An open label single arm extension study to further evaluate the safety, tolerability and treatment response of GBT440 in patients with Sickle Cell Disease who participated in the Phase 1 Study GBT440-001

Protocol Number:	**GBT440-024**
Quintiles Study Number:	**BYA73740**
EudraCT Number:	**2016-002123-28**
Product:	**GBT440**
Indication:	**Sickle Cell Disease**
Clinical Phase:	**IIa**
Principal Investigator:	**Professor Timothy Mant, FRCP, FFPM**
Sponsor:	**Global Blood Therapeutics, Inc.**
Version:	**Version 2**
Date:	**28 September 2016**

Summary of protocol amendments

Revisions

- Inclusion criteria has been changed from
  - Subjects with SCD who are currently enrolled in the GBT440-001 study, Cohort 15 or 17

    to:

  - Subjects with SCD who have participated in the GBT440-001 study.
- Dose titration section has been added allowing increase in dose by 300 mg increments every 2 weeks up to maximum of 1500 mg, if in the opinion of the investigator the subject is tolerating the current dose level and might derive further benefit from an increase in dose (e.g. the hemolysis measures have improved but not yet normalized).
- Placebo subjects in Cohort 15 will initiate treatment with GBT440 at 900 mg.
- Removed concomitant medication restrictions for CYP2D6 substrates
- Removed the collection of the SCD severity questionnaire
- Updated clinical experience with GBT440 in Study GBT440-001

Rationale for revisions

- Because of delays in initiating the GBT440-024 study, several subjects from Cohort 17 of GBT440-001 had already completed dosing and were unable to participate. In addition, many subjects from earlier cohorts expressed interest in longer term, open label dosing with GBT440 in GBT440-024. For this reason the inclusion criteria have been expanded to allow enrolment of subjects with SCD who have completed the GBT440-001 study. These individuals will follow the same schedule indicated in the relevant schedule of assessments (SOA) in Section17.0.
- Dose titration has been added because data from the GBT440-001 study has shown a linear and highly significant relationship between GBT440 blood level and improvement in hemolysis and no plateau effect has been reached. This suggests that subjects may derive greater benefit at higher doses achieving higher haemoglobin occupancy. Furthermore the target for optimal efficacy based on individuals with HbS/Hereditary persistence of fetal haemoglobin is 20-30% haemoglobin occupancy (Ngo 2011) and the preliminary PK data from Cohort 17 showed that the majority of subjects did not maintain haemoglobin occupancy

>20% at 900 mg daily dosing. In addition, no dose limiting toxicities or concerning dose-or exposure related toxicities pose a safety concern with higher doses. At 1500 mg, the predicted C_{max} is 167 µg/mL, which is less than the C_{max} already observed and found to be well-tolerated in healthy volunteers in GBT440-001 294 µg/mL, 900 mg [Cohort 10]). Provided the principal investigator determines that the 600 mg or the 900 mg dose is well tolerated (after at least 28 days of prior dosing), and that the subject may receive further benefit from higher dosing (further improvement in haemoglobin, reticulocyte count or unconjugated bilirubin) the dose may be increase by one capsule (300 mg) every two weeks up to a maximum of 1500 mg.

- Placebo subjects in Cohort 15 will initiate treatment with GBT440 at 900 mg to increase the likelihood of achieving haemoglobin occupancy ≥ 20%.
- The concomitant medication restrictions for CYP2D6 has been removed because preliminary data from the clinical drug-drug interaction study, GBT440-017, suggest that GBT440 does not inhibit metoprolol, a CYP2D6 substrate.
- The version of the SCD severity questionnaire used in this study is an older version, the updated, current version will be added to the upcoming Phase 3 study.

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3.0 TABULATED PROTOCOL SUMMARY

Name of Sponsor/Company:	**Global Blood Therapeutics, Inc.**
Name of Finished Product(s):	GBT440 300 mg capsules
Name of Active Ingredient(s):	GBT440

Title of Study:

An open label single arm extension study to further evaluate the safety, tolerability and treatment response of GBT440 in patients with Sickle Cell Disease who participated in the Phase 1 Study GBT440-001.

