CLINICAL STUDY PROTOCOL

GBT440-006

Study Number	GBT440-006
Study Title	**A Phase II randomized, placebo-controlled study of GBT440 to evaluate the safety, tolerability, pharmacokinetics and effect on hypoxemia in subjects with Idiopathic Pulmonary Fibrosis (IPF)**
Investigational Product	GBT440
IND Number	128319
Sponsor	400 East Jamie Court, Suite 101 South San Francisco, CA 94080 United States of America
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Version / Date	Amendment 3, 21 December, 2016

CONFIDENTIAL

The information in this study protocol is strictly confidential and is available for review to Investigators, study center personnel, the ethics committee and the health authorities. It will not be disclosed to third parties without written authorization from the Sponsor, except to obtain informed consent from persons receiving the study treatment. Once the protocol is signed, its terms are binding for all parties.

SPONSOR STATEMENT OF APPROVAL AND COMPLIANCE

A Phase II randomized, placebo-controlled study of GBT440 to evaluate the safety, tolerability, pharmacokinetics and effect on hypoxemia in subjects with Idiopathic Pulmonary Fibrosis (IPF)

Protocol Number: GBT440-006, Amendment 3

APPROVAL

The signature of the Sponsor representative below represents 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, 21, 312 and 812. GBT will provide the Investigator with all IND status updates pertinent to the conduct of the study.

Sponsor Representative: 

Date: 12/21/2016

Title: Senior Medical Director

INVESTIGATOR STATEMENT OF APPROVAL AND COMPLIANCE

A Phase II randomized, placebo-controlled study of GBT440 to evaluate the safety, tolerability, pharmacokinetics and effect on hypoxemia in subjects with Idiopathic Pulmonary Fibrosis (IPF)

Protocol Number: GBT440-006, Amendment 3

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: _____

Date: _____

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AT	Anaerobic threshold
ATS	American Thoracic Society
ATAQ	A Tool to Assess Quality of Life (ATAQ) in IPF
AUC	Area under the concentration time curve
$AUC_{(0\text{-inf})}$	Area under the concentration-time curve from zero extrapolated to infinity
$AUC_{(0\text{-inf})}/D$	Dose-normalized $AUC_{(0\text{-inf})}$
$AUC_{(0\text{-last})}$	Area under the concentration-time curve from time zero to the time of last quantifiable analyte concentration
$AUC_{(0\text{-tau})}$	Area under the concentration-time curve during a dosing interval
$AUC_{(0\text{-tau})}/D$	Dose-normalized $AUC_{(0\text{-tau})}$
BP	Blood Pressure
BUN	Blood urea nitrogen
C_L	Clearance
C_{max}	Maximum concentration
C_{max}/D	Dose-normalized C_{max}
C_{min}	Minimum concentration
CNS	Central nervous system
CPET	Cardiopulmonary Exercise Testing
CRA	Clinical research associate
CRF	Case Report Form
CrCl	Creatinine clearance
CRO	Contract research organization
CV	Coefficient of variation
CYP	Cytochrome
DL_{CO}	Diffusing Capacity of the Lung for Carbon Monoxide
ECG	Electrocardiogram
eCRF	Electronic case report form
FEV1	Forced expiratory volume in 1 second

FVC	Forced vital capacity
GBT	Global Blood Therapeutics
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
Hb	Hemoglobin
HbA	Adult hemoglobin
HbS	Hemoglobin S
HbsAg	Hepatitis B surface antigen
β HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
hERG	Human Ether-à-go-go-Related Gene
HIV	Human immunodeficiency virus
HV	Healthy volunteers
HR	Heart rate
HRR	Heart rate recovery
HRRes	Heart rate reserve
IB	Investigator 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
LC-MS	Liquid chromatography-tandem mass spectrometry
MDRD eGFR	Modification of diet in renal disease estimate glomerular filtration rate
MedDRA	Medical dictionary for regulatory activities
6MWT	6-minute walk test
NAC	N-acetylcysteine
OEC	Oxygen equilibrium curve
P20	Partial pressure of oxygen at which hemoglobin is 20% saturated

p50	Partial pressure of oxygen at which hemoglobin is 50% saturated
PD	Pharmacodynamic
PDE	phosphodiesterase
PK	Pharmacokinetic
PRO	Patient reported outcome
PT	Prothrombin time
PTT	Partial thromboplastin time
ODC	Oxy-hemoglobin dissociation curve
QTcF	Corrected QT interval using the Fridericia formula
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SaO2	Arterial oxygen saturation
SCD	Sickle cell disease
SD	Standard deviation
SGRQ	St George's Respiratory Questionnaire
SMC	Safety Monitoring Committee
SpO_2	Peripheral capillary oxygen saturation
$t_{1/2}$	Apparent terminal half life
t_{max}	Time of maximum concentration
t_{min}	Time of minimum concentration
UCSD SOBQ	University of California, San Diego Shortness of Breath Questionnaire
ULN	Upper limit of normal
VAS	Visual analog scale
VE/VCO2 slope	Slope of relation between minute ventilation and CO2 production
VO2 peak	Peak oxygen consumption
VO2 peak/kg	Peak oxygen consumption/kg
Vss	Volume at steady state
WBC	White blood cell
λz	Apparent terminal rate constant

PROTOCOL SYNOPSIS

Protocol Title	A Phase II randomized, placebo-controlled study of GBT440 to evaluate the safety, tolerability, pharmacokinetics and effect on hypoxemia in subjects with Idiopathic Pulmonary Fibrosis (IPF)
Protocol Number	GBT440-006
Sponsor	Global Blood Therapeutics 400 East Jamie Court Suite #101 South San Francisco, CA 94080
Study Drug	GBT440 capsules: 300 mg strength, administered orally. Matching placebo, administered orally.
Objectives	**Primary** • To evaluate the safety and tolerability of multiple doses of GBT440 administered to subjects with IPF. **Secondary** • To evaluate the effect of GBT440 on oxygen saturation at Days 15 and 28 compared to baseline during 6-minute walk testing (6MWT). • To evaluate the pharmacokinetic (PK) parameters of GBT440 in plasma and whole blood. **Exploratory** • To evaluate the effect of GBT440 on distance walked during the 6MWT at Days 15 and 28 compared to baseline. • To evaluate the effect of GBT440 on IPF-related symptoms using patient reported outcomes (PROs) at Day 28 compared to baseline. • To evaluate the effect of GBT440 on cardiopulmonary exercise testing (CPET) parameters at Day 29 compared to baseline. • To evaluate pulmonary function, including assessment of spirometry and Diffusing Capacity of the Lung for Carbon Monoxide (DLco) at Day 28 compared to baseline. • To evaluate the PK-pharmacodynamic (PD) relationship of GBT440 at Days 15 and 28 compared to baseline.
Study Design	This study is a randomized, placebo-controlled trial that will be conducted in two parts. Together, Parts A and B will provide safety and efficacy data across a range of GBT440 doses that are expected to improve oxygen saturation in the enrolled subjects. • In Part A, eligible IPF subjects will be randomized 1:1:1 to receive GBT440 900 mg (n = 6) or 600 mg (n = 6), or placebo (n = 6) administered orally as 300 mg capsules once daily for 28 days. The study site, subjects and Sponsor will be blinded to study treatment. • In Part B eligible IPF subjects will be randomized 3:1:1 to receive GBT440 1500 mg (n = 9) or 600 mg (n = 3), or placebo (n = 3) administered orally as 300 mg capsules once daily for 28 days in

	which the study site and subjects are blinded to study treatment. The Sponsor will be unblinded to study treatment. Subjects will participate in the study for approximately 79 days: screening (up to 21 days), treatment period (28 days) and follow-up period (30 days) with a total of 9 study site visits. The screening period for each subject commences when the subject undergoes the first study-specific screening assessment and must be completed and evaluated before randomization (Day 1). Subjects may be rescreened up to two times, if deemed appropriate by the Principal investigator. The rescreening visit should not occur sooner than 10 calendar days after the failed screening visit. Patients on a stable dose of pirfenidone or nintedanib and/or N-acetyl cysteine at screening are eligible for entry into the study. A Safety Monitoring Committee (SMC) is planned to review all safety data on an ongoing basis throughout the study. If the SMC does not identify any clinically significant safety concerns in Part A, following review of data from approximately 18 subjects who have completed Day 15, the Sponsor will initiate Part B of the study and randomise up to an additional 15 subjects, to the three study treatment arms to better characterize the safety, tolerability and/or potential treatment response of GBT440 in subjects with IPF. The dose levels predicted to achieve the hemoglobin (Hb) modification targets of ~20% to ~50% in IPF subjects are based on clinical PK and PD data from study GBT440-001. Dose levels of 600 mg or 900 mg per day administered to healthy subjects for 15 days resulted in a mean Hb modifications of 24% and 38%, respectively. A dose level of 300 mg per day resulted in a mean Hb modification of 11%, which is below the PD effect that showed benefit in animal models of hypoxemia. A dose of 1500 mg is expected to achieve a Hb modification target of ~50%. Part A Treatment: • GBT440 900 mg: 3 GBT440 300 mg capsules. • GBT440 600 mg: 2 GBT440 300 mg capsules and 1 placebo capsule. • Placebo: 3 placebo capsules. Part B Treatment: • GBT440 1500 mg: 5 GBT440 300 mg capsules • GBT440 600 mg: 2 GBT440 300 mg capsules and 3 placebo capsules. • Placebo: 5 placebo capsules. In Part A two unblinded interim analyses of the primary and secondary endpoints are planned: i) when approximately 9 subjects have completed their Day 28 study visit and ii) when approximately 18 subjects have completed their Day 15 study visit.

