoxia. Please refer to the GBT440 IB for further details.

IPF subjects in this study will be closely monitored for subclinical evidence of worsening tissue hypoxia including using assessments for erythrocytosis, increased resting heart rate and erythropoietin and laboratory tests indicating organ injury (e.g., liver aminotransferases).

2 STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the effect of GBT440 on oxygen saturation at rest, breathing room air, on Days 30 and 90 compared to baseline.

2.2 Secondary Objectives

- To evaluate the effect of GBT440 on the requirement for supplemental O_2 at rest and post-exercise at Days 30 and 90 compared to baseline
- To evaluate the effect of GBT440 on resting and post-exercise Alveolar-arterial O_2 tension difference [$P(A\text{-}a)O_2$] at Days 30 and 90 compared to baseline
- To evaluate the effect of GBT440 on 6MWD at Days 30 and 90 compared to baseline
- To evaluate the effect of GBT440 on IPF-related symptoms, using patient reported outcomes (PROs), at Days 30 and 90 compared to baseline
- To evaluate pulmonary function at Day 90 compared to baseline
- To evaluate the safety and tolerability of 900 mg and 1500 mg GBT440 dosed daily for 90 days
- To evaluate the PK of GBT440

2.3 Exploratory Objectives

- To evaluate the effect of GBT440 on the need for any O_2 while at rest at Days 30 and 90 compared to baseline
- To compare the change in O_2 requirement between the two O_2 flow rate allocation groups
- To evaluate the effect of GBT440 on extent of activity during daily living at Days 30 and 90 compared to baseline

3 INVESTIGATIONAL PLAN

3.1 Study Design

This is an open label study that will be conducted in two parts. Together, Parts A and B will provide safety and efficacy data across the two GBT440 doses that are expected to improve oxygen saturation in the enrolled subjects.

Approximately up to 32 eligible subjects will be enrolled in the study.

- In Part A (Figure 1), up to approximately 16 eligible IPF subjects will receive 900 mg of GBT440 administered orally as 3 × 300 mg capsules or tablets once daily for 90 days.
- In Part B (Figure 1), up to approximately 16 eligible IPF subjects will receive 1500 mg of GBT440 administered orally as 5 × 300 mg capsules or tablets once daily for 90 days.

Subjects enrolled in Part A will follow the GBT440 900 mg visit schedule. Subject enrolled in Part B will follow the GBT440 1500 mg visit schedule. Schedules of Assessments are provided in Appendix A (Table 15-1 for Part A; Table 15-2 for Part B).

A signed and dated informed consent form (ICF) must be obtained before any study-specific tests may be performed.

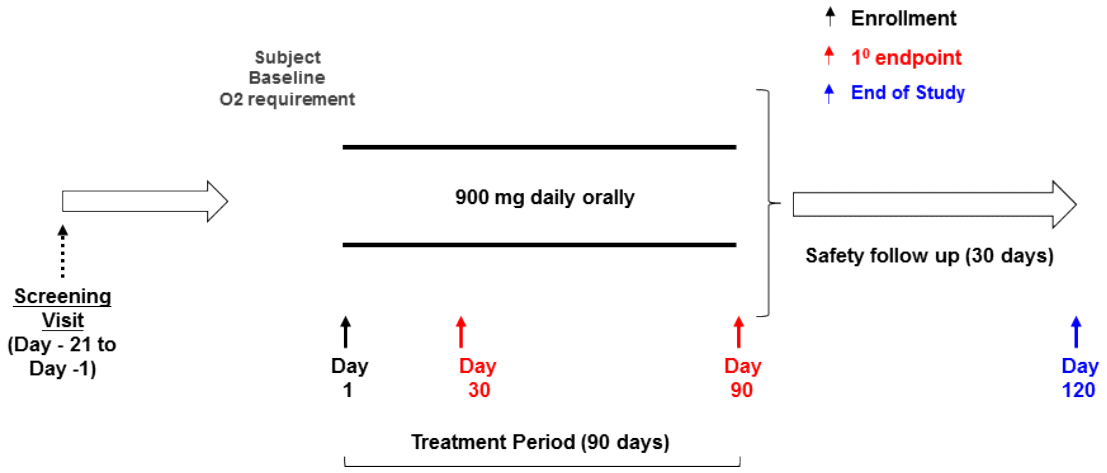
The screening period for each subject commences when the subject undergoes the first study-specific screening assessment and must be completed and tests evaluated before dosing (Day 1). Subjects may be rescreened up to 2 times, if deemed appropriate by the Principal Investigator. The rescreening visit should not occur sooner than 10 calendar days after the failed screening visit.

After the screening visit, the study includes the following study periods (Figure 3-1):

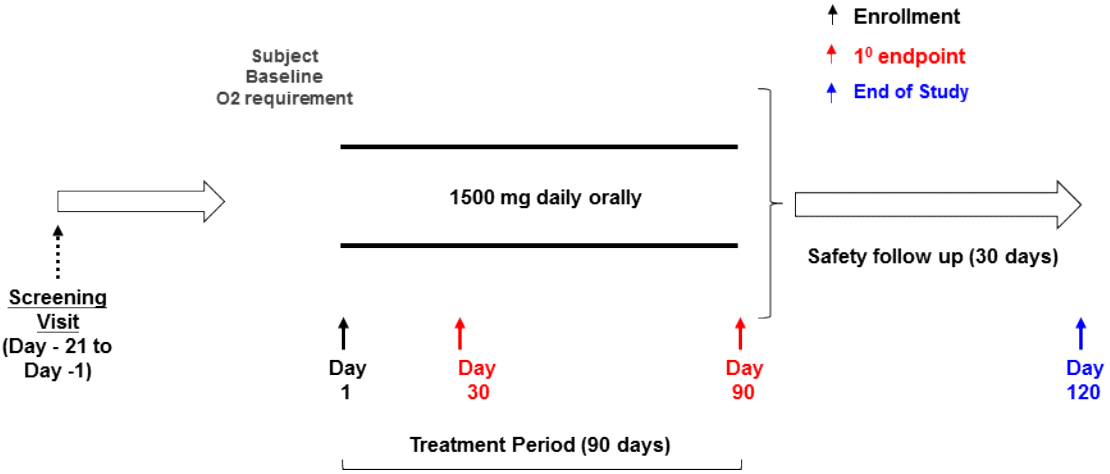
- Treatment period (90 days): subjects in Part A will receive 900 mg (3 × 300 mg) and subjects in Part B 1500 mg (5 × 300 mg) capsules or tablets daily
- Safety follow up (30 days): safety will be assessed for at least 5 half-lives after the last dose of GBT440 in both Parts A and B

Figure 3-1 Study Design

Part A



Part B



Subjects, who discontinue for reasons unrelated to toxicity, may be replaced if:

- the subject does not take at least 80% of their daily doses of study drug, prior to Day 30 (24 days) or Day 90 (72 days)

and/or

- the subject does not take study drug for at least 8 consecutive days prior to Days 30 or 90

The end of the study is defined as the date when the last subject last visit occurs, which is expected to be approximately 120 days after the last subject is enrolled.

This study will be performed in compliance with the protocol, ICH Good Clinical Practice (GCP), and applicable regulatory requirements. Aspects of the study concerned with the Investigational Medicinal Product (IMP) will meet the requirements of Good Manufacturing Practice.

3.2 Endpoints

3.2.1 Primary Endpoint

The primary endpoint is change and % change from baseline in oxygen saturation at rest (SpO_2 or SaO_2), measured while breathing room air, at Days 30 and 90.

3.2.2 Secondary Endpoints

- Change and % change from baseline in O2 flow rate (L/min), measured at rest, to maintain a target oxygen saturation (SpO_2) of 89 to 92%, at Days 30 and 90
- Change and % change from baseline in O_2 flow rate (L/min), measured post-exercise to maintain a target oxygen saturation (SpO_2 or SaO_2) of 89 to 92%, at Days 30 and 90
- Change and % change from baseline in resting P(A-a)O_2 at Days 30 and 90
- Change and % change from baseline in post-exercise P(A-a)O_2 at Days 30 and 90
- Change and % change from baseline in 6MWD, at Days 30 and 90
- Change in patient-reported IPF-related symptoms from baseline, measured by ATAQ and SGRQ, at Days 30 and 90
- Change from baseline in forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLco) at Day 90

3.2.3 Exploratory Endpoints

- Number and % of total subjects no longer requiring O_2 at rest, at Days 30 or 90
- Difference between the two O_2 allocation groups, in the change from baseline in resting O_2 flow rate (L/min), to maintain a target oxygen saturation (SpO_2 or SaO_2) of 89 to 92%, at Days 30 and 90
- Change from baseline in daily activity, measured by a pedometer, at Days 30 and 90

3.2.4 Safety Endpoints

The safety outcome measures for this study are the frequency and severity of treatment emergent adverse events (TEAEs) and tolerability of GBT440 administered daily orally for 90 days.

3.2.5 Pharmacokinetics Endpoints

Pharmacokinetic (PK) parameters of GBT440 in plasma and whole blood, including but not limited, minimum concentration (C_{min}) at steady-state.

4 STUDY POPULATION

4.1 Inclusion Criteria

All subjects must meet all of the following inclusion criteria:

1. 45 to 85 years of age inclusive, at randomization
2. Able and willing to provide signed informed consent to participate in this study
3. Documented diagnosis of IPF, as indicated in the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Respiratory Society (ALAT) 2011 Guidelines
4. Receiving supplemental O_2 for use at rest
5. Subjects using O_2 only with exercise will not be eligible
6. Resting oxygen saturation (SpO_2) between 85 and 88% for at least 30 consecutive seconds while breathing room air (refer to Section 5.1 and Section 5.5.2 for details regarding confirming eligibility)

   Or

   Resting SpO_2 <85% for 10 consecutive seconds or, if in the opinion of the site staff, it is not safe or tolerable for the subject to continue without using their supplemental oxygen for 10 consecutive seconds whilst the SpO_2 is <85%.