Principal Investigator:

Professor Timothy Mant, FRCP, FFPM

Investigational Site:

The BRC Clinical Research Facility, Floor 15, The Tower Wing , Guy's Hospital, Guy's and St Thomas's NHS Foundation Trust Great Maze Pond, London SE1 9RT, UK

Clinical Phase:	Phase IIa

Objectives:

Primary objective

To evaluate the safety and tolerability of up to a total of 6 months dosing in subjects with sickle cell disease (SCD) who participated in the GBT440-001 study.

Secondary objectives

To observe the pharmacokinetics (PK) of GBT440 in plasma and whole blood in subjects with SCD.

To characterize the effect on biomarkers of hemolysis in subjects with SCD.

Exploratory objectives

To obtain data on exploratory markers of sickle cell disease activity.

To obtain data on sickle cell disease symptoms.

Methodology:

This is an open label, single arm study.

Up to 16 subjects with SCD who are 1) enrolled in the GBT440-001 study (Cohorts 15 and 17 only) and are in the treatment period or have completed the treatment period within the prior 7 days or 2) have previously completed the GBT440-001 study will be eligible to initiate daily dosing in this study.

Subjects continuing directly from the GBT440-001 study will continue to receive the treatment and dose assigned or a lower dose if the dose was reduced in the GBT440-001 study. Placebo subjects will receive active treatment. Subjects who previously completed the GBT440-001 study will receive 900 mg daily. Prior to enrolment into this study the individual subject treatment allocations for eligible subjects from the GBT440-001 will be unblinded and subjects will be assigned to the following treatment groups:

Group 1

Subjects from Cohort 17 in the GBT440-001 study who have received GBT440 900 mg per day for 4 months will continue receiving GBT440 900 mg per day for a further 2 months in this study.

Group 2

Subjects from Cohort 17 in the GBT440-001 study who have received placebo for 4 months will receive GBT440 900 mg per day for 6 months in this study.

Group 3

Subjects from Cohort 15 in the GBT440-001 study who have received GBT440 600 mg per day for two months will continue receiving GBT440 600 mg for a further 4 months in this study or the dose may be increased if the subject has tolerated 600 mg in GBT440-001.

Group 4

Subjects from Cohort 15 in the GBT440-001 study who have received placebo for 2 months will receive GBT440 900 mg per day for 6 months in this study.

Group 5

Subjects from Cohort 7, 11, 12, 14 16 or 17 who received either GBT440 or placebo who are enrolled into this study will receive GBT440 at a dose of 900 mg per day for 6 months.

All Subjects will receive a total of 6 months treatment with GBT440 which will include treatment with GBT440 in the GBT440-001 study for subjects in Cohort 15 or 17. Subjects from Cohort 7, 11, 12, 14, 16 or 17 who received either GBT440 or placebo and are currently off study in GBT440-001 will receive a total of 6 months of treatment with GBT440 in this study..

The dose may be increased by 300 mg increments (1 capsule) every 2 weeks up to maximum of 1500 mg, if in the opinion of the investigator the subject is tolerating the current dose level and might derive further benefit from an increase in dose (e.g. hemolysis measures have improved but not normalized).

A Safety Monitoring Committee (SMC) consisting of the Principal Investigator, Sponsor Medical Monitor, and Independent Safety Physician will have overall responsibility for assessing safety and tolerability. The SMC will review cumulative data at least monthly to determine whether continued dosing may proceed. The responsibilities of the SMC will be described in a separate charter.

Number of Subjects:

Up to 8 SCD subjects from GBT440-001 cohort 17 (900 mg per day), up to 8 SCD subjects from GBT440-001 cohort 15 (600 mg per day), and additional SCD subjects who previously completed GBT440-001 may be enrolled up to a total sample size not exceeding 16 subjects.

Main Criteria for Inclusion:

Subjects with SCD who are currently enrolled in the GBT440-001 study, Cohort 15 or 17.

Subjects with SCD from Cohort 7, 11, 12, 14, 16 or 17 from the GBT440-001 study.

Eligibility may be determined from assessments obtained as part of the GBT440-001 study within 7 days of dosing in this study for subjects in Cohort 15 or 17.

Eligibility must be determined from assessments obtained during baseline visit for subjects who were previously enrolled in Cohorts 7, 11, 12, 14, 16 or 17.

Subjects who if female and of child bearing potential, are using highly effective methods of contraception from study start to 3 months after the last dose of investigational medicinal product (IMP).

Female subjects must continue to have a negative pregnancy test result.