Number of Subjects	In Part A, a total of approximately 18 subjects will be randomized 1:1:1 to either: 900 mg GBT440, 600 mg GBT440 or placebo. In Part B, up to an additional 15 subjects will be randomized 3:1:1 to either: 1500 mg GBT440, 600 mg GBT440 or placebo.
Replacement of Subjects	Subjects who do not complete at least 10 days of dosing for reasons unrelated to toxicity may be replaced.
Number of Centers	The study will be conducted at approximately 10–15 clinical sites in the United States
Duration of Study Participation	Approximately 79 days, including screening, treatment and follow-up periods
Study Population	Inclusion Criteria 1. Able and willing to provide signed informed consent to participate in this study. 2. Documented diagnosis of IPF, as indicated in the ATS/ERS/JRS/ALAT 2011 guidelines. 3. Adult males or females aged 45-80 years inclusive at randomization 4. Oxygen saturation (SpO_2) ≥ 88 % by pulse oximetry while breathing room air at rest 5. Oxygen saturation (SpO_2) <88% and at least a 5% absolute decrease during the baseline 6-minute walk test (6MWT) which is sustained for at least 10 seconds 6. Able to walk at least 100 meters at completion of the baseline 6 MWT 7. Weight ≥ 40 kg 8. Subject is seronegative for recent hepatitis A (IgM anti-HAV), hepatitis B surface antigen (HBsAg), hepatitis C (HCV) antibody (anti-HCV), and human immunodeficiency virus antibody (anti-HIV) within 3 months of screening. 9. Able, in the Investigator's opinion, to complete the 6MWT unassisted at baseline and Day 15 and Day 28 and comply with the study procedures, including attending all assessment visits and adhering to all study requirements and restrictions. 10. Male or female of child bearing potential willing and able to use highly effective methods of contraception from study start to 3 months after the last dose of study drug. Exclusion Criteria 1. FEV1/FVC <70%. 2. Requires supplemental oxygen therapy at rest. 3. History of other interstitial lung diseases including but not limited to radiation, drug toxicity, sarcoidosis, hypersensitivity pneumonia, bronchiolitis obliterans, organizing pneumonia. 4. History of clinically significant environmental exposure known to cause pulmonary fibrosis including but not limited to drugs (e.g., methotrexate or amiodarone), asbestos, beryllium, radiation and domestic birds.

	5. History of other medical conditions that are known or may result in interstitial lung disease. For example, any connective tissue disease including but not limited to scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus and rheumatoid arthritis. 6. AST, ALT or total Bilirubin >2 × ULN. 7. Creatinine Clearance (CrCl) <30 mL/min/1.73 m^2, calculated using the Modification of Diet in Renal Disease estimated Glomerular Filtration Rate (MDRD eGFR). 8. Significant polycythemia defined as hemoglobin value >18 mg/dL. 9. ECG with a QTcF >450 ms (males) or QTcF >470 ms (females). If ventricular pacing is noted on ECG, then QTcF intervals will not be calculated. 10. Family or personal history of congenital long QT syndrome. 11. Female who is breast-feeding or pregnant. 12. 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, or Stage 1 uterine cancer. 13. Subject has used any of the following therapies within 30 days of screening: • Any cytotoxic, immunosuppressive or cytokine-modulating therapy including but not limited to: azathioprine, bosentan, ambrisentan, cyclophosphamide, cyclosporine, etanercept, iloprost, infliximab, leukotriene antagonists, methotrexate, mycophenolate, tacrolimus • Imatinib mesylate, interferon gamma-1b, tyrosine kinase inhibitors (excluding nintedanib) 14. Pulmonary hypertension requiring active therapy including but not limited to endothelin receptor inhibitors or PDE inhibitors (e.g., sildenafil, tadalafil). • Note: intermittent use of a PDE inhibitor for erectile dysfunction may be allowed after approval by the Medical Monitor. 15. Hospitalization due to an exacerbation of IPF within 30 days of screening 16. Subject plans to begin or has commenced pulmonary rehabilitation within 30 days of screening • Subjects 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 17. Corticosteroids (>10 mg per day of prednisone or an equivalent) within 30 days of screening.

	18. Current smoker (including use of eCigarettes or vaporizing) or history of smoking within 3 months from screening. 19. Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, sinusitis, urinary tract infection or cellulitis, within 14 days of screening 20. Active tuberculosis requiring treatment within the last 12 months • Testing for latent tuberculosis is not required 21. Currently or, in the opinion of the investigator, soon to be listed for lung transplant. 22. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within 6 months of screening including but not limited to the following: • Unstable angina pectoris or myocardial infarction or elective coronary intervention • Congestive heart failure requiring hospitalization • Uncontrolled clinically significant arrhythmias 23. Any condition possibly affecting drug absorption, such as previous surgery on the stomach or small intestine. 24. 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). 25. Known hypersensitivity to any component of the study drug. 26. Subject who, for any reason, is deemed by the investigator to be inappropriate for this study; or has any condition (such as addictive or psychosocial issues) which would confound or interfere with the evaluation of the safety, tolerability, or PK of the investigational drug; or is unable to comply with the study protocol. 27. 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
Study Evaluations	<u>Safety Assessments</u> 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 (collected in triplicate), safety labs, urinalysis, concomitant medication usage and adverse event monitoring.

	Safety laboratory assessments include: hematology, serum chemistry, urinalysis, coagulation panel, Hepatitis A, B, C and HIV serologies and pregnancy tests. Clinical Assessments *Spirometry and Diffusing Capacity of the Lung for Carbon Monoxide (DLco) Measurements* All equipment, procedures, and personnel qualifications for the assessment of lung function are based on the recommendations of the American Thoracic Society (ATS 2005) and will be performed at each site using local equipment. Spirometry measurements will include FVC, FEV_1 and flow-volume loops. Pre and 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 *Oxygen Saturation* During screening and with all scheduled vital sign assessments resting, room air oxygen saturation (SpO_2) will be measured by pulse oximetry (provided by the Sponsor) whilst the subject is seated and resting for at least 5 minutes. 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 resting. SpO_2 will be also be collected as part of the 6MWT and during cardio-pulmonary exercise testing. *6-Minute Walk Test (6MWT) and Borg Scale of Perceived Exertion* Functional exercise capacity will be evaluated at baseline, Days 15, 28 and 58 using the 6-minute walk test. The 6MWT will be performed without the subject using supplementary oxygen. Oxygen may be used at any time during the 6MWT, if in the opinion of the Investigator or testing technician it is required for safety reasons. The 6MWT should then be stopped. Guidelines developed by the ERS/ATS will be used for conducting the test and interpreting the results (ATS 2002 and Holland 2014). As part of the 6MWT SpO_2, heart rate and the Borg dyspnea scale will be measured prior to starting the test, during the test, at completion of the test, 1 minute and 2 minutes after test completion. *Cardiopulmonary Exercise Testing (CPET)* Symptom-limited cardiopulmonary exercise testing using a bicycle ergometer will be performed at baseline and Day 29. At baseline and during the exercise period the collected data will include but is not limited to: SpO_2 and arterial blood gases, VO_2 max, ventilation and lactate thresholds. Guidelines developed by ATS and American College of Chest Physicians will be used for conducting the test and interpreting the results (ATS 2003). *St George's Respiratory Questionnaire (SGRQ)* The SGRQ is a symptom-specific 2-part, subject self-administered questionnaire that assesses shortness of breath while doing a variety of activities of daily living. This questionnaire comprises three domains: symptoms, activity and impact. Paper questionnaires will be provided to

	sites prior to subject enrollment *University of California, San Diego Shortness of Breath Questionnaire (UCSD)* The UCSD is a 24-item assessment of breathlessness associated with various activities of daily living. The response for each item is measured on a 5-point Likert scale from 0 (none at all) to 5 (maximal or unable to perform). Refer to the Procedure Manual for a copy of the questionnaire. Paper questionnaires will be provided to sites prior to subject enrollment. *Borg Dyspnea Scale* The Borg Dyspnea scale is a one-item assessment, self-administered by the patient administered as part of the 6 MWT. The instrument will be used to assess dyspnea from the patient's perspective. The Scale ranges from 0 (Nothing at all) to 10 (Absolute maximum/Highest possible). See Procedure Manual for a copy of the assessment. A paper scale will be supplied to sites prior to subject enrollment. *A Tool to Assess Quality of Life (ATAQ) in IPF* ATAQ questionnaires (IPF Symptoms Questionnaire and IPF Impacts Questionnaire) will be administered in Part B of this study. *End of Study Questionnaire* The end of study questionnaire is an 8-item 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 58 visit. The survey is to be completed by subjects enrolled under Part B of the trial. *Visual Analog Scale (VAS) for Cough Severity* Cough will be assessed using a VAS in which the subject will indicate the severity of their cough by drawing a mark on a 100 mm scale, which ranges from 0 - "no cough" to 100 mm - "worst cough severity". A paper scale will be supplied to sites prior to subject enrollment. <u>Pharmacokinetic Assessments</u> Plasma and whole blood concentrations of GBT440 will be measured. PK samples will be collected at the following times: on <u>Days 1 and 28</u>: pre-dose, and 2 hours post dose (+/- 15 minutes); <u>Day 2</u>: 24 hours (+/- 2 hours) after the Day 1 dose *and* prior to receiving the Day 2 dose; <u>Days 8 and 15:</u> pre-dose only; during follow-up on Days 45 and 58.
Restricted Concomitant Therapy	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 (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 (e.g., alfentanil, dihdroergotamine, ergotamine, fentanyl, pimozide, quindine; 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.
Statistical Methods	Sample Size The sample size in this study was not selected based on statistical considerations but to determine preliminary safety, tolerability, PK, laboratory and clinical effects of GBT440 in IPF subjects. Study Endpoints Primary Endpoint • Treatment-emergent adverse events and tolerability. Secondary Endpoints • Change and percentage change from baseline in resting SpO2 at Days 15 and 28 measured prior to beginning the 6MWT. • Change and percentage change from baseline in end-of-6MWT SpO2 at Days 15 and 28. • Change and percentage change from baseline in lowest SpO2 value measured during the 6MWT at Days 15 and 28. • Pharmacokinetic (PK) parameters of GBT440 in plasma and whole blood, including but not limited to maximum concentration (C_{max}), minimum concentration (C_{min}) at steady state in GBT440 treated subjects. Exploratory Endpoints • Change and percentage change from baseline in distance walked during the 6MWT at Days 15 and 28. • Time to first SpO2 <88% that is sustained for at least 10 seconds during the 6MWT at Days 15 and 28. • Area under the SpO_2 curve (AUC) during the 6MWT measured at baseline, Day 15 and Day 28. • Change from baseline in PRO scores using SGRQ, UCSD, ATAQ (only subjects enrolled in Part B) and the Borg Scale of Perceived Exertion questionnaires and cough VAS at Days 15 and 28. • Change and percentage change from baseline in cardiopulmonary exercise testing parameters at Day 29. • Change and percentage change from baseline in lung function, including FVC and DL_{CO} at Day 28. • PK/PD relationship in subjects receiving GBT440 from Baseline to Day 15 and Day 28.