   Either of these 2 criteria should be met at both screening and Day 1 visits.
7. Able, in the Investigator's opinion, to walk a total of at least 100 meters at completion of the baseline 6-minute walk test (6MWT)
8. Weight ≥40 kg
9. Able, in the Investigator's opinion, to complete the O_2 titration study unassisted at baseline (Day 1) and Days 30, 90, and 120
10. Able, in the Investigator's opinion, to comply with the study procedures, including attending the assessment visits and adhering to study requirements and restrictions.
11. Male or female of child-bearing potential willing and able to use highly effective methods of contraception from study start to 30 days after the last dose of study drug

4.2 Exclusion Criteria

Any subject who meets any one of the following criteria will be excluded from participation:

1. Forced expiratory volume in 1 second (FEV_1) / forced vital capacity (FVC) <70%
2. History of interstitial lung diseases secondary to other medical conditions (e.g., scleroderma, sarcoidosis or rheumatoid arthritis) or resulting from clinically significant environmental exposures including but not limited to, drug toxicity, hypersensitivity pneumonitis, or asbestos

3. Hospitalization due to an exacerbation of IPF within 30 days of screening
4. Documented pulmonary hypertension that is severe (World Health Organization [WHO] Functional Class IV) and/or clinically unstable, as determined by the study Investigator
   - Subjects with documented mild to moderate pulmonary hypertension on a stable regimen of therapy for at least 3 months prior to screening will be eligible for the study
5. Subject plans to begin, or has commenced, pulmonary rehabilitation within 30 days of screening
   - Subject who is on a stable exercise regimen at screening or whose regimen, in the opinion of the Investigator, is not expected to change at any time during the entire study will be considered eligible for the study
6. Corticosteroid therapy, for treatment of IPF, >10 mg per day of prednisone (or an equivalent), administered for 7 days or longer, within 30 days of screening
   - Subjects receiving a stable dose of ≤10 mg per day of prednisone (or an equivalent) for at least 14 days prior to screening, and in the opinion of the Investigator not anticipated to require a dose adjustment during the study, are eligible for the study
7. Corticosteroid therapy for treatment of non-IPF diseases, unless:
   - Receiving a stable dose of prednisone (or an equivalent) for at least 14 days prior to screening, and in the opinion of the Investigator not anticipated to require a dose adjustments during the study
8. Participated in another clinical trial of an investigational drug (or medical device) within 30 days or 5-half-lives, whichever is longer, prior to screening, or is currently participating in another trial of an investigational drug (or medical device)
9. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) or total bilirubin >2 × upper limit of normal (ULN)
10. Serum creatinine >2.0 mg/dL
11. Clinical evidence of active infection, within 14 days of screening, which may include but is not limited to bronchitis, pneumonia, urinary tract infection, or cellulitis.
12. Active viral hepatitis within the last 6 months
13. Active tuberculosis within the last 6 months
    - Testing for latent tuberculosis is not required
14. Electrocardiogram (ECG) with a corrected QT interval using the Fridericia formula (QTcF) >450 ms (males) or QTcF >470 ms (females)
    - If ventricular pacing is noted on ECG, then QTcF intervals will not be calculated
15. Family or personal history of congenital long QT syndrome
16. Female who is breast-feeding or pregnant

17. Known current malignancy or current evaluation for a potential malignancy or history of malignancy within the past 2 years prior to screening, except for appropriately treated non-melanoma skin carcinoma, carcinoma in situ of the cervix, Stage 1 uterine cancer
18. Current smoker (including use of eCigarettes or vaporizing) or history of smoking within 3 months from screening
19. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within 3 months of screening, including but not limited to, congestive heart failure requiring hospitalization or uncontrolled clinically significant arrhythmias
20. History of mental illness within the last 5 years, unless the subject fulfills one of the following conditions:
    - The subject has not required or been prescribed any psychiatric medication (including but not limited to antidepressants or anxiolytics) within 12 months before screening and, in the opinion of the Investigator, the subject is able and safe to participate in the study
    - The subject has been on a fixed regimen of psychiatric medications for at least 6 months before screening and displays no sign of acute mental illness and, in the opinion of the Investigator, the subject is able and safe to participate in the study
21. Other clinically significant medical disease that is uncontrolled despite treatment and is likely, in the study Investigator's opinion, to significantly impact the study's efficacy and safety assessments
22. Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable)
23. Known hypersensitivity to any component of the study drug

5 STUDY PROCEDURES AND EVALUATIONS

5.1 Subject Screening

The subject must be willing and able to sign and date the ICF before any screening procedures or study-specific tests may be performed.

All subjects who sign the informed consent will be given a unique study number. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The screening period for a particular subject commences at the point at which the subject undergoes the first study-specific screening assessment and must be completed and evaluated within the screening period, prior to the first day of study drug dosing (Day 1). Schedules of Assessments are provided in Appendix A (Table 15-1 for Part A; Table 15-2 for Part B).

SpO_2 measurement for study eligibility: Assessment of resting, room air SpO_2 for study eligibility (refer to Section 4.1, Inclusion Criteria 5) is to be performed on both the screening and Day 1 visits. If the criterion is not met on either study visit day, the subject is to be screen failed without completing the other study related assessments. If the criterion is met, then the subject should proceed with the remaining assessments scheduled for that visit.

The same process is to be followed for the Day 1 visit.

Subjects may be rescreened up to 2 times, if deemed appropriate by the Principal Investigator. The rescreening visit should not occur sooner than 10 calendar days after the failed screening visit.

5.2 Avoidance of Pregnancy

Instructions for Male Subjects

There is no information about the effects GBT440 could have on the development of the fetus in humans. Therefore, it is important that the partners of male subjects do not become pregnant during the entire study and for a total 30 days after the male subject has taken the last dose of GBT440.

The methods of acceptable (highly effective) contraception that should be used by male subjects and their partners are outlined in Section 8.6.

Women of Child-Bearing Potential

Pregnancy should be avoided by either absolute abstinence or the use of highly effective means of contraception (refer to Section 8.6) for the duration of the study and a total period of 30 days after the subject has taken the last dose of GBT440.

Female subjects who become pregnant during the study will have study drug discontinued but continue in the study to complete all safety follow-up assessments (refer to Section 6.3).

Women of Non Child-Bearing Potential

Female subjects are considered to be of non-child-bearing potential if they have had surgical sterilization (i.e., hysterectomy and/or bilateral oophorectomy) or if post-menopausal, having been amenorrheic for at least 2 years.

Surgical sterilization procedures should be supported with clinical documentation and noted in the relevant medical history/current medical conditions section of the eCRF.

5.3 Clinical Assessments

Screening assessments must be performed and evaluated prior to dosing on Day 1. This study has 8 visits (including the screening visit), and subjects will be enrolled for approximately 120 days from the time of first study drug dose until the last study visit. The timing of the visits, associated visit windows, and all assessments are outlined in the Schedules of Assessments provided in Appendix A (Table 15-1 for Part A; Table 15-2 for Part B).

5.3.1 Pregnancy

In women of childbearing potential, pregnancy testing will be performed during Screening, Day 1, Day 30, Day 60, Day 90 and Day 120 visits. During the screening visit (Day -21 to Day -1) a serum pregnancy test will be performed. Serum pregnancy test results must be available and negative prior to Day 1 dosing. During Day 1, a urine pregnancy test will be performed and the pregnancy test must be negative prior to proceeding with other study related assessments and Day 1 dosing.

5.3.2 Medical History and Demographic Data

Medical history includes currently active and past clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), smoking history, use of alcohol and drugs of abuse within the previous year, and IPF-associated conditions including but not limited to pulmonary hypertension, gastroesophageal reflux disease, and sleep disordered breathing.

Medical conditions that are a result of side effects (e.g., rash or diarrhea) from concomitant medications (e.g., pirfenidone or nintedanib) should be clearly defined and entered into the eCRF.

Any medical condition present at baseline should be followed during the study, and a change from the baseline status (intensity or frequency) should be reported as an AE by the Investigator (refer to Section 10.1).

All concomitant medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the subject within 14 days prior to the screening visit should be entered on the Concomitant Medications eCRF. A start date should be entered for all medication items entered into the Concomitant Medications eCRF, including those medications used chronically.

Demographic data will include age (date of birth), sex, and self-reported race/ethnicity.

5.3.3 Physical Examination

A complete physical examination should include the following: an evaluation of the head, eyes, ears, nose, throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. A rectal or pelvic examination is not required. Any abnormality identified during screening should be recorded on the eCRF.

At subsequent visits, limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in the subject's study source documents. New or worsened abnormalities should be recorded as AEs on the Adverse Event eCRF.

Vital signs will include measurements of respiratory rate, heart rate, body temperature, systolic and diastolic blood pressure and oxygen saturation (SpO_2) by pulse oximetry. Blood pressure and SpO_2 measurements should be taken while the subject is in a seated or semi-recumbent position, and resting for at least 5 minutes.

5.4 Laboratory Examination

5.4.1 Clinical Laboratory Studies

It is the responsibility of the Investigator to assess the clinical significance of all abnormal clinical laboratory values as defined by the list of normal values on file for the local clinical laboratory. All clinically significant laboratory value abnormalities are to be recorded as AEs.

For the purpose of this study, a clinically significant laboratory value is any abnormal result that, in the judgment of the Investigator, is an unexpected or unexplained laboratory value and is accompanied by clinical symptoms and/or results in a medical intervention or corrective action (e.g., abnormalities that have clinical sequelae, require study drug dose modification, discontinuation of study drug, more frequent follow-up assessments or further diagnostic investigation). Any abnormal values that persist should be followed at the discretion of the Investigator.

Laboratory assessment time points are outlined in the Schedules of Assessments provided in Appendix A (Table 15-1 for Part A; Table 15-2 for Part B).

5.4.1.1 Hematology

Hematology assessments will include RBCs, hematocrit, Hb, platelets, and white blood cells (WBCs) with differential (basophils, eosinophils, neutrophils, monocytes, and lymphocytes). Reticulocyte count and serum erythropoietin (EPO) will also be collected.