Subjects whose clinical laboratory test results are not clinically relevant and continue to be acceptable to the Investigator.

Subjects who if male are willing to continue to use barrier methods of contraception, from study start to 3 months after the last dose of investigational product.

Test Product, Dose and Route of Administration:

GBT440 300 mg oral capsules for oral administration.

Duration of Treatment:

Subjects will continue dosing until they have received a total of 6 months treatment with GBT440 which includes prior dosing with GBT440 in the GBT440-001 study for subjects enrolled in Cohorts 15 or 17. Subjects from Cohort 7, 11, 12, 14, 16 or 17 who received either GBT440 or placebo will receive a total of 6 months of treatment with GBT440 in this study.

Criteria for Evaluation

Pharmacokinetics:

Whole blood and plasma levels of GBT440 as indicated in the schedule of assessments (SOA).

Pharmacodynamics:

Haemolysis markers:

Haemoglobin, unconjugated bilirubin, LDH, absolute and % reticulocyte counts and % dense cells will be measured as indicated in the SOA.

Disease Related Assessments:

Inflammatory markers and exploratory biomarkers related to SCD disease severity will be assessed as indicated in the SOA.

Safety:

The safety evaluation will include blood pressure, pulse rate, body temperature, respiratory rate, ECG parameters, clinical laboratory tests (haematology, serum biochemistry (including erythropoietin), coagulation, urinalysis and urine microscopy) and adverse events.

Statistical Methods

Pharmacokinetic Parameters:

Whole blood and plasma levels of GBT440 will be listed and summarised using appropriate descriptive statistics by dose and study day.

Where appropriate an estimate of t1/2 will be computed and presented in tabular form with appropriate descriptive statistics.

Pharmacodynamic Parameters:

Haemolysis and Disease related assessments will be listed and summarised using appropriate descriptive statistics.

Safety Parameters:

Individual and summary blood pressures, heart rate, body temperature, respiratory rate, ECG parameters and clinical laboratory data (haematology, serum biochemistry and coagulation) will be presented in tabular form with appropriate descriptive statistics. Adverse events will be tabulated and summarized.

4.0 LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ALK	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
CI	Confidence interval
CK	Creatine kinase
CPMP	Committee for Proprietary Medicinal Products
CRF	Case report form
CRP	C reactive protein
CV	Coefficient of variation
C_{max}	Maximum plasma concentration
ECG	Electrocardiogram
EEG	Electroencephalogram
EU GMP	European Union – Good Manufacturing Practice
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICH	International Conference on Harmonization
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier
LS mean	Least squares mean
LDH	Lactate dehydrogenase
Max	Maximum
MHRA	Medicines and Healthcare products Regulatory Agency
Min	Minimum
NOAEL	No observed adverse effect level
PT	Prothrombin time
QP	Qualified person
SAE	Serious adverse event
$t_{½}$	Apparent terminal half life

5.0 INTRODUCTION

Sickle cell disease (SCD) is an inherited disorder caused by a point mutation in the β-globin gene leading to formation of haemoglobin S (HbS). Sickle cell disease predominantly occurs in individuals whose ancestors originated from sub-Saharan Africa, Spanish speaking regions of the Western Hemisphere (South America, Caribbean, Central America); Saudi Arabia; India; and Mediterranean countries including Turkey, Greece, and Italy. It is the most common single gene disorder in African Americans. A primary and obligatory event in the molecular pathogenesis of SCD is the polymerisation of deoxygenated HbS and the resultant sickling of red blood cells (RBC). Sickle cell disease is characterised by haemolytic anemia and vaso-occlusion leading to progressive end-organ damage with a clinical course of life-long pain, disability and early death.

Management strategies for SCD have evolved very slowly, and treatment of SCD remains a serious unmet medical need. Hydroxyurea (HU) is the only approved therapy for SCD but is limited by its side effect profile, poor patient adherence, variable patient responses, and concerns of long-term toxicity (Brandow *et al,* 2010). In addition to HU treatment, transfusions with normal blood are widely used in this patient population to alleviate symptomatic anaemia and reduce sickling. Attaining anti-sickling activity by blood transfusions has its own limitations: the treatments are expensive, not uniformly accessible and accompanied by risks (Wahl et al, 2009). The only curative treatment is bone marrow transplantation from a histocompatible donor, an option that has been available since the 1990s (Platt and Guinana, 2014), but bone marrow transplantation carries significant risks and is associated with a ~5% mortality rate (Nathan, 2013). Despite the current standard of care, including HU, blood transfusion, and palliative therapy for acute attacks, patients with SCD continue to suffer serious morbidity and premature mortality (Steinberg *et al*, 2003).