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 3-5 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 50-80 years, with a median age of 65 at diagnosis [Raghu 2006]. The natural course of IPF is variable. As the interstitial fibrosis and architectural distortion advance, the lung becomes increasingly non-compliant, and the work of breathing and dyspnea increase. The lungs lose their ability to transfer oxygen into the bloodstream resulting in hypoxemia, tissue hypoxia, and ultimately organ dysfunction and symptoms. Subjects with IPF typically experience slowly progressive worsening of lung function over time, with the development of significant co-morbidities, the use of supplemental oxygen and frequent hospitalizations in the late stage of the disease [Raghu 2011]. Supplemental oxygen relieves dyspnea, prevents secondary pulmonary hypertension and improves functional status, but requires equipment for oxygen administration which can limit patient mobility and quality of life.

There are two marketed products available for the treatment of IPF, nintedanib and pirfenidone which were added to the American Thoracic Society treatment recommendations in 2015 [Raghu 2015]. In clinical studies, these products demonstrated an effect on forced vital capacity and decline in lung function, but did not show an effect on survival or disease modification. Furthermore, these therapies do not improve hypoxemia nor did they clearly or consistently improve disease symptoms such as dyspnea [Richeldi 2014, King 2014]. IPF remains a disease with high unmet medical need requiring novel therapies that address not only the underlying fibrosis but also secondary co-morbidities and that provide improvement in the 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 Hb α chain, and thus has the same pharmacodynamics effect on normal adult hemoglobin (HbA) than on sickle hemoglobin (HbS). In SCD, GBT440's effect on HbS was expected to decrease red blood cell sickling, which was confirmed in preliminary Phase I/II data [Lehrer-Graiwer 2015]. Likewise for IPF, GBT440's effect on HbA is expected to increase oxygen uptake in the lungs, improve hypoxemia and oxygen delivery to tissues and in turn provide significant benefit to IPF patients.

In IPF, hypoxemia results from ventilation-perfusion mismatch and inefficient gas exchange at the alveolar-capillary barrier. The resultant reduced oxygen saturation (SpO_2) leads to

insufficient oxygen delivery to tissues and tissue hypoxia, and in turn numerous adverse systemic effects including exercise intolerance with associated desaturation and pulmonary hypertension. As demonstrated by the use of supplemental oxygen therapy, improving oxygenation clearly provides clinical benefit; with improvement in dyspnea, functional capacity, quality of life, and prevention of disease associated complications. [Eaton. 2004] Based on it's mechanism of action, GBT440 is expected to increase Hb-O_2 saturation at low alveolar oxygen tensions and provide similar benefit to patients with IPF. 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. [Eaton 1974, Yalcin and Cabrales 2012] Based on these observations and its ability to safely increase Hb oxygen affinity in humans (both healthy subjects and patients with SCD in the ongoing GBT440-001 study), GBT440 may improve arterial oxygenation, tissue oxygen delivery, symptoms and functional status in subjects with IPF.

1.3. Rationale for Study

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 O_2 saturation, resulting in improved oxygen delivery to tissues. A key therapeutic goal for IPF patients with GBT440 is to reduce hypoxemia and improve the associated debilitating symptoms and functional impairment. Supplemental oxygen therapy is a well-established treatment in IPF and other chronic hypoxemic pulmonary diseases where it improves symptoms, functional status and (in the case of Chronic Obstructive Pulmonary Disease) improves survival. Supplemental oxygen therapy has disadvantages, however, which can negatively impact patient quality of life including the burden and decreased mobility from the required oxygen delivery devices, local complications, poor compliance and inadequate symptomatic relief. GBT440 therapy may be able to provide many of the same clinical benefits of oxygen therapy without the negative aspects of oxygen supplementation. GBT440 could also be useful as an adjunct to oxygen therapy in more severe subjects who are not adequately oxygenated despite noninvasive oxygen therapy or to allow the use of lower flow, more convenient oxygen equipment for the same clinical benefit. This study will gather preliminary data, across a range of GBT440 doses, to determine whether GBT440 could improve: oxygen saturation at rest and with exercise, IPF-related symptoms and exercise capacity.

GBT440 has been administered to healthy subjects and subjects with SCD. Overall, multiple doses of GBT440 have been well tolerated across a broad range of doses (300 mg–1000mg) for up to 90 days. Results from this study will inform future development of GBT440 in IPF subjects.

1.4. Nonclinical Data

An overview of the key nonclinical data is provided below. For a more detailed discussion of the nonclinical pharmacology, pharmacokinetic (PK) and toxicology studies conducted to date, please 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 hemoglobin 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. These in vivo studies demonstrated that pharmacologically increasing Hb-O_2 affinity in these mouse models of pulmonary hypoxemia resulted in improved O_2 saturation, translating into improved physiologic endpoints and survival.

1.4.2. Safety Pharmacology

Safety assessments of GBT440 in three 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. Pharmacokinetics

Pharmacokinetic (PK) evaluation showed that GBT440 had low blood clearance (CL), low blood V_{ss}, and long terminal t½ 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 to date have been conducted primarily in healthy subjects and subjects with SCD. They include an ongoing Phase I/II study (GBT440-001), Phase II adolescent SCD study (GBT440-007) and 8 (4 complete and 4 ongoing) Phase I clinical pharmacology studies in healthy subjects. GBT440 is also being evaluated in an ongoing Phase II study in IPF subjects using oxygen at rest (GBT440-026).

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 of GBT440 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 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.

The eight clinical pharmacology studies (GBT440-002, GBT440-003, GBT440-004, GBT440-005, GBT440-008, GBT440-017, GBT440-018 and GBT440-019) are evaluating the absorption, metabolism, excretion, food effect, relative bioavailability and drug-drug- interactions (DDI) of GBT440.

The Phase II IPF study (GBT440-026) is an open label trial evaluating the safety of GBT440 and its effects on oxygen saturation and supplemental oxygen requirements in IPF subjects who use oxygen at rest. GBT440 is being dosed at 900 mg orally daily for 90 days.

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

1.5.1. Safety Findings in Study GBT440-001

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.

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); one event of presumed infection with hemolysis (Grade 2) (GBT440); one event of an ovarian cyst (Grade 3), occurring after the last dose of study drug (GBT440) and one 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 C_{max} and AUC increased proportionally with study drug dose for both single or multiple doses. 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 GBT440 doses for investigation in IPF patients is based on pharmacodynamic (PD) targets that are expected to correspond to an increase in Hb-O_2 affinity which may result in a clinically significant increase in oxygenation. These PD targets are derived from data from three nonclinical pharmacology studies that included a hypoxia challenge model and two models of pulmonary hypoxemia (refer to the IB for details of these studies). Based on the in vivo data the lower limit for treatment response during exercise-induced desaturation is expected to be ~20% Hb occupancy by GBT440.

The dose levels predicted to achieve the Hb modification targets of ~20% to ~50% in IPF subjects are based on clinical PK and PD data from study GBT440-001. Dose levels of 600 mg or 900 mg per day administered to healthy subjects for 15 days resulted in a mean Hb modifications of 24% and 38%, respectively. A dose level of 300 mg per day resulted in a mean Hb modification of 11%, which is below the PD effect that showed benefit in animal models of hypoxemia.

The safety of the proposed doses of 600 mg and 900 mg in the initial cohort (Part A) of approximately 18 subjects and the safety of pursuing parallel dosing in this study are based on the totality of available nonclinical and clinical safety data. The expansion Cohort (Part B) of 15 subjects will have 3 dose arms: 1500 mg, 600 mg and placebo. Addition of a higher dose is supported by: the acceptable safety profile collected from the Part A subjects dosed to date in this study; review by the Safety Monitoring Committee of safety data from 12 subjects who completed up to 28 days and 16 subjects who completed 15 days of dosing in Part A and Safety Monitoring Committee agreement to proceed with the evaluation of GBT440 1500 mg; continued favorable safety profile in ongoing studies evaluating GBT440 in subjects with SCD, including continued dosing for up to 6 months; and an anticipated dose-dependent improvement in oxygen saturation. Guidelines for the safety review of Part A and Part B of the trial are outlined in the Safety Monitoring Committee section (Section 10.1).