5.4.1.2 Blood Chemistries

Blood chemistry assessments will include measurement of albumin, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, creatine kinase, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total protein, and uric acid.

5.4.1.3 Liver Function

Liver function assessments will include measurements of serum ALT, AST, alkaline phosphatase (ALK), gamma glutamyl transferase (GGT), and bilirubin (total, direct and indirect).

5.4.1.4 Plasma Protein Samples

Blood samples for plasma protein binding assessment will be collected as indicated in the Schedules of Assessments provided in Appendix A (Table 15-1 for Part A; Table 15-2 for Part B).

5.4.1.5 Urinalysis

Urine will be assessed for color and appearance. Dipstick analysis for specific gravity, pH, protein, glucose, ketones, and occult blood and microscopic analysis (RBCs, WBCs, bacteria and casts) will be performed.

5.4.1.6 Electrocardiograms

12-lead ECGs should be performed after the subject has been resting in a supine or semi-recumbent position for at least 5 minutes and prior to all other non-PRO assessment. A single ECG tracing will be obtained at the indicated study visit, and must be stored at the study site. If in the opinion of the Investigator there is a clinically significant abnormality the ECG parameters should be entered into the eCRF as indicated.

5.4.1.7 Other Clinical Laboratory Tests

For women of child-bearing potential, a pregnancy test (serum hCG) will be performed at screening, and a urine pregnancy test will be performed at Days 1, 30, 60, 90, 120 and early termination (if applicable) visits. The urine pregnancy test at Day 1 must be completed and confirmed negative before any other assessments are performed, including investigational product administration. If the urine pregnancy test is positive, the result must be confirmed with a serum pregnancy test and if positive, the subject is to be discontinued from the study.

Coagulation (Panel) including PT, PTT, and INR will be collected at screening.

5.5 Disease-Related Evaluations

5.5.1 Oxygen Titration Test (OTT)

The OTT will be used to assess the subjects' O_2 requirements at rest and with exercise, as measured by pulse oximetry and arterial blood gases (ABG). Subjects will exercise by walking along a 6MWT or equivalent course.

Refer to the separate OTT manual for complete instructions on the conduct of the OTT.

ABGs will be performed twice during the OTT:

1. Prior to the beginning of the test (i.e., prior to beginning to walk) while resting and **breathing room air** (i.e., with no oxygen being delivered to the subject)
2. Immediately after completion of the OTT while receiving oxygen at the flow rate being delivered at the end of the test

During the OTT, the flow of O_2 will be *titrated to maintain an SpO_2 of 89 to 92%*, using the lowest possible flow rate.

The OTT should be performed at each of the scheduled visits (Days 1, 30, 90, and 120) at approximately the same time of day (e.g., in the morning) and prior to performing the 6MWT assessment (if scheduled on the same Visit day). For safety reasons, all subjects should be clinically stable, as assessed by the study Investigator or performing technician, prior to performing the OTT.

5.5.2 Oxygen Saturation Measurement

The measurement of peripheral oxygen saturation (SpO_2) will be performed using the pulse oximeter provided by the Sponsor.

Screening and Day 1 Visit

SpO_2 measured at these visits are to determine eligibility for inclusion into the study, and will be performed at rest, breathing room air.

Prior to measuring SpO_2 breathing room air, subjects must be rested for at least 10 minutes breathing their usually prescribed flow rate of O_2. Then the subject's supplemental O_2 should be turned off to measure resting, room air SpO_2 as noted in Section 4.1 Inclusion Criteria and reproduced below.

- Resting oxygen saturation (SpO_2) between 85 and 88% for at least 30 consecutive seconds while breathing room air (refer to Section 4.1 Inclusion Criteria)

  Or

- Resting SpO_2 <85% for 10 consecutive seconds or, if in the opinion of the site staff, it is not safe or tolerable for the subject to continue without using their supplemental oxygen for 10 consecutive seconds whilst the SpO_2 is <85%.

Either of these 2 criteria should be met at both screening and Day 1 visits.

Vital Sign Assessments

At all scheduled vital sign assessments, SpO_2 will be measured with the subject breathing supplemental O_2, set at their usual O_2 flow rate, and after resting for at least 5 minutes. SpO_2 will be also be collected during conduct of the OTT and 6MWT (refer to the respective manuals for complete instructions).

Before recording the SpO_2 value in the eCRF, the study staff should ensure the measurement is stable, which may require continuous or repeated measurements and ensuring the subject is adequately rested.

5.5.3 Arterial Blood Gases (ABG)

Arterial blood samples will be taken at each scheduled OTT: Day 1 (baseline), Days 30, 90, and 120. Two samples will be drawn at each test:

- Prior to the beginning of the test (i.e., prior to beginning to walk) while resting and **breathing room air** (i.e., with no oxygen being delivered to the subject) and
- Immediately after completion of the OTT while receiving oxygen at the flow rate being delivered at the end of the test

An Allen's test should be performed prior to the resting ABG at each OTT.

The necessary equipment for performing the ABG should be prepared prior to beginning the OTT and readily available for both samples. Likewise, the necessary materials and equipment to transport the ABG samples for analysis should be readily available to ensure the integrity of the samples is not compromised.

5.5.4 6-Minute Walk Test (6MWT)

Functional exercise capacity will be evaluated at Day 1 (baseline) and Days 30, 90, and 120 using the 6MWT.

Refer to the 6MWT manual for complete instructions.

Guidelines developed by the ERS/ATS will be used for conducting the test and interpreting the results (ATS 2002 and Holland 2014). Instructions for the conduct of the 6MWT will be provided in a separate manual.

The 6MWT should be performed at each scheduled visit at approximately the same time of day (e.g., in the morning) and after spirometry and DL_{CO} assessments (if scheduled on the same visit day).

As part of the 6MWT, SpO_2, heart rate, and the Borg Dyspnea Scale will be measured at the following time points: prior to starting the test, during the test, at completion of the test, and 1 minute and 2 minutes after test completion.

Refer to the 6MWT manual for complete instructions.

For safety reasons, all subjects should be clinically stable, as determined by the study Investigator or the performing technician, prior to performing the 6MWT.

5.5.5 Spirometry and Diffusing Capacity of the Lung for Carbon Monoxide (DL_{CO})

All equipment, procedures, and personnel qualifications for the assessment of lung function should be based on the recommendations of the American Thoracic Society (ATS 2003) and will be performed at each site using local equipment and procedures

Spirometry measurements will include FVC, FEV_1, DL_{CO} and other measures per the site's local practices. Post-bronchodilator assessments will not be performed.

DL_{CO} will be measured at each site by determining the diffusing/transfer capacity of the lung for carbon monoxide. DL_{CO} adjusted for Hb will also be measured.

Spirometry and DL_{CO} should be performed at screening and Day 90 at approximately the same time of day (e.g., in the morning) and before the 6MWT, if scheduled on the same visit.

Local reports from the spirometry and DL_{CO} testing will be stored on site.

5.5.6 Patient Reported Outcome (PRO) Measures

PRO assessments should be self-administered by the subject, using the paper questionnaires provided by the Sponsor, at the investigational site prior to all other non-PRO assessments and before the subject receives any disease-status information during that assessment. They will be administered as indicated in the Schedules of Assessments provided in Appendix A (Table 15-1 for Part A; Table 15-2 for Part B).

5.5.6.1 A Tool to Assess Quality of Life (ATAQ) in IPF Symptoms Questionnaire

The ATAQ-IPF Symptoms Questionnaire is an IPF-specific, self-administered questionnaire that assesses the subject's disease symptoms across three domains (physical activity, cough, and energy level) and a set of questions pertaining to O_2 use. Items are assessed using a Likert scale with a 24-hr recall period.

5.5.6.2 A Tool to Assess Quality of Life (ATAQ) in IPF Impacts Questionnaire

The ATAQ-IPF Impact Questionnaire is an IPF-specific, self-administered questionnaire that assesses how IPF affects the subjects' quality of life. Items are assessed using a Likert scale with a 1-week recall period.

5.5.6.3 St George's Respiratory Questionnaire (SGRQ)

The SGRQ is a symptom-specific 2-part, patient self-administered questionnaire that assesses shortness of breath while doing a variety of activities of daily living. This questionnaire is comprised of three domains: symptoms, activity and impact. Items are assessed on various response scales, including a 5-point Likert scale and True/False scale. The SGRQ has a recall period of 4 weeks.

5.5.6.4 Borg Dyspnea Scale

The Borg Dyspnea Scale is a 1-item assessment, self-administered by the subject as part of the 6MWT. The instrument will be used during the 6MWT to assess dyspnea from the subject's perspective. The Scale ranges from 0 (Nothing at all) to 10 (Absolute maximum/Highest possible

5.5.6.5 End of Treatment Period Questionnaire

The End of Treatment Questionnaire is survey to evaluate the subjects' experience while on the study including symptoms, changes in oxygen saturation and use. This is a self-administered survey to be completed during the Day-90 visit. A paper version of the End of Treatment Questionnaire will be provided to the sites. Subject responses will be entered in the eCRF by the site.

5.6 Pharmacokinetic Samples

Plasma and whole blood concentrations of GBT440 will be determined using validated assays and collected pre and post drug administration (refer to Table 5-1).

Pre-dose PK samples should be obtained as soon as possible after PROs, ECG, AEs and Concomitant Medications history and vitals have been obtained and before any other assessments are performed.

Post-dose PK samples should be obtained following administration of study drug at the time points indicated in Table 5-1, below. Collection of these PK samples should occur after completion of all other scheduled assessments, including spirometry and DLco, OTT, 6MWT and investigational product dosing.

Up to eleven PK samples will be collected at the following times outlined in Table 5-1 (also refer to the Schedules of Assessments provided in Appendix A [Table 15-1 for Part A; Table 15-2 for Part B]).