To date, no drugs have been approved that specifically target the underlying mechanism of sickle cell disease. The mechanism of action of HU involves a highly variable increase in the level of foetal haemoglobin (HbF) in a limited subset of RBCs (F-cells), resulting in limited protection from sickling. Foetal haemoglobin is the predominant haemoglobin during foetal development and begins to decline in production shortly after birth. Synthesis of adult haemoglobin, HbA begins shortly before birth and nears its adult proportion approximately 6 to 9 months postpartum. HbF powerfully inhibits the polymerization of deoxyHbS due to its high oxygen affinity as well as intrinsic structural characteristics that block polymer formation. Individuals who are homozygous for the β^S gene show no disease manifestations until late in the first year of life when the declining level of HbF no longer protects against deoxyHbS polymerization. The protective effect of HbF has been further validated by the observation that rare individuals who are

compound heterozygotes for the β^S gene and a gene deletion resulting in persistent HbF expression (HbS-HPFH) do not have manifestations of sickle cell disease. HbS-HPFH is typically associated with 20-30% HbF levels distributed equally among erythrocytes (pancellular). In addition, a form of deletional HbS-HPFH has been described with pancellular HbF levels of 10% and few, if any, sickle-cell related events [Akinsheye et al, 2011]. Taken together, the data from subjects with HbS-HPFH suggests that pancellular HbF of 20-30% prevents sickle cell disease and that levels as lows as 10% may be sufficient for protection.

Because oxyhaemoglobin is a potent inhibitor of HbS polymerization, allosteric modification of haemoglobin to increase the proportion of oxyhaemoglobin is a promising strategy to achieve inhibition of HbS polymerization in all RBCs [Noguchi et al, 1988]. Prior experimental haemoglobin modifying agents (BW12C and tucaresol) have provided proof of concept for the haemoglobin modification approach by demonstrating an increase in oxyhaemoglobin and a decrease in clinical biomarkers of haemolysis [Keidan et al, 1986; Arya et al, 1996]. Despite the increase in haemoglobin oxygen affinity, these drugs were well tolerated by healthy volunteers and they remained well-compensated both at near maximal exercise and at rest with little change in basal oxygen consumption or resting heart rate [Nicholls et al, 1989].

GBT440

Global Blood Therapeutics (GBT) has developed GBT440, a small molecule allosteric modulator of haemoglobin oxygen affinity, for the treatment of SCD. GBT440 is administered orally in capsules.

The mechanism of action of GBT440 involves inhibition of HbS polymerisation by increasing the affinity of haemoglobin for oxygen. Haemoglobin exists in both a relaxed (R) and a tense (T) state with high and low affinity for oxygen, respectively (Eaton et al, 1999). Upon binding to HbS, GBT440 effectively maintains a targeted fraction of HbS in the R state. Haemoglobin S molecules that are in the R (oxygenated) state are potent inhibitors of HbS polymerisation and, conversely, only deoxygenated HbS is capable of polymerising to create sickling of red blood cells. Because GBT440 binds to the haemoglobin α chain, its effects on the oxygen equilibrium curves (OEC) are expected to be similar in normal and sickle blood. Nonclinical data and data from prior experimental haemoglobin modifying agents demonstrate that only a fraction of haemoglobin (20 to 30%) must be maintained in the R state in order to inhibit sickling. Based on data from prior experimental compounds and genetic data from high affinity haemoglobin mutations in humans, 20 to 30% haemoglobin modification by GBT440 should be safely achievable in humans.

GBT440 was rationally designed, based on a knowledge of the chemical structure and mode of haemoglobin binding of prior haemoglobin modifying agents in order to improve potency and specificity for haemoglobin (Abdulmalik *et al*, 2011). A medicinal chemistry program was used to optimise activity in *in vitro* haemoximetry and polymerisation assays and to achieve a 1:1 stoichiometry of binding per haemoglobin tetramer compared to the 2:1 stoichiometry of prior compounds. Subsequently, GBT440 was found to be considerably more potent than all reported predecessor compounds in *in vitro* assays and to have sustained exposure following oral dosing in multiple animal species.