1.5.4. Potential Risk of GBT440 Treatment

1.5.4.1. Tissue Hypoxia

There is a theoretical risk of tissue hypoxia in subjects treated with GBT440 based on the mechanism of action and potential associated 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 as measured by erythrocytosis, increased resting heart rate and erythropoietin and laboratory tests indicating organ injury (e.g. liver aminotransferases). To date, none of these findings have been documented in Part A subjects dosed in this study.

1.5.5. Conclusions Based on Clinical Study Data

The emerging experience from clinical studies in healthy volunteers, SCD and approximately 16 IPF subjects from Part A of this study (reviewed by the SMC), having received GBT440 across a wide range of doses, has shown that GBT440 is well tolerated and no clinically significant safety signal has been identified. Based on these results it is anticipated that GBT440 will have favorable benefit-to-risk profile in IPF subjects, enrolled in both Parts A and B of this study.

The steady-state exposure and PD effect, which are predicted for the 600 mg and 900 mg dose levels in Part A, have been demonstrated to be safe and tolerated in the healthy subjects treated with GBT440 for 15 days in the Phase I/II study (GBT440-001). The 1500 mg dose to be included in Part B is supported by the safety profile of the subjects in the 600 mg and 900 mg dose arms in this study and an anticipated dose-dependent improvement in oxygen saturation. Furthermore, safety experience in SCD subjects treated for 90 days supports the proposed 28 day treatment duration in IPF subjects.

2. STUDY OBJECTIVES

2.1. Primary Objective

To evaluate the safety and tolerability of multiple doses of GBT440 administered to subjects with IPF

2.2. Secondary Objectives

- To evaluate the effect of GBT440 on oxygen saturation at Days 15 and 28 compared to baseline during the 6-minute walk testing (6MWT).
- To evaluate the pharmacokinetic (PK) parameters of GBT440 in plasma and whole blood.

2.3. Exploratory Objectives

- To evaluate the effect of GBT440 on distance walked during the 6MWT at Days 15 and 28 compared to baseline.
- To evaluate the effect of GBT440 on IPF-related symptoms using patient reported outcomes (PROs) at Day 28 compared to baseline.
- To evaluate the effect of GBT440 on cardiopulmonary exercise testing parameters at Day 29 compared to baseline.
- To evaluate pulmonary function, including assessment of spirometry and Diffusing Capacity of the Lung for Carbon Monoxide (DLco) at Day 28 compared to baseline.
- To evaluate the PK-PD relationship of GBT440 at Days 15 and 28 compared to baseline.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This study is a randomized, placebo-controlled trial that will be conducted in two parts. Together, Parts A and B will provide safety and efficacy data across a range of GBT440 doses that are expected to improve oxygen saturation in the enrolled subjects.

- In Part A (Figure 1) eligible IPF subjects will be randomized 1:1:1 to receive GBT440 900 mg (n = 6) or 600 mg (n = 6), or placebo (n = 6) administered orally as 300 mg capsules once daily for 28 days. The study site, subjects and Sponsor will be blinded to study treatment.
- In Part B (Figure 2) eligible IPF subjects will be randomized 3:1:1 to receive GBT440 1500 mg (n = 9) or 600 mg (n = 3), or placebo (n = 3) administered orally as 300 mg capsules once daily for 28 days in which the study site and subjects are blinded to study treatment. The Sponsor will be unblinded to study treatment.

A signed and dated informed consent form (ICF) must be obtained before any screening procedures or 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 randomization (Day 1). Subjects may be rescreened up to two times, if deemed appropriate by the Principal investigator. The rescreening visit should not occur sooner than 10 calendar days after the failed screening visit.

Patients on a stable dose of pirfenidone or nintedanib and/or N-acetyl cysteine are eligible for entry into the study.

After the Screening visit the study includes the following study periods:

- Treatment period (28 days)**:** subjects will be randomized (1:1:1) to one of three treatment groups in Part A (Figure 1) and randomized (3:1:1) to one of three treatment groups in Part B (Figure 2); subjects will receive:

  Part A:
  - Group 1: GBT440 900 mg; three 300 mg GBT440 capsules, daily orally.
  - Group 2: GBT440 600 mg; two 300 mg GBT440 capsules and one placebo capsule, daily orally.
  - Group 3: Placebo: three placebo capsules, daily orally.

  Part B:
  - Group 1: GBT440 1500 mg; five, 300 mg GBT440 capsules, daily orally.
  - Group 2: GBT440 600 mg; two 300 mg GBT440 capsules and three placebo capsule, daily orally.
  - Group 3: Placebo: five placebo capsules, daily orally.

- Safety follow up (30 days)**:** safety will be assessed for at least 5 half-lives after the last dose of GBT440.

Figure 1 Study Design – Part A

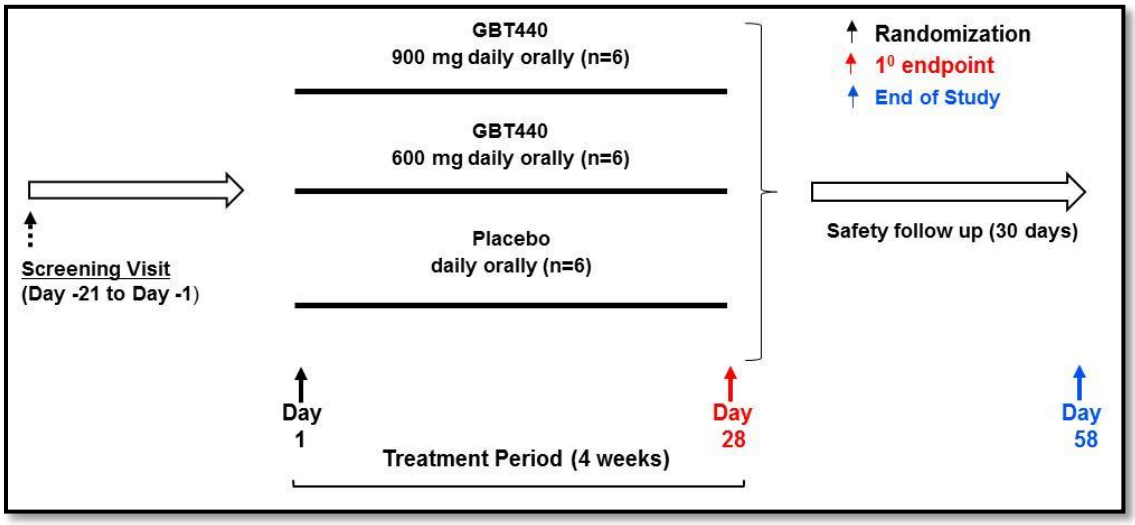
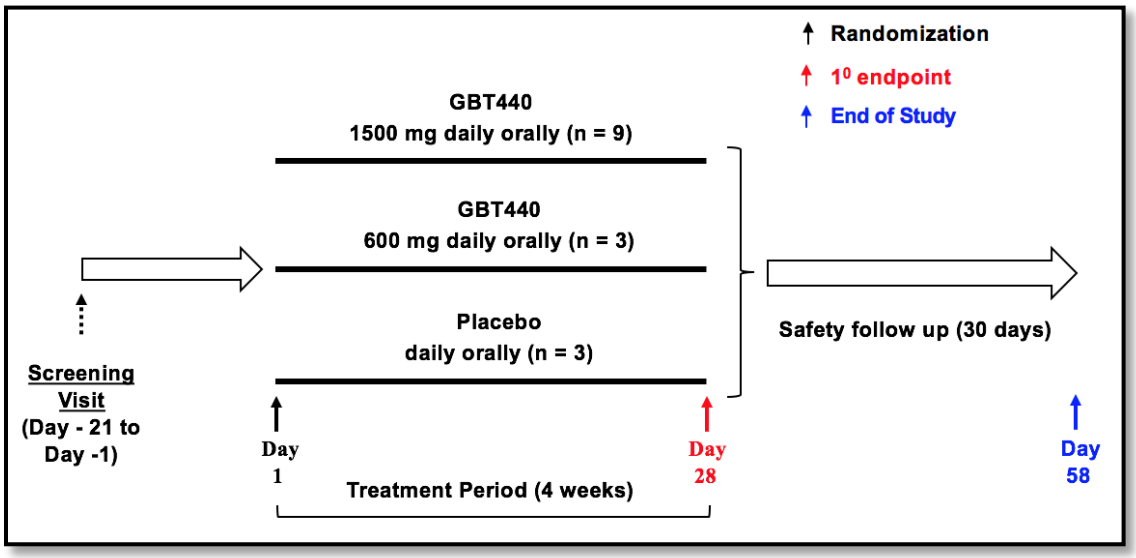


Figure 2 Study Design – Part B



Subjects who do not complete at least 10 days of dosing for reasons unrelated to toxicity may be replaced.

In Part A, two unblinded interim analyses of the primary and secondary endpoints are planned: i) when approximately 9 subjects have completed their Day 28 study visit and ii) when approximately 18 subjects have completed their Day 15 study visit.

A Safety Monitoring Committee (SMC) is planned to review all safety data on an ongoing basis throughout the study (refer to Section 10.1). If the SMC does not identify any clinically significant safety concerns in Part A, following review of data from approximately 18 subjects who have completed Day 15, the Sponsor will initiate Part B of the study and randomise up to an additional 15 subjects, to the three study treatment arms to better

characterize the safety, tolerability and/or potential treatment response of GBT440 in subjects with IPF.