Table 5-1 PK Sample Collection Schedule

	Pre-dose	15 minutes Post-dose	Between 2–4 hours Post-dose	During Study Visit
Day 1 (Visit 2)		X	X*	
Day 15 (Visit 3)	X*			
Day 30 (Visit 4)	X			
Day 60 (Visit 5)	X		X	
Day 90 (Visit 6)	X			
Day 105 (Visit 7)				X
Day 120 (Visit 8)				X

* Blood sample collection for protein binding assessment should also be collected at this time (refer to the Schedules of Assessments provided in Appendix A [Table 15-1 for Part A; Table 15-2 for Part B]).

Instructions for sample collection, processing and shipment are described in a separate laboratory manual.

6 EARLY DISCONTINUATION OF STUDY OR INDIVIDUAL SUBJECTS

6.1 Early Discontinuation of the Study and/or Site

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to:

- Incidence or severity of AEs in this or other studies indicating a potential health hazard to subjects.
- Unsatisfactory subject recruitment e.g., excessively slow
- Poor protocol adherence
- Incomplete or inaccurate data recording
- Poor compliance with the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP)

In any instance of early discontinuation of the study, the Sponsor will notify, in writing, the Investigators, regulatory authorities and ethics committees, and will specify the reason(s) for termination.

6.2 Early Discontinuation of Individual subjects

Reasons for subject withdrawal from the study may include but are not limited to any of the following reasons:

- Subject withdrawal of consent
- Discretion of the Investigator, if it is deemed not safe, or in the subject's best interest, to continue
- Subject is lost to follow-up

The date and reason for discontinuation should be documented in the eCRF.

Subjects who discontinue the study should return to the site to complete the Early Termination visit assessments within 2 weeks (± 7 days) from the date of discontinuation.

6.3 Study Drug Discontinuation

Subjects should discontinue study drug for any of the following reasons:

- Malignancy: not including local and non-serious basal or squamous cell skin cancer
- Pregnancy
- Anaphylaxis, anaphylactoid or serious hypersensitivity reaction
- Grade 3 or higher rash
- Use of any medication to treat IPF, other than those documented at screening.
- AE, which in the opinion of the Investigator, precludes the subject from safely continuing in the study
- Pulmonary rehabilitation started at any time from screening until the end of the study
- Subject is noncompliant with study requirements

The date and reason for discontinuation should be documented in the eCRF.

Subjects who discontinue study drug *should continue in the study to complete all scheduled assessments.*

Those subjects who are unwilling or unable to complete all remaining scheduled assessments should return to the site to complete the Early Termination visit assessments within 2 weeks (± 7 days) from the date of discontinuation. In this way, all subjects will be assessed at least 5 half-lives after the last dose of study drug.

7 STUDY DRUG AND ACCOUNTABILITY

7.1 Study Drug

7.1.1 Physical Description

GBT440 is a synthetic small molecule bearing the chemical name 2-hydroxy-6-((2-(1-isopropyl-1H-pyrazol-5-yl) pyridin-3-yl) methoxy) benzaldehyde. The chemical formula is $C_{19}H_{19}N_3O_3$ and the molecular weight is 337.38.

7.1.2 Formulation

During this study GBT440 may be administered in the form of capsules or tablets as determined by the Sponsor

GBT440 Capsules: GBT440 will be provided as 300 mg capsules which contain GBT440 drug substance in Swedish orange, opaque, size 0, hypromellose capsules, along with several formulation excipients including hypromellose, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and magnesium stearate. All the excipients used for the formulation are also FDA IID (Inactive Ingredients Database) listed.

GBT440 Tablets: The GBT440 300 mg tablets contain GBT440 drug substance along with several formulation excipients. All the excipients used for the formulation are FDA IID listed.

7.1.3 Packaging and Labeling

GBT440 capsules will be supplied to the site in 100 mL bottles of 30 capsules. GBT440 tablets will be supplied to the site in 60 mL bottles of 30 tablets.

7.1.4 Supply

GBT or their representative will supply the packaged and labeled drug product to the investigational sites. Additional details are provided in the pharmacy manual.

7.1.5 Storage and Handling Procedure

All study medications will be stored at controlled room temperature between 15°C to 25°C protected from light in the storage area of the investigational site pharmacy, which is a secure, temperature-controlled, locked environment with restricted access.

No special procedures for the safe handling of GBT440 are required. The Sponsor will be permitted upon request to audit the supplies, storage, dispensing procedures and records.

7.2 Drug Accountability

In accordance with GCP, the Investigational Site will account for all supplies of GBT440. Details of receipt, storage, dispensing and return will be recorded. All drug received must be reconciled or explained.

All unused supplies of GBT440 will either be destroyed by the investigational site or returned to the study Sponsor's designee at the end of the study in accordance with instructions from the Sponsor.

Additional details are provided in the pharmacy manual.

8 DOSAGE AND TREATMENT ADMINISTRATION

8.1 Treatment Regimen

GBT440 will be administered orally each day for 90 days. GBT440 will be administered as 300 mg capsules or tablets.

Part A:

- GBT440 900 mg: three 300 mg capsules or tablets

Part B:

- GBT440 1500 mg: five 300 mg capsules or tablets

Instructions for administration of study drug:

- Self-administered by subject in the morning
- May be taken with or without food
- May be taken with water or another non-alcoholic beverage
- Swallow the capsules or tablets whole

Subjects must be instructed not to take study drug on the day of their scheduled visits (refer to the Schedules of Assessments provided in Appendix A [Table 15-1 for Part A; Table 15-2 for Part B]).

Study drug will be administered at the site on these days, after completion of all the assessments scheduled for that visit. The subject should be instructed to swallow the capsules or tablets whole.

If a subject misses a dose of the study drug, they should resume normal dosing the next day; i.e., on the next day, the dose of study drug should be unchanged — not increased or decreased.

8.2 Study Drug Dispensing

Study drug will be dispensed to subjects at each of the study visits (refer to the Schedules of Assessments provided in Appendix A [Table 15-1 for Part A; Table 15-2 for Part B]).

8.3 Dose Modification

Modification of study drug dosing may be considered if, in the opinion of the study Investigator, an AE may be possibly/probably related to study drug, and it would be unsafe for the subject to continue receiving their current dose of study drug.

The Investigator's assessment of AE relatedness should take into account the toxicity profile of all concomitant medications including pirfenidone and nintedanib.

Not all AEs require study drug modifications and may be managed as determined by the Investigator and based on the clinical nature of the AE.

The Sponsor's Medical Director should be contacted prior to any change in dosing.

8.3.1 Dose Adjustment

Dose adjustments may be initiated by the Investigator based on their assessment of the associated AE severity and overall subject safety.

The Investigator, in discussion with the Sponsor's Medical Director, may choose to reduce the total daily dose.

- The initial reduction in dose should be by one (300 mg) study drug capsule or tablet.
- A second dose reduction by another one (300 mg) capsule or tablet may be initiated, if deemed necessary by the Investigator and based on a safety assessment of the subject. The timing of the second dose reduction will be based on the Investigator's clinical assessment and in prior discussion with the Sponsor's Medical Director.
- Any further dose reduction deemed necessary by the Investigator should be by one (300 mg) capsule at a time and based on a safety assessment of the subject.

The Investigator must make every effort to return the subject to the dose level administered at the time of study enrollment.

Once, in the opinion of the study Investigator, it is safe to increase dosing, this may be performed by:

- Initiating the full dose, administered at study enrollment
- Increasing the dose in a step-wise fashion by single capsule or tablet increments. The timing of the increase in dosing should be at the discretion of the Investigator. Instructions for increasing study drug dosing are listed below.

Part A: If the subject is receiving a reduced dose of 300 mg (a total of 1 capsule or tablet) or 600 mg (a total of 2 capsules or tablets), the dose may be increased by 1 capsule or tablet (300 mg) at a time up to 900 mg (a total of 3 capsules or tablets) or a dose best tolerated by the subject.

Part B: If the subject is receiving a reduced dose of 300 mg, 600 mg, 900 mg or 1200 mg (a total of 1, 2, 3 or 4 capsules or tablets respectively), the dose may be increased by 1 capsule or tablet (300 mg) at a time up to 1500 mg (a total of 5 capsules or tablets) or a dose best tolerated by the subject.

Rash

In the case that a subject develops a rash, the Investigator must assess whether the rash might be due to study drug or concomitant medications, in particular pirfenidone or nintedanib which may both cause rash.

If, in the opinion of the Investigator, the rash may be possibly/probably related to study drug, the dose should be modified based on the instructions outlined in this section and in Section 8.3.2.

An increase in dosing beyond the dose at the time of subject enrollment, is not allowed.

8.3.2 Dose Interruption

Dose interruption may be initiated by the Investigator due to an AE, based on their assessment of the associated AE severity and overall subject safety and in discussion with the Sponsor's Medical Director.

Study drug should be restarted when, in the Investigator's opinion, it is safe to do so and in discussion with the Sponsor's Medical Director.

Part A

Study drug may be restarted at 900 mg (3 capsules or tablets) or at a lower dose (600 mg or 300 mg) as tolerated. If study drug is restarted at a lower dose the dose may be increased by 300 mg (1 capsule or tablet) at a time to a total of 900 mg (3 capsules or tablets) or a dose best tolerated by the subject. Refer to Section 8.3.1 for instructions on dose escalation.

Part B

Study drug may be restarted at 1500 mg (5 capsules or tablets) or at a lower dose (900 mg, 600 mg or 300 mg) as tolerated. If study drug is restarted at a lower dose the dose may be increased by 300 mg (1 capsule or tablet) at a time to a total of 1500 mg (5 capsules or tablets) or a dose best tolerated by the subject.

For both Parts A and B, study drug may be discontinued due to an AE if, in the opinion of the Investigator, it is unsafe for the subject to continue receiving study drug. Subjects who discontinue study drug should remain in the study and complete all scheduled assessments (refer to Section 6).

8.3.3 Pirfenidone or Nintedanib Background Therapy

If, in the opinion of the Investigator, the subject experiences significant side effects, judged to be related to pirfenidone or nintedanib therapy, treatment of symptoms and/or dose modifications of these medications are allowed.