5.1 Nonclinical Experience

5.1.1 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.

5.1.2 Pharmacokinetics

Pharmacokinetic evaluation showed that GBT440 had low blood clearance (CL), low blood V_{ss}, a 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 pharmacokinetic (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 of GBT440 is increased less than dose-proportional.

5.1.3 Nonclinical Pharmacology

An overview of the key nonclinical data is provided below. For a more detailed discussion of the nonclinical pharmacology, pharmacokinetic and toxicology studies conducted to date, please refer to the Investigator's Brochure for GBT440 for the treatment of SCD.

Primary PD studies of GBT440 consisted of in vitro and in vivo studies to characterize (a) GBT440 binding and affinity for Hb, (b) the effect of GBT440 on HbS modification using purified Hb, washed RBCs, and whole blood, and (c) the efficacy of GBT440 in vivo in a mouse model of SCD. The in vitro assays of increasing complexity included measuring Hb-O_2 affinity via haemoximetry, quantifying stabilization of the

oxyhaemoglobin state conformation, delaying HbS polymerization at low oxygen tension, preventing in vitro sickling induced by a low oxygen environment, and decreasing viscosity and improving deformability of RBCs in blood from patients with SCD. In addition, these studies show that GBT440-modified Hb retains the Bohr Effect, which is the ability to augment oxygen delivery in metabolically active (low pH) tissues.

Collectively, these studies demonstrate that GBT440 potently increases Hb-O_2 affinity with high specificity of binding to Hb; stabilizes the oxy or R-state conformation of Hb; prevents HbS polymerization and RBC sickling in vitro; improves sickle blood viscosity, and deformability in vitro; and increases HbS-oxygen affinity and RBC half-life, while decreasing ex vivo sickling and reticulocyte count in a SCD mouse model.

5.1.4 Metabolism

Studies in rat and dog indicate that metabolism was the major route of elimination involving both Phase I and Phase II metabolism pathways. Renal excretion of GBT440 was a minor elimination pathway. GBT440 metabolites were excreted in both urine and feces.

Evaluation of enzymes involved in the metabolism of GBT440 was conducted with 13 recombinant human CYP450 enzymes and recombinant human aldehyde oxidase and aldehyde dehydrogenase 1A1. The data suggests that GBT440 could be metabolized by CYP1A1, 1B1, 2B6, 2C9, 2C19, 3A4, and 3A5. The clinical relevance for potential drug interactions when GBT440 is co-administered with CYP inducers or inhibitors is unknown at this time.

GBT440 inhibited CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 enzymes in vitro with K_i values from 0.8 to 112 µM. However, based on preliminary data from the GBT440-003 drug-drug interaction (DDI) study, GBT440 does not appear to inhibit CYP1A2, CYP2C9 or 2C19 but may be a weak inhibitor of CYP3A4. Clinical DDI studies to assess whether GBT440 inhibits CYP2C8 or CYP2D6 are planned.

A CYP450 induction study was assessed for CYP1A2, CYP2B6, and CYP3A4 using human cryopreserved hepatocytes. GBT440 at ≥ 10 µM may cause increases in CYP2B6 expression and may be acting through the constitutive androstane receptor. The clinical implications are not known.

GBT440 was evaluated as a potential inhibitor of human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE2K, BCRP, P-gp, and BSEP-mediated transporters. GBT440 has potential to inhibit OAT3 transporter which may result in a higher concentration of co-administered drug(s) that is a substrate for this transporter. However, since GBT440 does not appear to be excreted unchanged in urine the likelihood of an interaction is low. GBT440 was also tested as a potential substrate for human Pgp,

BCRP, OATP1B1-, OATP1B3-, OATP1A2-, and BSEP-mediated transporters. The data indicates that GBT440 was not a substrate for any of these transporters tested.

5.1.5 Toxicology

Nonclinical toxicology studies have defined no observed adverse effect levels (NOAEL) for GBT440 in rats and monkeys for up to 13 weeks and for dogs following 28 days of dosing, assessed toxicokinetics in 4 species (rat, dog, monkey, and rabbit), and determined the reversibility of any effects. The majority of effects in rats were considered related to the mechanism of action or adaptive, reversible effects. In dogs and monkeys, gastrointestinal (GI) effects appeared to be dose-limiting. A genotoxicity battery indicated a low risk of genotoxic effects and dose range-finding embryo-fetal studies in rats and rabbits did not reveal notable effects on embryo-fetal development.