In the eventuality that one treatment arm is discontinued, subjects may be randomised 1:1 to the remaining study drug treatment group or placebo. Therefore, the trial size is approximately 33 subjects.

The end of the study is defined as the date when the last patient last visit occurs, which is expected to be approximately 58 days after the last patient is randomised.

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 treatment-emergent adverse events and tolerability.

3.2.2. Secondary Endpoints

- Change and percentage change from baseline in resting SpO_2 at Days 15 and 28 measured prior to beginning the 6MWT.
- Change and percentage change from baseline in end-of-6MWT SpO_2 at Days 15 and 28.
- Change and percentage change from baseline in lowest SpO_2 value measured during the 6MWT at Days 15 and 28.
- Pharmacokinetic (PK) parameters of GBT440 in plasma and whole blood, including but not limited to maximum concentration (C_{max}), minimum concentration (C_{min}) at steady state in GBT440 treated subjects.

3.2.3. Exploratory Endpoints

- Change and percentage change from baseline in distance walked during the 6MWT at Days 15 and 28.
- Time to first SpO_2 <88% that is sustained for at least 10 seconds during the 6MWT at Days 15 and 28.
- Area under the SpO_2 curve (AUC) during the 6MWT measured at baseline, Day 15 and Day 28.
- Change from baseline in PRO scores using SGRQ, UCSD, A Tool to Assess Quality of Life (ATAQ) in IPF (only subjects enrolled in Part B), and the Borg Scale of Perceived Exertion questionnaires and cough VAS at Days 15 and 28.
- Change and percentage change from baseline in cardiopulmonary exercise testing parameters at Day 29.
- Change and percentage change from baseline in lung function, including FVC and DL_{CO} at Day 28.
- PK/PD relationship in subjects receiving GBT440 from Baseline to Days 15 and 28

4. STUDY POPULATION

4.1. Inclusion Criteria

All subjects must meet the following inclusion criteria:

1. Able and willing to provide signed informed consent to participate in this study.
2. Documented diagnosis of IPF, as indicated in the ATS/ERS/JRS/ALAT 2011 guidelines.
3. Adult males or females aged 45–80 years inclusive at randomization.
4. Oxygen saturation (SpO_2) ≥88 % by pulse oximetry while breathing room air at rest.
5. Oxygen saturation (SpO_2) <88% and at least a 5% absolute decrease during the baseline 6MWT which is sustained for at least 10 seconds.
6. Able to walk a total of at least 100 meters at completion of the baseline 6MWT.
7. Weight ≥ 40 kg
8. Subject is seronegative for hepatitis A (IgM anti-HAV), hepatitis B surface antigen (HBsAg), hepatitis C antibody (anti-HCV), and human immunodeficiency virus antibody (anti-HIV) within 3 months of screening.
9. Able, in the Investigator's opinion, to complete the 6MWT unassisted at baseline and Day 15 and Day 28 and comply with the study procedures, including attending all assessment visits and adhering to all study requirements and restrictions.
10. Male or female of child bearing potential willing and able to use highly effective methods of contraception from study start to 3 months after the last dose of study drug.

4.2. Exclusion Criteria

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

1. FEV1/FVC <70%
2. Requires supplemental oxygen therapy at rest.
3. History of other interstitial lung diseases including but not limited to radiation, drug toxicity, sarcoidosis, hypersensitivity pneumonia, bronchiolitis obliterans or organizing pneumonia.
4. History of clinically significant environmental exposure known to cause pulmonary fibrosis, including but not limited to drugs (e.g. methotrexate or amiodarone), asbestos, beryllium, radiation and domestic birds.
5. History of other medical conditions that are known or may result in interstitial lung disease. For example, any connective tissue disease including but not limited to scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus and rheumatoid arthritis.
6. AST, ALT or total Bilirubin >2 × ULN

7. Creatinine Clearance (CrCl) <30 mL/min/1.73 m^2, calculated using the Modification of Diet in Renal Disease estimated Glomerular Filtration Rate (MDRD eGFR).
8. Significant polycythemia defined as hemoglobin value >18 mg/dL.
9. ECG with a QTcF >450 ms (males) or QTcF >470 ms (females).
    - If ventricular pacing is noted on ECG, then QTcF intervals will not be calculated
10. Family or personal history of congenital long QT syndrome.
11. Female who is breast-feeding or pregnant.
12. 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, or Stage 1 uterine cancer.
13. Subject has used any of the following therapies within 30 days of screening:
    - Any cytotoxic, immunosuppressive or cytokine-modulating therapy including but not limited to: azathioprine, bosentan, ambrisentan, cyclophosphamide, cyclosporine, etanercept, iloprost, infliximab, leukotriene antagonists, methotrexate, mycophenolate, tacrolimus
    - Imatinib mesylate, Interferon gamma-1b, tyrosine kinase inhibitors (excluding nintedanib)
14. Pulmonary hypertension requiring active therapy including but not limited to endothelin receptor inhibitors or PDE inhibitors (e.g., sildenafil, tadalafil).
    - Note: intermittent use of a PDE inhibitor for erectile dysfunction may be allowed after approval by the Medical Monitor.
15. Hospitalization due to an exacerbation of IPF within 30 days of screening.
16. Subject plans to begin or has commenced pulmonary rehabilitation within 30 days of screening
    - Subjects 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
17. Corticosteroids (>10 mg per day of prednisone or an equivalent) within 30 days of screening.
18. Current smoker (including use of eCigarettes or vaporizing) or history of smoking within 3 months from screening.
19. Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, sinusitis, urinary tract infection or cellulitis, within 14 days of screening.
20. Active tuberculosis requiring treatment within the last 12 months.
    - Testing for latent tuberculosis is not required
21. Currently or, in the opinion of the investigator, soon to be listed for lung transplant.

22. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within 6 months of screening including but not limited to the following:
    - Unstable angina pectoris or myocardial infarction or elective coronary intervention
    - Congestive heart failure requiring hospitalization
    - Uncontrolled clinically significant arrhythmias
23. Any condition possibly affecting drug absorption, such as previous surgery on the stomach or small intestine.
24. 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).
25. Known hypersensitivity to any component of the study drug.
26. Subject who, for any reason, is deemed by the investigator to be inappropriate for this study; or has any condition (such as addictive or psychosocial issues) which would confound or interfere with the evaluation of the safety, tolerability, or PK of the investigational drug; or is unable to comply with the study protocol.
27. 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

5. STUDY PROCEDURES AND EVALUATIONS

5.1. Subject Screening

The subject must be willing and able to sign and date the informed consent form (ICF) before any screening procedures or study-specific tests may be performed. The baseline 6MWT performed at screening must be performed within 7 days of the Day 1 visit. If the 6MWT falls outside of the 7-day window, it must be repeated (the repeat may occur at the time of the Day 1 visit prior to any Day 1 visit assessments).

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 (refer to Appendix A), prior to any Day 1 visit assessments.

Subjects may be rescreened up to two 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

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 3 months 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 of non-child-bearing potential are defined as; bilateral oophorectomy, hysterectomy or post-menopausal females being amenorrhoeic for at least 2 years.

For female subjects who report surgical sterilization (i.e., hysterectomy and/or bilateral oophorectomy), surgical sterilization procedures should be supported with clinical documentation and noted in the Relevant Medical History/Current Medical Conditions section of the CRF.

Instructions for Male Subjects

There is no information about effects that 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 3 months after the male subject has taken the last dose of GBT440.

All male subjects should use the methods of contraception as outlined in Section 8.6).

5.3. Clinical Assessments

Screening assessments must be performed and evaluated prior to randomization on Day 1. This study has nine visits in total including the screening visit and patients will be enrolled for approximately 58 days from the time of randomization until the last study visit. The timing of the visits, associated visit windows and all assessments are outlined in Appendix A: Schedule of Study Assessments.

5.3.1. Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), inflammatory/autoimmune disease, smoking history, use of alcohol and drugs of abuse within the previous year, and IPF-associated conditions including but not limited to pulmonary hypertension, familial IPF and gastroesophageal reflux disease. Medical conditions that are a result of side effects from concomitant medications 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 adverse event if deemed clinically significant by the investigator (refer to Section 10).

All concomitant medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 30 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.

5.3.2. 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 patient notes. New or worsened abnormalities should be recorded as adverse events on the Adverse Event eCRF.

Vital signs will include measurements of respiratory rate, pulse rate, body temperature, systolic and diastolic blood pressure and SpO_2 by pulse oximetry. Blood pressure and SpO_2 measurements should be taken while the patient 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 will be any abnormal result that, in the judgment of the Investigator, is an unexpected or unexplained laboratory value or if medical intervention or corrective action is required. Any abnormal values that persist should be followed at the discretion of the Investigator.

Please refer to Appendix A Schedule of Study Assessments for all time points.

5.4.1.1. Hematology

Hematology assessments will include red blood cells (RBCs), hematocrit, hemoglobin, platelets and white blood cells (WBCs) with differential (basophils, eosinophils, neutrophils, monocytes and lymphocytes). Reticulocyte count and serum erythropoietin 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 alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma glutamyl transferase (GGT), and total bilirubin (direct and indirect).

5.4.1.4. 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.

5.4.1.5. 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. The ECGs will be collected in triplicate. Three separate recordings approximately 1 minute apart should be performed. All three tracings must be stored at the study site. If ventricular pacing is noted on ECG, then QTcF intervals will not be calculated.

5.4.1.6. Other Clinical Laboratory Tests

Screening tests will include serology for hepatitis A (IgM anti-HAV), hepatitis B surface antigen (HBsAg), hepatitis C (HCV) and HIV-1/0/2 antibodies if there is no documented testing results within 3 months of screening.