The decision to modify pirfenidone or nintedanib dosing is ultimately the responsibility of the Investigator. Any modifications to dosing will be managed by the Investigator throughout the study, taking in to account the United States Prescriber Information (USPI) of the drugs

and past history of care from the subject's IPF health care provider and must be entered into the eCRF.

8.4 Study Drug Overdose

To date, no events of overdose have been reported. Based on the mechanism of action of GBT440, the result of an overdose might include, but is not limited to, increased severity of previously reported associated AEs or decreased oxygen delivery to tissues (refer to Section 1). In the event of a medical emergency due to suspected GBT440 overdose, the Medical Monitor should be contacted as soon as possible.

8.5 Concomitant Medications

A concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements.

In the interests of subject safety and acceptable standards of medical care the Investigator will be permitted to prescribe treatment(s) at his/her discretion. For all subjects, concomitant medications taken from signing of the informed consent until the last study visit must be recorded in the subjects' eCRFs.

All reported prior and concomitant medications will be coded using the WHO Drug Dictionary.

8.5.1 Permitted Therapy

Use of the following therapies is allowed during the study:

- Pirfenidone, nintedanib or N-acetylcysteine (NAC) for the treatment of IPF
  - Only if at the time of screening, the dose has been stable for at least 1 month prior to screening and with no anticipated need for dose adjustments during the study
- Corticosteroids for the treatment of IPF
  - Only if the dose at screening is ≤ 10 mg per day of prednisone (or an equivalent) and has been stable for at least 14 days prior to screening and with no anticipated need for dose adjustments, including reductions in dose, during the study
- Corticosteroids for the treatment of non-IPF conditions
  - Only if the dose of prednisone (or an equivalent) has been stable for at least 14 days prior to screening, and in the opinion of the Investigator not anticipated to require dose adjustments during the study
- Maintenance therapy for other medical conditions listed in the subject's medical history at the time of screening

Medications such as acetaminophen, non-steroidal anti-inflammatories and routinely-taken dietary supplements, including vitamins are allowed at the discretion of the Investigator and provided that the medications have no discernable impact on the study.

8.5.2 Restricted Therapies

Subjects should not take the following medications within 14 days prior to screening and during the entire study:

- Strong inducers of CYP3A4/CYP3A5, CYP2B6, CYP2C9 and CYP2C19 (refer to Appendix B; these medications may decrease the blood concentration of GBT440)
- Herbal medications (e.g., St. John's Wort)

The following medications should be used with caution:

- CYP3A4 substrates with a narrow therapeutic index (refer to Table 8-1; GBT440 may increase the plasma concentration of these medications)

Table 8-1 CYP Substrates with Narrow Therapeutic Range

CYP Enzymes	Substrates with Narrow Therapeutic Range
CYP3A4	Alfentanil, astemizole, cisapride, cyclosporine, dihdroergotamine, ergotamine, fentanyl, pimozide, quindine, sirolimus, tacrolimus, terfenadine
Note that this is not an exhaustive list. For an updated listed, refer to the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#4 Substrates with a 'narrow therapeutic range' refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns. Adapted from: FDA DRAFT Guidance for Industry: Drug Interactions Studies-Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. February 2012.	

8.5.3 Therapies for treatment of IPF

Therapies, other than those used at the time of screening, for the treatment of IPF are not allowed.

If in the opinion of the Investigator an escalation in therapy for IPF is required, then study drug should be discontinued and the subject should complete all remaining scheduled assessments (refer to Section 6.3).

8.6 Fertility/Contraceptive Requirements

Highly effective birth control should be used from the screening period until 30 days following the last study drug administration.

8.6.1 Acceptable Forms of Contraception

Highly effective methods of birth control are considered acceptable in this study. Highly effective is defined as those methods of birth control which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly.

For female subjects:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
    - **Note:** Hormonal contraception must be supplemented with a barrier method (preferably male condom).
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner. Note that vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of child-bearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

For male subjects:

- Vasectomy
- Two acceptable methods of contraception: Must agree to use, at least one of which must be a barrier method (e.g., spermicidal gel plus condom) for the entire duration of the study, and for 30 days following last study drug administration.
- Sexual abstinence:

  This method of contraception is considered highly effective only if the subject is refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

9 RANDOMIZATION PROCEDURE

Subject randomization will not be carried out in this study.

Approximately up to 32 subjects (up to approximately 16 subjects in Part A and 16 subjects in Part B) will be enrolled.

9.1 Blinding

The study is open label.

10 SAFETY ASSESSMENTS

GBT440 is not an approved drug and, as a result, the entire safety profile is not known at this time. This Phase 2 study will contribute to the understanding of the safety profile for GBT440 and for its use in IPF patients.

Safety assessments will consist of recording all AEs and SAEs, protocol-specified laboratory variables, vital signs, ECGs, and the results from other protocol-specified tests that are deemed critical to the safety evaluation of GBT440. Dedicated eCRFs will be used to collect information on specific AEs including SAEs, SUSARs, rashes and pregnancies.

10.1 Adverse Events (AE)

An AE is defined as any untoward medical occurrence in any subject enrolled in a clinical investigation administered a pharmaceutical product,-regardless of causal attribution.

An AE can be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not it is thought to be related to the investigational product. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs is considered an AE. This includes any side effect, injury, toxicity or sensitivity reaction.

Subjects will be monitored throughout the study for AEs, from the time informed consent is obtained until the last study visit (Day 120). Reporting of AEs prior to enrollment should only include SAEs or AEs resulting from any protocol-related interventions.

AEs that are identified at the last assessment visit as specified in the protocol must be recorded in the eCRF. All events that are ongoing at this time will be recorded as ongoing on the eCRF. All (both serious and non-serious) AEs must be followed until they are resolved or stabilized, or until reasonable attempts to determine resolution of the event are exhausted. The Investigator should use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events.

All reported AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

All procedures specified in Section 10.3 are to be followed for reporting SAEs.

10.2 Recording Adverse Events

Adverse events are to be recorded on the AE page of the eCRF. The following information will be recorded at the time the AE is reported and during follow up during the course of the AE:

- Whether or not the AE is an SAE (Section 10.2.2)
- AE severity using National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (NCI CTCAE v4.03) (Section 10.2.3)

- AE relationship to investigational product (Section 10.2.4)
- Action taken, including but not limited to: none, study drug dose modification or discontinuation, required concomitant medication, required procedure, or other
- Outcome: recorded as event resolved, resolved with sequelae, ongoing, or death

10.2.1 Assessment of Adverse Events

The Investigator will assess each AE for seriousness, severity, and relationship to study drug.

10.2.2 Serious Adverse Event (SAE)

The Investigator is responsible for determining whether an AE meets the definition of an SAE. An SAE is any AE that results in any of the following outcomes:

- Death
- Life-threatening, i.e., an AE that places the subject at immediate risk of death
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacity, i.e., a substantial disruption in the subject's ability to conduct normal life functions
- A congenital anomaly or birth defect in a neonate or infant born to a mother exposed to study drug
- Significant medical events that, in the opinion of the Investigator, may jeopardize the subject or may require medical or surgical intervention to prevent any of the outcomes listed in this definition.

SAEs will be reported to the Sponsor's designated CRO's Drug Safety Department within 24 hours of the Investigator, designee, or site personnel's knowledge of the event. Refer to "Reporting Serious Adverse Events" (details are provided in Section 10.3.4).

Note: Hospitalization is not considered to be an SAE if a subject has a hospitalization or procedure (e.g., elective surgery) during the study, that was scheduled prior to the subject entering the study (i.e., before the subject signed the informed consent) for a pre-existing condition (i.e., one that occurred before the study). However, if the event/condition worsens during the study, it must be reported as an AE (or SAE, if the event/ condition results in a serious outcome such as hospitalization).

10.2.3 Protocol-Defined Events of Special Interest

An adverse event of special interest (AESI) is any AE occurring from signing of the informed consent form (ICF) until the end of the study (Day 58) that results in:

- An allergic reaction/hypersensitivity Grade 2 or higher (as defined by NCI CTCAE v4.03)

AESIs will be reported to the CRO's Drug Safety Department within 24 hours of the investigator, designee, or site personnel's knowledge of the event.

10.2.4 Severity of Adverse Events

The severity of an event describes the degree of impact upon the subject and/or the need for medical care necessary to treat the event. AEs reported for subjects participating in this study will be graded using the NCI CTCAE v4.03 (Table 10-1).

The Investigator will grade the severity of each AE using, when applicable, the NCI CTCAE v4.03. For AEs not included in the NCI CTCAE v4.03, the criteria outlined in Table 10-1 should be used as a general guideline.

Table 10-1 Grading for Adverse Events Not Covered in the NCI CTCAE

Severity	Description
Grade 1 – Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 – Moderate	Minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living (ADL)
Grade 3 – Severe	Medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4 – Life-threatening	Life-threatening consequences; urgent intervention indicated
Grade 5 – Fatal	Death

ADL = activities of daily living; NCI CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events

10.2.5 Relationship to Study Drug

The relationship of an AE to the investigational product should be determined by the Investigator according to the following definitions:

- **Not Related:** Evidence exists that the AE has an etiology other than the study drug (such as a preexisting condition, underlying disease, intercurrent illness, or concomitant medication); and/ or the temporal relationship of the AE/SAE to the investigational product administration makes the relationship unlikely.
- **Possibly/Probably Related:** A temporal relationship exists between the event onset and administration of the study drug; and it cannot be readily explained by the subject's clinical state or concomitant therapies; and it may appear with some degree of certainty to be related based on the known therapeutic and pharmacologic actions of the drug. Additional criteria to consider include in the case of cessation or reduction of the dose,

the event abates or resolves and reappears upon re-challenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If it is felt that the event is not related to study drug therapy, then an alternative explanation should be provided.

10.2.6 Unexpected Adverse Events

An adverse reaction is 'unexpected' if its nature and severity are not consistent with the information contained within the current GBT440 IB.

10.3 Reporting Adverse Events

Reporting of AEs prior to dosing should only include SAEs resulting from any protocol-related interventions**.**

10.3.1 Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom or sign of the eventual diagnosis.