A six month toxicology study in rats and a 9-month toxicology study in monkeys are currently ongoing with projected data availability in Q3 2016 (rat) and Q1 2017 (monkey) respectively.

More details on the completed studies are contained in the GBT440 Investigator Brochure.

5.1.6 Toxicokinetics

The steady state PK parameters (whole blood) on Day 28 in rats dosed with 250 mg/kg/day (NOAEL) was 1055 µg/mL (3,127 µM) Cmax and 17950 µg*hr/mL AUC0-24. The adverse effects in the dog study occurred at much lower exposures than observed in the rat study (285 µg/mL [845 µM] Cmax and 5840 µg*hr/mL AUC0-24, 1000 mg/kg dose group), and were possibly secondary to changes caused by chronic vomiting and faecal changes (soft stool, liquid, diarrhoea).

5.2 Clinical Experience

5.2.1 Overview of Clinical Studies to Date

As of 01 August 2016, 251 subjects, including 204 healthy subjects and 47 subjects with SCD, have been treated with single or multiple doses (up to 15 days in healthy subjects, and up to 90 days in subjects with SCD) of GBT440 across 9 clinical studies.

A Phase 1/2 study (Protocol GBT440-001) evaluating the safety, tolerability, pharmacokinetics (PK), and PD effects of single and multiple doses of orally administered GBT440 in healthy subjects and subjects with SCD is ongoing. A total of 95 subjects (48 healthy subjects and 47 subjects with SCD) have received GBT440. Healthy subjects have received single doses of GBT440 ranging from 100 to 2800 mg, and have received multiple-doses of 300, 600, or 900 mg/day for up to 15 days. In subjects with SCD, GBT440 has also been evaluated in multiple doses of 500, 700, and

1000 mg/day for up to 28 days, and multiple doses of 700 and 900 mg/day for up to 90 days. An additional cohort is subjects with sickle cell–hemoglobin C (HbSC) or HbS/β+thalassemia is currently ongoing at a dose of 600 mg for 28 days.

In addition to the studies noted above, there are 8 clinical pharmacology studies (GBT440-002, GBT440-003, GBT440-004, GBT440-005, GBT440-008, GBT440-017, GBT440-018 and GBT440-019) in which a total of 156 healthy subjects received GBT440.

Study GBT440-001

GBT440-001 is an ongoing, Phase 1, randomized, placebo-controlled, double-blind, single and multiple ascending dose study of the tolerability and PK of GBT440 in healthy subjects and in subjects with SCD that is being conducted at a single study site in the United Kingdom. The study was initiated in December 2014. The study is being conducted under the supervision of a Study Monitoring Committee (SMC), consisting of the Principal Investigator from the study site, the Sponsor's medical monitor, and an independent safety physician. The investigator and study subjects are blinded to treatment assignment. The SMC has conducted regular reviews of the safety data collected in this study through 9 June 2016.

The study includes 3 parts (Parts A, B, and C):

- Part A consists of a single ascending dose evaluation in healthy subjects and in subjects with SCD
- Part B consists of a 15-day multiple ascending dose evaluation in healthy subjects and a 28-day multiple ascending dose evaluation in subjects with SCD
- Part C consists of a 90-day multiple dose evaluation in subjects with SCD. An amendment has been submitted to extend the dosing period by a further 30 days.

In addition to the above, within Part A, the effect of food (low-fat meal) on the PK profile of GBT440 was evaluated in 1 of the healthy subject cohorts in a crossover design. Subjects in this cohort received 2 doses of GBT440 or placebo; the first dose followed an 8- to 10-hour fast and, following a washout period, the second dose followed a meal.

Part A

Forty-eight (48) subjects have been dosed in 6 single dose cohorts comprised of 40 healthy volunteer subjects (30 received single doses of GBT440 ranging from 100 to 2800 mg and 10 received placebo- Cohorts 1 to 5) and 8 subjects (cohort 7) with SCD (6 received GBT440 1000 mg and 2 received placebo) in this study.