For women of child bearing potential, a pregnancy test (serum HCG) will be performed at screening and urine pregnancy testing will be performed during the study. If the urine pregnancy test is positive the result must be confirmed with a serum pregnancy test.

Coagulation (Panel) including PT, PTT and INR will be collected at screening and Day 28.

5.5. Disease Related Evaluations

5.5.1. 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 2005) 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.

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

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

5.5.2. Oxygen Saturation

During screening and with all scheduled vital sign assessments resting, room air oxygen saturation (SpO_2) will be measured by pulse oximetry (provided by the Sponsor) whilst the subject is seated and resting for at least 5 minutes. 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 resting.

SpO_2 will be also be collected at baseline, during and following completion of the 6MWT and cardio-pulmonary exercise testing.

5.5.3. 6-Minute Walk Test (6MWT)

Functional exercise capacity will be evaluated at Baseline and Days 15, 28 and 58 using the 6-minute walk test. The 6MWT will be performed without the subject using supplementary oxygen. Oxygen may be used at any time during the 6MWT, if in the opinion of the Investigator or testing technician it is required for safety reasons. The 6MWT should then be stopped.

The baseline 6MWT performed at screening must be performed within 7 days of the Day 1 visit. If the 6MWT falls outside of the 7-day window, it must be repeated (the repeat may occur at the time of the Day 1 visit prior to any Day 1 visit assessments).

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, 1 minute and 2 minutes after test completion.

For safety reasons, all patients should be clinically stable prior to performing the 6MWT.

Absolute contraindications to the 6MWT include unstable angina or myocardial infarction during the previous month.

Relative contraindications to participation in the 6MWT include:

- Resting heart rate >120 or <60 beats per minute
- Systolic blood pressure >180 mmHg
- Diastolic blood pressure >100 mmHg

5.5.4. Cardiopulmonary Exercise Testing (CPET)

Symptom-limited cardiopulmonary exercise testing using a bicycle ergometer will be performed on Day 2 and Day 29. At baseline and during the exercise period the collected data will include but is not limited to: SpO_2 and arterial blood gases, VO_2 max, ventilation and lactate thresholds. Guidelines developed by ATS and American College of Chest Physicians will be used for conducting the test and interpreting the results (ATS 2003). Instructions for the conduct of the CPET will be provided in a separate manual. An arterial line placement will be part of the CPET procedure. If the subject refuses arterial line placement they may still undergo the CPET assessments without the arterial line.

Agreement to undergo the CPET is not required for entry into the study; but participation is strongly encouraged.

5.5.5. 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 (except in cases when the screening 6MWT is being repeated on Day 1 prior to any Day 1 visit assessments) and before the patient receives any disease-status information during that assessment. They will be administered as indicated in the schedule of assessments (Appendix A).

5.5.5.1. 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 comprises 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 specification of 4 weeks. Paper questionnaires will be provided to sites prior to subject enrollment.

5.5.5.2. University of California, San Diego Shortness of Breath Questionnaire (UCSD)

The UCSD is a 24-item assessment of breathlessness associated with various activities of daily living. The response for each item is measured on a 5-point Likert scale from 0 (none at all) to 5 (maximal or unable to perform). Paper questionnaires will be provided to sites prior to subject enrollment.

5.5.5.3. Borg Dyspnea Scale

The Borg Dyspnea scale is a 1-item assessment, self-administered by the patient administered as part of the 6 MWT. The instrument will be used to assess dyspnea from the patient's perspective. The Scale ranges from 0 (Nothing at all) to 10 (Absolute maximum/Highest possible). Refer to the Procedure Manual for a copy of the assessment. A paper scale will be provided to sites prior to subject enrollment.

5.5.5.4. A Tool to Assess Quality of Life (ATAQ) in IPF

ATAQ questionnaires will be administered in Part B of this study. Paper questionnaires will be provided to sites prior to subject enrollment in Part B of the trial.

5.5.5.4.1. 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 oxygen use. Items are assessed using a Likert scale with a 24-hr recall period.

5.5.5.4.2. 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 one week recall period.

5.5.5.5. Visual Analog Scale (VAS) for Cough Severity

Cough will be assessed using a VAS in which the subject will indicate the severity of their cough by drawing a mark on a 100 mm scale, which ranges from 0 - "no cough" to 100 m - "worst cough severity". A paper scale will be provided to sites prior to subject enrollment.

5.5.5.6. End of Study Questionnaire

The End of Study Questionnaire is an 8-item 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 58 visit. The survey is to be completed by subjects enrolled under Part B of the trial. A paper End of Study Questionnaire will be provided to the sites prior to subject enrollment in Part B. Subject responses will be entered in the eCRF by the site. At completion of the study the paper questionnaires will be returned to the Sponsor.

5.6. Pharmacokinetic Samples

Plasma and whole blood concentrations of GBT440 will be measured using validated LCMS methods. Instructions for sample collection, processing and shipment are described in a separate lab manual. Up to nine PK samples will be collected at the following times (also refer to the Schedule of Assessments, Appendix A):

	During Treatment Period	
	Pre-dose	**2 hrs ± 15 min post -dose**
Day 1 (Visit 2)	X	X
Day 2 (Visit 3)	X*	
Day 8 (Visit 4)	X	
Day 15 (Visit 5)	X	
Day 28 (Visit 6)	X	X
	During Follow-Up Period	
Day 45 (Visit 8)	X	
Day 58 (Visit 9)	X	

* On Day 2 the PK sample should be drawn 24 hours (± 2 hours) after the Day 1 dose and prior to receiving the Day 2 dose.

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 adverse events 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 Harmonisation (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
- SMC recommendation
- 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 Visit 8 (Day 45) assessments within 2 weeks (± 7 days) from the date of discontinuation.

6.3. Study Treatment 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
- Use of any medication (refer to Section 8.5), intended to chronically treat IPF, other than those documented at screening
- Adverse event 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 study assessments, should return to the study site 2 weeks (+ 7 days) after the last dose of study drug to complete the Visit 8 (Day 45) assessments.

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 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

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 FDA IID (Inactive Ingredients Database) listed.

Placebo Capsules: The placebo capsules contain microcrystalline cellulose in Swedish orange, opaque, size 0, hypromellose capsules. All the excipients used for the formulation are FDA IID (Inactive Ingredients Database) listed. The placebo capsules do not contain any GBT440 drug substance.

7.1.3. Packaging and Labeling

GBT440 and placebo capsules will be supplied to the site in 100 mL high-density polyethylene (HDPE) bottles induction sealed with child-resistant polypropylene (PP) screw caps bottles of 30 capsules.

An unblinded study pharmacist will prepare daily doses of study drug dispensed into 30 mL high-density polyethylene (HDPE) bottles with child-resistant polypropylene (PP) screw caps. Packaging and labeling of each bottle and its contents are specific to each subject in the study and is based on the treatment group assignment at randomization.

Each 30 mL bottle (or dose) is packaged individually with 3 capsules of active or placebo or both specific to each subject's assigned treatment group.

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 or placebo are required. The Sponsor will be permitted upon request to audit the supplies, storage, dispensing procedures and records provided that the blind of the study is not compromised.

7.2. Drug Accountability

In accordance with GCP, the Investigational Site will account for all supplies of GBT440 and placebo. Details of receipt, storage, assembly and return will be recorded.

All unused supplies of GBT440 and placebo will either be destroyed by the investigational site or returned to the study Sponsor or 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 and placebo will be administered orally each day for 28 days. GBT440 will be administered as 300 mg capsules. Placebo will be provided as capsules matching the GBT440 capsules. Subjects randomized to the following treatment groups will receive:

Part A:

- GBT440 900 mg: 3 GBT440 300 mg capsules.
- GBT440 600 mg: 2 GBT440 300 mg capsules and 1 placebo capsule.
- Placebo: 3 placebo capsules.

Part B:

- GBT440 1500 mg: 5 GBT440 300 mg capsules
- GBT440 600 mg: 2 GBT440 300 mg capsules and 3 placebo capsule.
- Placebo: 5 placebo capsules.

Instructions for Administration of Study Drug:

- Self-administered by subject in the morning
  - except on study visit days when the subject must not take study drug. It will be administered at the site after completion of scheduled assessments.
- May be taken with or without food
- May be taken with water or other non-alcoholic beverage

Subjects must be instructed not to take study drug the day of their scheduled visits (refer to Appendix A). Study drug will be administered at the site on these days, after completion of all the assessments scheduled for that visit.

8.2. Study Drug Dispensing

Study drug will be dispensed to subjects on study Days 2, 8 and 15 as indicated in the schedule of assessments (refer to Appendix A). Each daily dose will be dispensed into separate containers and provided to the subject at the study site.

If a dose reduction is required subjects must return to the study site for study drug to be re-dispensed. Subjects must return any remaining study drug and all study drug containers to the site where they will be destroyed as instructed by the Sponsor.

8.3. Dose Modification

Modification of study drug dosing may be considered if, in the opinion of the study Investigator, the AE may be 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.

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 and in discussion with the Sponsor's Medical Director.

The Investigator, in discussion with the Sponsor's Medical Director, may choose to:

- Change dosing frequency, to one capsule 3 times per day
- Reduce the total daily dose

A reduction in dose should be by one active study drug capsule. Dose reductions will require the subject to return to the study site for the unblinded pharmacist to dispense new study drug capsules. Subjects will continue to take 3 capsules per day if in Part A and 5 capsules per day if in Part B of the study.

A second dose reduction by another one active study drug capsule 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 discussion with the Sponsor's Medical Director.