10.3.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade of events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the eCRF.

However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the eCRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the eCRF.

10.3.3 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between subject evaluation time points. Such events should only be recorded once in the eCRF unless the severity changes (increases or decreases). If a persistent AE becomes more or less severe, the AE should be recorded as separate AEs for each Grade of severity.

If the event becomes serious, it should be reported to the Sponsor or the Sponsor's designated CRO's Drug Safety Department within 24 hours of the Investigator, designee, or site personnel's knowledge of the event. The AE eCRF should be updated to add the SAE, providing the date that the event became serious. The updated eCRF should include both the non-serious and serious designated AEs.

A recurrent AE is one that resolves between subject evaluation time points and subsequently recurs. All recurrent AEs should be recorded separately on an Adverse Event eCRF.

10.3.4 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities will be recorded as AEs or SAEs on the eCRF (e.g., abnormalities that require study drug dose modification, discontinuation of study drug, more frequent follow-up assessments, further diagnostic investigation).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., increased alkaline phosphatase and bilirubin associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the Adverse Event eCRF, unless their severity increases or decreases, or the seriousness or etiology changes.

10.3.5 Reporting Serious Adverse Events (SAEs)

All SAEs and AESIs, regardless of causal attribution, that occur in this study will be reported to the Sponsor's designated CRO's Drug Safety Department within 24 hours of the Investigator, designee, or site personnel's knowledge of the event. The SAE/AESI will be reported by completing the SAE/AESI eCRF in the EDC system.

In the event that the EDC system is not available, a paper SAE/AESI report form must be submitted to the CRO's Drug Safety Department (drugsafety@wwctrials.com or faxed to 1-866-387-5539) within 24 hours of becoming aware of the event. The Principal Investigator or designee must complete the SAE/AESI eCRF page as soon as the EDC system becomes available.

Follow-up reports must be submitted in a timely fashion as additional information becomes available. The Sponsor or designee may request additional source documentation pertaining to the SAE/AESI from the investigational site. If a subject is permanently withdrawn from the study due to a SAE, this information must be included in the initial or follow-up SAE report in the eCRF.

The Investigator is responsible for notifying the Institutional Review Board (IRB) or Independent Ethics Committees (IEC) of SAEs, in accordance with local regulations. The Sponsor or designee is responsible for reporting SAEs to the relevant regulatory authorities, and participating Investigators, in accordance with ICH guidelines, FDA regulations, and/or local regulatory requirements.

Properly anonymized and de-identified documents (e.g., hospital discharge summaries, autopsy reports, and/or death certificates) as available will be provided to the CRO's Drug Safety Department for all reported SAEs/AESIs.

10.3.6 Suspected Unexpected Serious Adverse Reaction (SUSAR) Reporting

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the study drug and is not listed in the current IB (i.e., an unexpected event). The Sponsor or its designee is responsible for reporting SUSARs associated with the use of the study drug to the regulatory agencies and competent authorities after being notified of the event.

10.4 Discontinuation due to Adverse Events

Any subject who experiences an AE, serious or non-serious, may have study drug discontinued at any time at the discretion of the Investigator. The AE(s) should be noted on the appropriate eCRFs, and the subject's progress should be followed until the AE is resolved or stabilized as determined by the Investigator. The Sponsor's Medical Director and the CRO Medical Monitor must be notified. If the AE relates to overdose of study treatment, the IB should be consulted for details of any specific actions to be taken.

Subjects should return to the study to complete assessments as outlined in Section 6.

10.5 Pregnancy

Pregnancies occurring in female subjects or in a male subject's partner while enrolled in this clinical study through 30 days after the last dose of study drug administration, must be reported on a Pregnancy Monitoring Form and sent to the CRO's Drug Safety Department within 24 hours of the Investigator, designee, or site personnel learning of the pregnancy (in accordance with Section 10.3).

If a subject becomes pregnant while taking study drug, the study drug will be immediately discontinued, and the pregnancy must be reported to the CRO's Drug Safety Department within 24 hours The Investigator will discuss with the subject the risks and concerns of investigational drug exposure to a developing fetus and counsel the subject and/or pregnant partner (or ensure such counseling is provided).

All pregnancies will be followed through to a definitive outcome (i.e., birth and 3 months post-delivery, spontaneous/elective abortion or miscarriage). An uncomplicated pregnancy will not be considered an AE or SAE. Pregnancy complications (e.g., spontaneous abortion/miscarriage or congenital anomalies) are considered an SAE. The outcome of any pregnancy and the presence or absence of any congenital abnormality will be recorded in the source documentation and reported to the CRO's Drug Safety Department in accordance with Section 10.3.

The Investigator will complete a Pregnancy Monitoring Form and report the information regarding the pregnancy, outcome, and status of the newborn and mother, as appropriate.

11 DATA ANALYSIS AND STATISTICAL PLANS

This section describes the statistical methodology to be used in the analysis of the protocol endpoints. Details of all planned analyses will be specified in a separate Statistical Analysis Plan (SAP).

Data will be summarized using descriptive statistics. Continuous variables will be summarized using mean, standard deviation (SD), coefficient of variation (CV%, as appropriate), median, minimum, maximum, and, as appropriate, geometric mean. Categorical variables will be summarized by presenting the number (frequency) and percentage in each category.

Data will be summarized by dose level (900 mg, 1500 mg) and overall (total subjects). All collected data will be presented in data listings.

11.1 Sample Size

The study will enroll up to approximately 32 subjects; up to approximately 16 subjects in Part A and up to approximately 16 subjects in Part B.

11.2 Analysis Populations

The following populations will be considered in the analysis of data for this study.

Efficacy Evaluable (EE) Population: All subjects who complete dosing for at least 20 days within the first 30 days of the treatment period or at least 60 days for the entire 90-day treatment period will be included in the EE Population. The EE Population will be the primary Population for all efficacy data presented.

Safety Population: All subjects who receive any amount of study drug will be included in the Safety Population. The Safety Population will be the primary population for all safety data presented.

PK Population: The PK Population will consist of all subjects who receive active study drug and have at least one measured concentration at a scheduled PK time point after start of dosing for at least one PK analyte. If any subjects are found to be noncompliant with respect to dosing or have incomplete data, protocol violations, or clinical events that affect PK, a decision will be made on a case-by-case basis as to their inclusion in the analysis. Subjects in this Population will be used for all PK summaries.

11.3 Statistical Analyses

11.3.1 Efficacy Analyses

The analysis of the primary and secondary endpoints will be summarized descriptively. Each endpoint will be summarized by dose group and overall (total subjects).

Full details of the analysis methods, including how missing data will be handled, will be provided in the SAP.

11.3.2 Safety Analyses

Safety and tolerability will be assessed by incidence, severity and changes from baseline of all relevant parameters including AEs, laboratory evaluations, vital signs, and ECGs.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects experiencing 1 or more AEs will be summarized by dose group and overall, relationship to study drug and severity according to system organ class and preferred term. Additional summaries will be provided for SAEs and events resulting in permanent discontinuation of study drug.

Laboratory parameters will be summarized using descriptive statistics and by post-dose shifts relative to baseline. Laboratory values outside normal limits will be identified in the subject listings and will include flags for high and low values.

Vital sign results and ECGs will also be summarized descriptively for each scheduled protocol time point.

11.3.3 PK and PK/PD Analyses

A listing of PK sample collection times as well as derived sampling time deviations will be provided. A subject listing of all concentration-time data for each treatment, and study day will be presented. PK variables will be summarized using appropriate descriptive statistics (e.g., n, mean, SD, CV%, minimum, median, and maximum, and/or geometric mean) by part, dose, and study day.

Graphical presentations of key PK parameters and concentrations will be used as appropriate. Figures of individual concentrations versus time will be presented by subject.

PK/PD analyses will be performed.

12 REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

12.1 Ethical Consideration

It is the responsibility of the Investigator to assure that the study is conducted in accordance with the protocol, current country and local regulations, FDA regulations, ICH GCP guidelines, and the Declaration of Helsinki.

12.2 Institutional Review Board (IRB) and Regulatory Approval

The Investigator must inform, and obtain approval from, the IRB/IEC for the conduct of the study at named sites, for the protocol, the Subject Informed Consent Form, any other written information that will be provided to the subjects, and any advertisements that will be used. Written approval must be obtained prior to recruitment of subjects into the study and shipment of investigational drug.

Proposed amendments to the protocol and aforementioned documents must be discussed among the Sponsor and CRO, and then submitted to the IRB/IEC for approval. Amendments may be implemented only after a copy of the local EC approval letter has been transmitted to the Sponsor. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor or IRB/IEC approval. However, in this case, notification to the Sponsor and IRB approval must be obtained as soon as possible after implementation.

The Investigator will be responsible for ensuring that an annual update is sent to the IRB/IEC to facilitate their continuing review of the trial (if needed) and that the IRB/IEC is informed about the end of the study. Copies of the update, subsequent approvals and final letter must be sent to the Sponsor.

12.3 Insurance and Financial Disclosure

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

The Investigator and sub Investigator(s) must complete, sign and date a Financial Disclosure Form prior to their participation in the study. This Form will be maintained with the study records. The Investigator and sub Investigator(s) will provide an updated Financial Disclosure Form if any of the factors change during the trial and for 1 year after the trial's completion or termination.

12.4 Essential Documentation Requirements

The Sponsor will collect from the investigational site the required essential regulatory documents per ICH guidance prior to GBT440 shipment to the site.

12.5 Informed Consent

It is the Investigator's responsibility to obtain written informed consent from the subject after adequate explanation of the objectives, methods, anticipated benefits, and potential hazards of the study and before any study procedures are commenced. This information is contained within the informed consent form (ICF).

The Investigator also commits to providing each subject with a copy of the revised ICF if any changes are made to the study.

For both the original and all updated ICFs: (a) the subject and the person executing the informed consent process must personally sign and date the document, (b) a copy of the ICF in the subject's native language must be provided to the subject, and (c) the informed consent process should be recorded in the source documentation. All original signed/dated ICFs must be retained with the study records.