Note: Cohort 6 was not required.

Part B

Sixty two subjects have been dosed in 6 multiple dose cohorts comprised of 24 healthy volunteer subjects (cohorts 8, 9 and10) dosed for up to 15 days (18 received GBT440 at doses of 300, 600 or 900 mg/day and 6 received placebo), 16 subjects (cohort 11) with SCD dosed for 28 days (12 receiving GBT440 700 mg/day and 4 receiving placebo),14 subjects (Cohort 12) with SCD dosed for 28 days (GBT440 500 mg/day /placebo), 8 subjects (Cohort 14) with SCD dosed for 28 days (6 receiving GBT440 500 mg twice a day/2 receiving placebo). One subject (cohort 15) with SCD (HbSC and HbS/β^+thalassemia) has been dosed GBT440 600mg/day/placebo for 28 days. A further 7 subjects (Cohort 15) with SCD (HbSC and HbS/β^+thalassemia) are to commence dosing with GBT440 600mg/day/placebo for 60 days.

Note: Cohorts 6 and 13 were not required.

Part C

Eight subjects (Cohort 16) with SCD have commenced dosing for 90 days (6 receiving GBT440 700 mg/day and 2 receiving placebo). All eight subjects have completed.

In Cohort 17, 8 subjects with SCD have commenced dosing for up to 118days receiving GBT440 900 mg/day /placebo). Two of these subjects have completed 90 days of dosing, four of these subjects have completed 118 days of dosing, and two are ongoing. As of 03 August 2016 two subjects from Cohort 17 have enrolled into this study (GBT440-024).

Results

Safety data are now available and have been reviewed by the SMC through end of the dosing period for subjects in Part A, for 24 healthy subjects who received doses of GBT440 300, 600, or 900 mg/day for up to 15 days in Part B, and 38 SCD subjects in Cohorts 11, 12 and 14 who received GBT440 700 mg/day, GBT440 500 mg/day for 28 days and GBT440 500 mg/twice a day respectively. All serious and severe AE data are reviewed by the sponsor and principal investigator as events emerge on an ongoing basis. To date no drug related serious or severe adverse events have occurred.

In Parts A and B the most frequently reported events were primarily gastrointestinal events (stomach ache, stomach pain, abdominal pain, diarrhea and loose stools), headache and rash. Adverse events in healthy subjects and SCD subjects were generally similar except for sickle cell related pain and nausea which were reported in SCD but not healthy volunteer subjects.

The majority of adverse events were mild (Grade 1). In Part A (Cohort 1), one Grade 2 event of upper respiratory tract infection was considered by the investigator to be possibly related to study drug and in Part B (Cohorts 8, 10 and 11) three Grade 2 events of

headache were considered possibly related to study drug. As described above, there have been no drug-related severe or serious adverse events.

Safety Monitoring Committee data review has not identified any abnormal or clinically significant trends in vital signs, ECG or safety laboratory data across cohorts. No adverse events or protocol-defined dose limiting toxicity criteria associated with tissue hypoxia or hyperviscosity have been observed and there have been no cases of moderate or severe suspected drug hypersensitivity. Furthermore, the SMC has also provided approval to proceed with 2 cohorts of SCD subjects who will receive 90-day dosing of study drug. In Part C, which includes fourteen subjects who have completed dosing with GBT440/Placebo there have been no severe or serious drug-related adverse events.

Treatment with GBT440 resulted in a large and sustained reduction in clinical markers of hemolysis (as evidenced by declining unconjugated bilirubin and reticulocyte counts and an improvement in anemia). The increase in Hb after 90 days of dosing is shown in Figure 1. No significant changes from Baseline were observed for subjects receiving placebo. These results are consistent with inhibition of HbS polymerization leading to decreased RBC damage, improved RBC lifespan, and improvement in tissue oxygen delivery. Additional treatment response data, including data from 28-day cohorts, is provided in the GBT440 IB.