The Investigator must make every effort to restart the dosing regimen assigned to the subject at randomization, as soon as it is safe to do so.

8.3.2. Dose Interruption

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

Re-initiation of dosing will be based on the Investigator's clinical assessment and in discussion with the Sponsor's Medical Director. Dosing should be restarted at the dose assigned to the subject at randomization.

The Investigator must make every effort to restart the dosing regimen assigned to the subject at randomization as soon as it is safe to do so.

Study treatment 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. Patients 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 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. Treatment 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 adverse events 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 randomized subjects, all administered concomitant medications from signing the informed consent until the last study visit must be recorded in the subjects' eCRF.

All prior and concomitant medications that have been reported, will be coded using the current version of 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
  - 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:
  - if the dose at screening is ≤10 mg per day of prednisone (or an equivalent) and has been stable for at least 2 weeks prior to screening and with no anticipated need for dose adjustments, including reductions in dose, during the study.
  - Use of corticosteroids for other non-IPF related reasons, including but not limited to intra-articular or intramuscular delivery, should be discussed with the medical monitor before administering.
  - 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 1; GBT440 may increase the plasma concentration of these medications)

Table 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, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#4 Substrates with 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

8.6.1. Acceptable Forms of Contraception

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

- 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
- Vasectomised partner. Note that vasectomised 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 vasectomised partner has received medical assessment of the surgical success.
- Sexual abstinence. Sexual abstinence is considered a highly effective method only if the subject is refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. 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.

For male subjects:

- Men must agree to use two acceptable methods of contraception, 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 3 months following last study drug administration.

9. RANDOMIZATION PROCEDURE

Subject randomization will be carried out centrally through an Interactive Response System (IxRS).

In Part A, eligible subjects will be randomized 1:1:1 to either: 900 mg GBT440, 600 mg GBT440 or placebo, respectively. A total of approximately 18 subjects will be randomized.

In Part B, up to an additional 15 subjects will be enrolled and randomized 3:1:1 to either: 1500 mg GBT440, 600 mg GBT440 or placebo to further characterize the safety, tolerability and potential treatment response of GBT440. In the eventuality that one treatment arm is discontinued subjects may be randomised 1:1 to the remaining study treatment group or placebo.

Randomization will be stratified by background IPF therapy used at the time of entry into the study, that is pirfenidone or nintedanib.

9.1. Blinding

The GBT440 and placebo oral capsules will be matched for shape, size and color.

If at any time during the study a decision about a subject's medical condition requires knowledge of the treatment assignment, the study blind may be broken (through IxRS) for that specific subject only. If in the opinion of the Investigator, there is no impact on patient safety, the Investigator is encouraged to contact the Sponsor's Medical Director prior to unblinding. The reason for unblinding must be documented in the appropriate section of the eCRF.

At the study site, only the Principal Investigator should be unblinded. If, in the Investigator's opinion, and for the safety of the subject other study site personnel are required to be aware of the treatment assignment, the Investigator will ensure that the minimum number of personnel are informed.

The SMC must be informed by the Sponsor's Medical Director of any case of unblinding. Additionally, the SMC may unblind individual treatment assignment for further safety evaluation at their discretion.

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 II study will contribute to the understanding of the safety profile for GBT440 and for its use in IPF patients.

10.1. Safety Monitoring Committee (SMC)

The Safety Monitoring Committee (SMC) consisting of the Sponsor's Medical Director, one Independent Physician with clinical IPF expertise and one Independent Physician with clinical trial experience. The SMC, along with the CRO's statistician and data manager, will review the safety data throughout the study.

The SMC may meet at any time during the study to review blinded or unblinded data when deemed necessary by the SMC.

In Part A, the SMC will initially convene to review all available safety data after approximately 9 randomized subjects have completed the Day 15 visit. The SMC will also convene to review all available safety data after approximately 18 subjects have completed the Day 15 visit. If the SMC does not identify any clinically significant safety concerns the Sponsor will randomise up to an additional 15 subjects, to three study treatment arms (1500 mg GBT440, 600 mg GBT440 or placebo) to better characterize the safety, tolerability and/or potential treatment response of GBT440.

In Part B, the SMC will initially convene to review all available safety data after approximately 9 randomized subjects have completed the Day 15 visit. The SMC will also convene to review all available safety data after approximately 15 subjects have completed the Day 28 visit. At this time, the SMC will review safety data from all subjects, in Parts A and B, who have received at least one dose of study drug.

Details of the SMC are described in a separate charter.

10.2. 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 therefore 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 58). Reporting of AEs prior to randomization should only include SAEs or AEs resulting from any protocol related interventions.

Adverse events 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 nonserious) 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).

The procedures specified in Section 10.7 are to be followed for reporting SAEs.

10.3. Recording Adverse Events

Adverse events are to be recorded on the AE eCRF. The following information will be recorded:

- Whether or not the AE is an SAE (Section 10.4.1)
- AE severity (Section 10.4.2)
- AE relationship to investigational product (Section 10.4.4)
- 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.

10.4. Assessment of Adverse Events

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

10.4.1. Serious Adverse Event (SAE)

The investigator is responsible for determining whether an AE meets the definition of an SAE. An SAE is any AE occurring from signing of the informed consent form (ICF) until the end of the study (Day 58) 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 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" (Section 10.7) for details.

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).

10.4.2. 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 NCICTC Version 4.03)

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. Refer to Section 10.7 for details.

10.4.3. 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. Adverse events reported for subjects participating in this study will be graded using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03

The Investigator will grade the severity of each AE using, when applicable, the NCI CTCAE, version 4.03. For AEs not included in the NCI-CTCAE Version 4.03, the criteria outlined in Table 2 should be used as a general guideline.

Table 2 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.

10.4.4. 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 adverse event has an etiology other than the study drug (such as a preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Possibly/Probably Related:** A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the subject's clinical state or concomitant therapies and appears with some degree of certainty to be related based on the known therapeutic and pharmacologic actions of the drug. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event 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.

10.4.5. Unexpected Adverse Reactions

An adverse reaction is 'unexpected' if its nature and severity are not consistent with the information about the study drug:

- In the case of a product with a marketing authorization, in the summary of product characteristics for that product.
- In the case of any other IMP, in the Investigator's Brochure relating to the trial in question.

10.5. Reporting Adverse Events

10.5.1. 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, it should be reported as follow-up information and the diagnosis entered in the eCRF.

10.5.2. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade 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.

10.5.3. 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 their severity increases. If a persistent AE becomes more severe, it should be recorded again on the Adverse Event eCRF.

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

10.5.4. Abnormal Laboratory Values

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

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, seriousness, or etiology changes.

10.6. Discontinuation due to Adverse Events

Any subject who experiences an AE, serious or nonserious, 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’ Medical Director and the CRO medical monitor must be notified. If the AE relates to overdose of study treatment, the Investigator’s Brochure 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.

10.7. Reporting Serious Adverse Events and Adverse Events of Special Interest

SAEs/AESIs occurring in this study 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. 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 Investigator is responsible for notifying the Institutional Review Board (IRB) or Independent Ethics Committees (IEC) in accordance with local regulations, of all SAEs. The Sponsor or designee may request additional source documentation pertaining to the SAE from the investigational site. If a subject is permanently withdrawn from the study due to an SAE, this information must be included in the initial or follow-up SAE report in the eCRF.

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.

10.8. Choosing Adverse Event Terms

Whenever possible, reported event terms for AEs (including SAEs) should be the names of medical events, not lists of symptoms or event outcomes. Below are some examples of terms to avoid and more accurate alternatives.

Examples of Terms to Avoid	Examples of More Accurate Terms
Death (this is an outcome)	Fatal myocardial infarction (best choice) Death due to unknown cause, autopsy results pending (if no other information is available)
Hospitalized (this is a serious criterion)	Myocardial infarction (best choice) Hospitalized with chest pain, rule out myocardial infarction (if no other information is available)
Chest pain, shortness of breath, diaphoresis, anxiety, left arm pain	Myocardial infarction (best choice) Hospitalized, rule out myocardial infarction (if no other information is available)

10.9. Pregnancy

Pregnancies occurring in a female subject or in a male subject's partner while enrolled in this clinical study through 3 months 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 (refer to Section 10.5).

If a subject becomes pregnant while taking study drug, the study treatment will be immediately discontinued and the pregnancy must be reported within 24 hours. The investigator will discuss the risks and concerns of investigational drug exposure to a developing fetus and counsel the subject and/or pregnant partner (or ensure such counselling is provided).

An uncomplicated pregnancy will not be considered an AE or SAE; however, all pregnancies will be followed through birth and 3 months post-delivery.

Any congenital abnormalities in the offspring of a subject who received investigational product will be reported as 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.

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

11. DATA ANALYSIS AND STATISTICAL PLANS

Details of all planned analyses will be specified in a separate statistical analysis plan.

The study data will be reported using summary tables, figures and data listings. 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 from Parts A and B of the study will be pooled across the common treatment arms, i.e., GBT440 600 mg and placebo arms.

11.1. Sample Size

The sample size in this initial study was not selected based on statistical considerations but to determine preliminary safety, tolerability, PK, laboratory and clinical effects of GBT440 in IPF subjects.

The study will enroll approximately 33 subjects: approximately 18 subjects in Part A and approximately 15 subjects in Part B.

11.2. Populations for Analysis

The following populations will be considered in the analysis of data for this study. Assignment or exclusion of subjects from the analysis populations will be performed prior to study unblinding.