12.6 Confidentiality

The Investigator must ensure that the subject's privacy is maintained. On the CRF or other documents submitted to the Sponsor, subjects will be identified by a subject study number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the Investigator.

The Investigator shall permit authorized representatives of the Sponsor, regulatory agencies and IRBs/IECs to review the portion of the subject's medical record that is directly related to the study. As part of the required content of informed consent, the subject must be informed that his/her records will be reviewed in this manner.

12.7 Trial Documentation and Data Storage

The Investigator must retain a comprehensive and centralized filing system of all trial-related documentation that is suitable for inspection by the Sponsor and representatives of regulatory authorities.

The Investigator must retain essential documents until at least 2 years after the last approval of a marketing application. Subject files and other source data (including copies of protocols, original reports of test results, investigational drug dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the trial) must be kept for the maximum period of time permitted by the institution. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No trial document will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the trial records to another party or move them to another location, written agreement must be obtained from the Sponsor.

12.8 Study Record Retention

In accordance with 21 CFR 312.62(c), the Investigators will retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, the Investigator will retain these records until 2 years after the investigation is discontinued and the US FDA or applicable regulatory authorities are notified.

The Investigators must retain protocols, amendments, IRB/IEC approvals, copies of the Form FDA 1572, signed and dated consent forms, medical records, eCRFs, drug accountability records, all correspondence and any other documents pertaining to the conduct of the study.

If the Principal Investigator moves, withdraws from an investigation or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

12.9 Disclosure of Information

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The Investigator may use this information for the purposes of the study only.

It is understood by the Investigator that the Sponsor will use information developed in this clinical study in connection with the development of GBT440 and, therefore, may disclose it as required to other clinical Investigators and to regulatory agencies. In order to allow the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

12.10 Publication

The Sponsor intends to publish the results of the study as a whole once all subjects have completed the study and the study results have been analyzed.

If the publication includes study Investigators:

- The Investigator may not submit the results of the study for publication without the prior consent of the Sponsor.
- The Investigator or the Sponsor may not submit for publication or present the results of this study without allowing each of the other parties adequate time to review and comment on the pre-publication manuscript.

Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors authorship requirements.

13 ADMINISTRATIVE OBLIGATIONS

13.1 Source Data

Original documents, data, records (e.g., clinic records; laboratory reports; memoranda; subject diaries or evaluation checklists; study drug accountability records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate and complete; microfiches; photographic negatives; microfilm or magnetic media; X-rays; ECGs: questionnaires, subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial) and all relevant sections of the subject's medical records and all other data collection made specific to this trial constitute source documents.

The completed eCRF is not a source document. The Investigator/institution will permit trial-related monitoring, audits, IRB review and regulatory inspection by providing direct access to source documents.

13.2 Data Collection

The Investigator will be responsible for maintaining accurate and adequate case records (source documents) from which data will be transcribed (or if electronically captured [EDC] source data, transferred) to eCRFs designed to record data pertinent to this study. All relevant observations and data related to the study will be so recorded. This will include medical and medication history, physical examinations, a checklist of inclusion and exclusion criteria, investigational treatment administration, and a record of sample collection, clinical assessments, AEs, and final evaluation. The clinical site Clinical Research Associate (CRA) will review all eCRFs and compare data to that contained in clinic notes and subjects' source documents/medical records.

Data collected regarding each subject will be entered into the eCRF. The Investigator will be responsible for the timeliness, completeness, and accuracy of the documentation entered into the eCRFs.

13.3 Monitoring

It is understood that monitors and any authorized personnel contracted to Sponsor may contact and visit the Investigator, and that they will be allowed to inspect the various records of the trial on request (source documents and other pertinent data), provided that subject confidentiality is maintained, and that the inspection is conducted in accordance with local regulations.

It is the monitor's responsibility to inspect the source data at regular intervals throughout the trial to verify adherence to the protocol; the completeness, accuracy and consistency of the data and adherence to Good Clinical Practice guidelines.

The Investigator agrees to co-operate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

13.4 Quality Control and Quality Assurance

Quality Control will be performed according to the Sponsor's or Sponsor's designee internal procedures. A Quality Assurance representative of the Sponsor may audit the study. All necessary data and documents will be made available for inspection, and the Investigator agrees to co-operate with the auditor to ensure that any issues detected during the course of audit are addressed.

14 REFERENCES

American Thoracic Society statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-117.

American Thoracic Society. Pulmonary Function Laboratory Management and American Thoracic Society/ American College of Chest Physicians statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167(2):211-277.

Eaton JW. Extreme altitude: Protective effect of increased hemoglobin-oxygen. Science. 1974;183.

Eaton T, Lewis C, Young P, Kennedy Y, Garrett JE, et al. Long-term oxygen therapy improves health-related quality of life. Respir Med. 2004;98:285-293.

FDA: The Voice of the Patient
www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm440829.pdf

Hebbel RP, Eaton JW, Kronenberg RS, Zanjani ED. Adaptation to altitude in subjects with high hemoglobin oxygen affinity. J Clin Invest. 1978;62(3):593-600.

Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44:1428-1446.

King TE, Bradford WZ, Castro-Bernardini S, et al. A Phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. NEJM. 2014;370 (22);2083-2092.

King TE, Tooze JA, Schwarz MI, et al. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med. 2001;164:1171-1181.

Lehrer-Graiwer J, Howard J, Hemmaway CJ, Awogbade M, Telfer P, Layton M, et al. GBT440, a potent anti-sickling hemoglobin modifier reduces hemolysis, improves anemia and nearly eliminates sickle cells in peripheral blood of patients with sickle cell disease. Oral presentation: American Society of Hematology Annual Meeting; Orlando, FL. 2015.

Michaelson JE, Aguayo SM, Roman J. Idiopathic pulmonary fibrosis; a practical approach for diagnosis and management. Chest. 2000;118:788-794.

National Institute for Health Care and Excellence, nice.org.uk/guidance/cg163.

Nicholson AG, Colby TV, du Bois RM, et al. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med. 2000;162:2213-2217.

Olson AL, Swigris JJ. Idiopathic pulmonary fibrosis; diagnosis and epidemiology. Clin Chest Med. 2012;33:41-50.

Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788-824.

Raghu G, Rochwerg B, Zhang Y. An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. Am J Respir Crit Care Med. 2015;192(2):e3-e19.

Raghu G, Weycker D, Edelsberg, et al. Incidence and prevalence of Idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006;174:810-816.

Richeldi L, du Bois Rm, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. NEJM. 2014:370(22):2071-2082.

Visca D, Montgomery A, de Lauretis A, et al. Ambulatory oxygen in interstitial lung disease. Eur Respir J. 2011;38:987.

Xin G, Dufu K, Hutchaleelaha A, et al. Increased hemoglobin–oxygen affinity ameliorates bleomycin-induced hypoxemia and pulmonary fibrosis. Physiological Reports Published 13 September 2016 Vol. 4 no. e12965 DOI: 10.14814/phy2.12965

Yalcin O, Cabrales P. Increased hemoglobin O2 affinity protects during acute hypoxia. Am J Physiol Heart Circ Physiol. 2012;303(3):H271-81.

15 APPENDICES

APPENDIX A SCHEDULES OF STUDY ASSESSMENTS

Table 15-1 Schedule of Assessments: Part A — 900 mg Dose

	Screening[a]	**Treatment Phase**						**End of Study (EOS)**	**Early Term (ET)[b]**
	Day -21 to Day -1	Day 1	Day 15 ±3	Day 30 ±3	Day 45 ±3	Day 60 ±5	Day 90 ±5	Day 120 ±5	
Procedures and Assessments	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**ET**
Informed consent[c]	X								
Eligibility assessment	X								
Medical history, demographics, and baseline conditions	X	X[d]							
Concomitant medications	X	X	X	X	X	X	X	X	X
Review adverse events[e]	X	X	X	X	X	X	X	X	X
Complete physical exam[f]	X								
Limited physical exam[g]		X	X	X	X	X	X	X	X
Height	X								
Weight	X			X		X	X	X	X
Vital signs[h]	X	X	X	X	X	X	X	X	X
SpO2[i]	X	X	X	X	X	X	X	X	X
12-lead ECG[j]	X						X		X
Urine pregnancy test[k]		X		X		X	X	X	X
Serum pregnancy test[l]	X								
Hematology, serum chemistry, liver function tests	X			X		X	X	X	X
Urinalysis	X					**X**	X		X
Coagulation	X								
Serum erythropoietin		X		X			X	X	X
PK Blood Samples			X	X		X	X	X	

	Screening[a]	**Treatment Phase**						**End of Study (EOS)**	**Early Term (ET)[b]**
	Day -21 to Day -1	Day 1	Day 15 ±3	Day 30 ±3	Day 45 ±3	Day 60 ±5	Day 90 ±5	Day 120 ±5	
Procedures and Assessments	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**ET**
Spirometry	X						X		
DLco	X						X		
Oxygen titration test[m]		X		X			X	X	
Arterial blood gas[m]		X		X			X	X	
6 MWT[m]		X		X			X	X	
Borg scale[m]		X		X			X	X	
SGRQ[n]		X		X		X	X	X	
ATAQ[n]		X		X		X	X	X	
Study drug dispensing to subject		X	X	X	X	X			
Study drug administration at site [o]		X	X	X	X	X	X		
Pedometer dispensing to subject		X							

Abbreviations for Table and Footnotes: ATAQ = A Tool for Assessment of Quality of Life; DLco = lung diffusing capacity measured using carbon monoxide; ECG = electrocardiogram; eCRF = electronic Case Report Form; EOS = end of study; ET = early term; 6MWT = 6-minute walk test; PK = pharmacokinetic; PRO = patient reported outcome; SAE = serious adverse event; SGRQ = St. George's Respiratory Questionnaire; SpO_2 = oxygen saturation measured by pulse oximetry.