- Safety population: All subjects who receive any amount of study medication will be included in the safety population. Subjects will be analyzed based on medication received. This is the primary population for all safety analyses performed for this study.
- Efficacy evaluable population: All randomized subjects who received at least 15 days of study drug treatment will be included in the Efficacy evaluable population. The Efficacy evaluable population will be used for analysis of all secondary and exploratory efficacy endpoints, and subjects will be analyzed as treated.
- PK population: All subjects who receive investigational treatment and provide adequate data to evaluate the relevant PK parameter.

11.2.1. Primary Endpoint

The primary endpoint for this study is the safety and tolerability of GBT440.

Analysis will be based on data from all subjects who were randomized and received at least one dose of study drug. Safety will be assessed by AEs, laboratory evaluations, vital signs and ECGs. Data from these subjects will be used for analysis of all baseline demographics and safety summaries.

11.2.2. Secondary endpoints

Analysis of data for secondary efficacy endpoints will be based on all randomized subjects who received at least 15 days of study drug treatment.

The treatment group for these analyses will be based on the treatment received at randomization.

11.2.3. Pharmacokinetics

Analysis of data for PK will be based on data from all subjects who received at least 1 dose of GBT440 and have sufficient PK data to derive at least 1 PK parameter.

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. Analyses

Demographic and baseline characteristics, primary and secondary endpoints, and safety parameters will be summarized using descriptive statistics and presented in individual listings.

AEs will be reported by severity and relatedness to study treatment and classified according to the current version of MedDRA.

11.3.1. Safety Data

Safety data analysis will be performed on all randomized subjects who have received at least 1 dose of study drug. Individual and summary blood pressures, heart rate, ECG parameters, exercise testing endpoints and clinical laboratory data (hematology, serum biochemistry and coagulation) will be summarized.

For the laboratory safety data, out of range values will be flagged in the data listings and a list of clinically significantly abnormal values will be presented.

Adverse events and medical history will be tabulated and summarized according to the current version of MedDRA.

11.3.2. Efficacy Data

For secondary and exploratory endpoints, binary data will be analyzed via Fisher's exact test. Data for other endpoints will be analyzed with Wilcoxon's test or analysis of covariance (ANCOVA) with baseline value as covariate. Full details of analysis methods, including how missing data will be handled, will be provided in the SAP which will be finalized prior to study unblinding.

11.3.3. PK Data

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.

Steady state of GBT440 will be assessed graphically.

Exploration of exposure-response relationships of GBT440 to exploratory efficacy data, and safety data (described below) will be performed as data permits.

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 current country and local regulations, FDA, ICH GCP, the Declaration of Helsinki, and Good Clinical Practice.

The study will be conducted according to the protocol, and guidelines established by the ICH for GCP in clinical trials.

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, and 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 between the Sponsor and CRO, and then submitted to the IRB/IEC for approval. Amendments may be implemented only after a copy of the local IRB 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, 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.

Financial Disclosure statements will be handled in a separate agreement apart from the protocol, kept on file and submitted as applicable with any subsequent license application.

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. The subject should be given a

copy of the Informed Consent Form (ICF) in their native language. The informed consent process should be recorded in the source documentation. The original copy of the signed and dated informed consent must be retained in the institution's records, and is subject to inspection by representatives of the Sponsor, or representatives from regulatory agencies.

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 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.

12.9.1. Publication

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

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. ADMINSTRATIVE OBLIGATIONS

13.1. Source Data

Original documents, data, records (e.g., clinic records, laboratory notes, memoranda, subject diaries or evaluation checklists, pharmacy dispensing 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, 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 CRF 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 CRFs 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 CRFs and compare data to that contained in clinic notes and subjects' source documents/medical records.

Data collected for each subject will be entered into the CRF. The investigator will be responsible for the timeliness, completeness, and accuracy of the documentation entered into the CRFs.

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 (CRFs and other pertinent data), provided that subject confidentiality is maintained, and that the monitoring is conducted in accordance with local regulations.

It is the monitor's responsibility to inspect the CRFs 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 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.

14. REFERENCES

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15. APPENDICES

APPENDIX A SCHEDULE OF STUDY ASSESSMENTS

	Screening[a]		Treatment Period					Follow-up Visits	
Study Day (Window)	**Day -21 to Day -1**	**Day 1**	**Day 2**	**Day 8** (+/- 2)	**Day 15** (+/- 2)	**Day 28** (+/- 2)	**Day 29** (+3)	**Day 45[b]** (+/- 3)	**Day 58** (+/- 3)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Informed Consent[c]	X								
Eligibility Assessment	X	X							
Demographic data	X	X[d]							
Medical History and baseline conditions	X	X[d]							
Concomitant Medications	X	X	X	X	X	X	X	X	X
Complete Physical Examination[e]	X								X
Limited Physical Examination[f]		X		X	X	X	X	X	
Height	X								
Weight	X					X			
Vital Signs[g]	X	X	X	X	X	X	X	X	X
SpO_2[h]	X	X	X	X	X	X	X	X	X
ECG (12-lead)[i]	X			X	X	X		X	X
Adverse Events[j]	X[j]	X	X	X	X	X	X	X	X
Serum Pregnancy Test (females only)[k]	X								
Urine Pregnancy Test (females only)[l]				X	X	X		X	X
Hematology	X			X	X	X		X	X
Serum Chemistry	X			X	X	X		X	X
Urinalysis	X				X	X		X	X

Study Day (Window)	**Screening**[a]		**Treatment Period**					**Follow-up Visits**	
	Day -21 to Day -1	**Day 1**	**Day 2**	**Day 8** (+/- 2)	**Day 15** (+/- 2)	**Day 28** (+/- 2)	**Day 29** (+3)	**Day 45**[b] (+/- 3)	**Day 58** (+/- 3)
Coagulation Panel (PT, PTT, INR)	X					X			
Serum Erythropoietin	X					X		X	X
Serology (Hepatitis A, B, C, and HIV)	X								
PK Blood Samples[m]		X	X	X	X	X		X	X
Spirometry and DL_{CO}	X					X			X
6 Minute Walk Test[n]	X[n]				X	X			X
Cardiopulmonary Exercise Testing[n]			X				X		
Randomization (IxRS)		X							
Study Drug Dispensing to Subject[o]			X	X	X				
Study Drug Administration at site[p]		X	X	X	X	X			
St. George's Respiratory Questionnaire[q]		X				X			X
UCSD Shortness of Breath Questionnaire[q]		X		X	X	X		X	X
ATAQ-IPF Symptoms[q]		X		X	X	X		X	X
ATAQ-IPF Impacts[q]		X		X	X	X		X	X
End of Study Questionnaire[r]									X
Cough Visual Analogue Scale[q]		X		X	X	X		X	X

Abbreviations: ATAQ = A Tool to Assess Quality of Life; DL_{CO} = lung diffusing capacity measured using carbon monoxide; ECG = electrocardiogram; HIV = human immunodeficiency virus; INR = international normalized ratio; PK = pharmacokinetic; PRO = patient reported outcome; PT = prothrombin time; PTT = partial thromboplastin time; SGRQ = St. George's Respiratory Questionnaire; SpO_2 = oxygen saturation measured by pulse oximetry; UCSD = University of California San Diego.

Note: All assessments should be performed within the number of days (Window) as indicated for each scheduled visit day. All assessments should be performed prior to receiving study drug during the treatment period unless otherwise indicated. SGRQ, ATAQ, UCSD, Cough VAS should be performed before all other non-PRO assessments, followed by 12-lead ECG and then vital sign assessments.

[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 randomization to the treatment period. In cases when the screening 6MWT is done more than 7 days prior to Visit 2, it must be repeated, up and through Day 1, prior to any Day 1 assessments.

[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 Day 45 (Visit 8) 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 at this visit and any changes since screening updated in the eCRF

[e] 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

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

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

[h] Performed while the subject is seated and resting for at least 5minutes.

[i] Perform 12-lead ECG in triplicate; three separate tracings with approximately 1 minute between each tracing, after resting in a semi-recumbent or supine position for at least 5 minutes.

[j] After informed consent but prior to randomization only serious adverse events (SAEs) resulting from a protocol-mandated intervention should be reported. After randomization, all adverse events will be reported until study completion (Day 58).

[k] Performed for all female patients who are not post-menopausal or surgically sterile

[l] If a urine pregnancy test is positive the result must be confirmed with a serum pregnancy test

[m] PK blood samples during the treatment period should be collected on Days 1 and 28: Pre-dose and 2 hours post dose (+/- 15 minutes); Day 2: 24 hours (+/-2 hours) after the Day 1 dose *and* prior to receiving the Day 2 dose; Days 8 and 15: Pre-dose only.

[n] Instructions for per-protocol performance of the 6-minute walk (and Borg dyspnea scale) and cardio-pulmonary exercise tests are provided in the procedure manual. Note: The baseline 6MWT performed during screening must be performed within 7 days of the Day 1 visit.

[o] An unblinded study pharmacist will prepare daily doses of study drug, dispensed into 30 mL high-density polyethylene (HDPE) bottles. Each bottle (or dose) is packaged individually with 3 capsules of active or placebo or both specific to each subject's assigned treatment group. Subjects who have their dose modified during the study must return to the site to have the modified dose of study drug dispensed by the unblinded pharmacist.

[p] Subjects should not 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.

[q] The SGRQ, ATAQ and UCSD questionnaires and cough VAS 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 patient receives any disease-status information during that assessment. ATAQ questionnaires should be administered to subjects enrolled in Part B of the study.

[r] The End of Study Questionnaire should be administered to subjects enrolled in Part B of the study.

APPENDIX B STRONG INDUCERS OF CYP ISOENZYMES

CYP Enzymes	Medications
CYP3A4/3A5	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort
CYP2B6, CYP2C9, CYP2C19	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.