Note: All assessments should be performed within the window indicated for each scheduled visit. All assessments should be performed prior to receiving study drug. SGRQ and ATAQ should be performed before all other assessments, followed by 12-lead ECG and then vital signs.

a. All screening evaluations must be completed and reviewed prior to Day 1 (Visit 2) to confirm the subject meets all eligibility criteria prior to dosing.
b. All subjects who discontinue study or study drug prior to study completion and who are unwilling or unable to complete the remaining scheduled visits should return to the study site to complete all ET assessments (see Section 6)
c. Written informed consent must be obtained and documented prior to performing any study-specific screening procedure
d. Demographics, medical history and baseline conditions obtained at screening should be reviewed again and any changes since screening noted in the eCRF
e. After informed consent but prior to randomization only SAEs resulting from a protocol-mandated intervention should be reported. After randomization, all adverse events will be reported until study completion (Day 120).

f. Includes evaluation of the head, eyes, ears, nose and throat and cardiovascular, respiratory, musculoskeletal, gastrointestinal, neurological, dermatologic systems. No rectal or pelvic examination is required. Record any observed abnormalities in the eCRF. At subsequent visits record new or worsened clinically significant findings on the eCRF.
g. Perform a limited, symptom-directed examination as clinically indicated. Record new or worsened clinically significant findings in the eCRF.
h. Includes heart rate, respiratory rate, systolic and diastolic blood pressure and temperature measured in a semi-recumbent or supine position and resting for at least 5 minutes.
i. Performed at the time of Vital Signs assessment, with the subject breathing their supplemental O2 delivered at the usual prescribed rate and after the subject has rested for at least 5 minutes.
j. Perform 12-lead ECG after the subject has been resting in a semi-recumbent or supine position for at least 5 minutes.
k. Perform for all female subjects who are not post-menopausal or surgically sterile. On Day 1, urine pregnancy must be performed before any other assessments. The Investigator is to ensure that the result is negative prior to completing any other study related assessments and prior to administering investigational product to the subject.
l. If a urine pregnancy test on Day 1 is positive, confirm the result with a serum pregnancy test. The serum pregnancy test must be available (and negative) prior to Day 1 dosing.
m. Instructions for per-protocol performance of the oxygen titration and 6-minute walk (and Borg dyspnea scale) tests are provided in the procedure manual.
n. The ATAQ and SGRQ questionnaires should be self-administered by the subject, using the paper forms provided by the Sponsor prior to all other non-PRO assessments and before the subject receives any disease-status information during that assessment.
o. Subjects should <u>not</u> administer study drug on the morning of these study visits. Study drug will be administered by the study staff after completion of all pre-dose assessments.

Guidance for PK Sample Collection:

<u>Pre-dose PK samples</u> should be obtained as soon as possible after PROs, ECG, AEs and Concomitant Medications history and vitals have been obtained and before any other assessments are performed.

<u>Post-dose PK samples</u> should be obtained following administration of study drug. Collection of these PK samples should occur after completion of all other scheduled assessments, including spirometry and DLco, oxygen titration test, 6MWT and investigational product dosing.

These samples may be drawn at the same time as the blood draw for other scheduled laboratory assessments during the visit.

Table 15-2 Schedule of Assessments: Part B — 1500 mg Dose

	Screening[a]	**Treatment Phase**						**End of Study (EOS)**	**Early Term (ET)[b]**
	Day -21 to Day -1	Day 1	Day 15 ±3	Day 30 ±3	Day 60 ±5	Day 90 ±5	Day 105 ±5	Day 120 ±5	
Procedures and Assessments	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**ET**
Informed consent[c]	X								
Eligibility assessment	X								
Medical history, demographics, and baseline conditions	X	X[d]							
Concomitant medications	X	X	X	X	X	X	X	X	X
Review adverse events[e]	X	X	X	X	X	X	X	X	X
Complete physical exam[f]	X								
Limited physical exam[g]		X	X	X	X	X	X	X	X
Height	X								
Weight	X			X	X	X		X	X
Vital signs[h]	X	X	X	X	X	X	X	X	X
SpO_2[i]	X	X	X	X	X	X	X	X	X
12-lead ECG[j]	X					X			X
Urine pregnancy test[k]		X		X	X	X		X	X
Serum pregnancy test[l]	X								
Hematology, serum chemistry, liver function tests	X			X	X	X		X	X
Urinalysis	X				X	X			X
Coagulation	X								
Serum erythropoietin		X		X		X		X	X
PK blood samples		X	X	X	X	X	X	X	
Protein binding sample (plasma)		X	X						

	Screening[a]	**Treatment Phase**						**End of Study (EOS)**	**Early Term (ET)**[b]
	Day -21 to Day -1	Day 1	Day 15 ±3	Day 30 ±3	Day 60 ±5	Day 90 ±5	Day 105 ±5	Day 120 ±5	
Procedures and Assessments	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**ET**
Spirometry	X					X			
DLco	X					X			
Oxygen titration test[m]		X		X		X		X	
Arterial blood gas[m]		X		X		X		X	
6MWT[m]		X		X		X		X	
Borg scale[m]		X		X		X		X	
SGRQ[n]		X		X	X	X		X	
ATAQ[n]		X		X	X	X		X	
End of Treatment Questionnaire [n]						X			
Study drug dispensing to subject		X	X	X	X				
Study drug administration at site [o]		X	X	X	X	X			
Pedometer dispensing to subject		X							
Pedometer return								X	

Abbreviations for Table and Footnotes: ATAQ = A Tool for Assessment of Quality of Life; DLco = lung diffusing capacity measured using carbon monoxide; ECG = electrocardiogram; eCRF = electronic Case Report Form; EOS = end of study; ET = early term; 6MWT = 6-minute walk test; PK = pharmacokinetic; PRO = patient reported outcome; SAE = serious adverse event; SGRQ = St. George's Respiratory Questionnaire; SpO_2 = oxygen saturation measured by pulse oximetry.

Note: All assessments should be performed within the window indicated for each scheduled visit. All assessments should be performed prior to receiving study drug. SGRQ, ATAQ and End of Treatment questionnaires should be performed before all other assessments, followed by 12-lead ECG, AEs/concomitant medication changes, vital signs, bloodwork, pre-dose PK, OTT, 6MWT, study drug administration, and post dose PK.

[a] All screening evaluations must be completed and reviewed prior to Day 1 (Visit 2) to confirm the subject meets all eligibility criteria prior to dosing. SpO_2 assessment for study eligibility (refer to Section 4.1, Inclusion Criteria 5) is to be performed on both the screening and Day 1 visits. If the criteria are not met at either study visit, the subject is to be screen failed without the completion of other study related assessments. If the criteria are met, then the subject should proceed with the remaining assessments.

[b] All subjects who discontinue study or study drug prior to study completion (Day 120) and who are unwilling or unable to complete the remaining scheduled visits should return to the study site to complete all Early Termination (ET) assessments (refer to Section 6).

[c] Written informed consent must be obtained and documented prior to performing any study-specific screening procedure.

[d] Demographics, medical history and baseline conditions obtained at screening should be reviewed again and any changes since screening noted in the eCRF

[e] After informed consent but prior to randomization only serious adverse events (SAEs) resulting from a protocol-mandated intervention should be reported. After randomization, all AEs will be reported until study completion (Day 120).

[f] Includes evaluation of the head, eyes, ears, nose and throat and cardiovascular, respiratory, musculoskeletal, gastrointestinal, neurological, dermatologic systems. No rectal or pelvic examination is required. Record any observed abnormalities in the eCRF. At subsequent visits, record new or worsened clinically significant findings on the eCRF.

[g] Perform a limited, symptom-directed examination as clinically indicated. Record new or worsened clinically significant findings in the eCRF.

[h] Includes heart rate, respiratory rate, systolic and diastolic blood pressure and temperature measured in a semi-recumbent or supine position and resting for at least 5 minutes.

[i] Performed at the time of Vital Signs assessment, with the subject breathing their supplemental O_2 delivered at the usual prescribed rate and after the subject has rested for at least 5 minutes. On Screening and Day 1 visits must be performed prior to other assessments to ensure eligibility.

[j] Perform 12-lead ECG after the subject has been resting in a semi-recumbent or supine position for at least 5 minutes.

[k] Perform for all female subjects who are not post-menopausal or surgically sterile. On Day 1, urine pregnancy must be performed before any other assessments. The Investigator is to ensure that the result is negative prior to completing any other study related assessments and prior to administering investigational product to the subject.

[l] If a urine pregnancy test on Day 1 is positive, confirm the result with a serum pregnancy test. The serum pregnancy test must be available (and negative) prior to Day 1 dosing.

[m] Instructions for per protocol performance of the oxygen titration, 6-minute walk (and Borg Dyspnea Scale) and ABG tests are provided in the procedure manual.

[n] The ATAQ, SGRQ and End of Treatment questionnaires should be self-administered by the subject using the paper forms provided by the Sponsor prior to all other non-PRO assessments and before the subject receives any disease-status information during that assessment. The End of Treatment questionnaire is to be administered at the Day 120 visit, if it was not administered at the Day 90 visit.

[o] Subjects should not administer study drug on the morning of these study visits. The study staff will administer study drug after completion of all pre-dose assessments.

Guidance for PK Sample Collection:

Pre-dose PK samples should be obtained as soon as possible after PROs, ECG, AEs and Concomitant Medications history and vitals have been obtained and before any other assessments are performed.

Post-dose PK samples should be obtained following administration of study drug. Collection of these PK samples should occur after completion of all other scheduled assessments, including spirometry and DLco, oxygen titration test, 6MWT and investigational product dosing.

Protein Binding samples should be obtained at **Day 1** between 2-4 hours post-dose and **Day 15** pre-dose.

These samples may be drawn at the same time as the blood draw for other scheduled laboratory assessments during the visit.

APPENDIX B STRONG INDUCERS OF CYP ISOENZYMES

CYP Enzymes	Medications
CYP3A4/3A5	avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort, mitotane, enzalutamide
CYP2B6	Carbamazepine
CYP2C19	rifampin and ritonavir
CYP2C9	Currently no known inducers

Please note the following: This is not an exhaustive list. For an updated list, refer to the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.