Figure 1 **Hemoglobin (g/dL): Relative Change from Baseline, Median and 25th and 75th Percentiles**

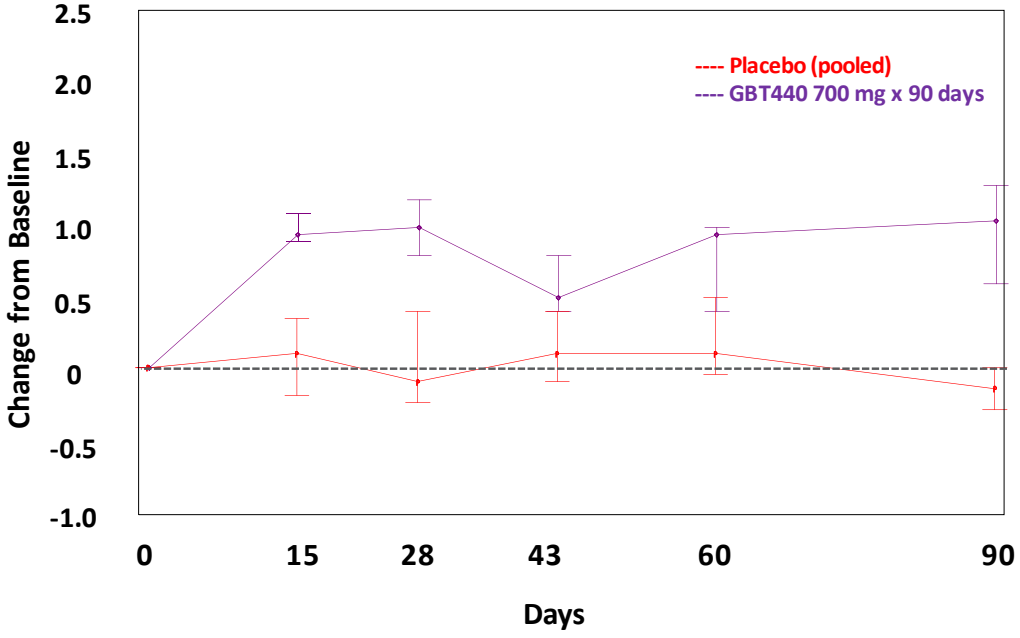


Figure 2 Changes in Lactate Dehydrogenase Levels

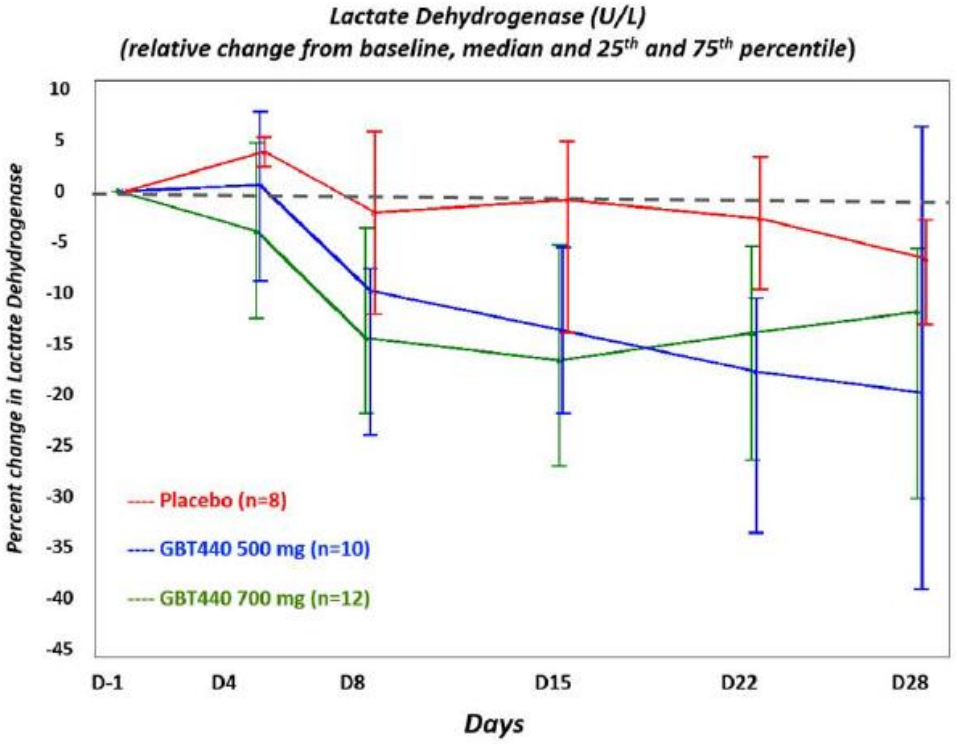
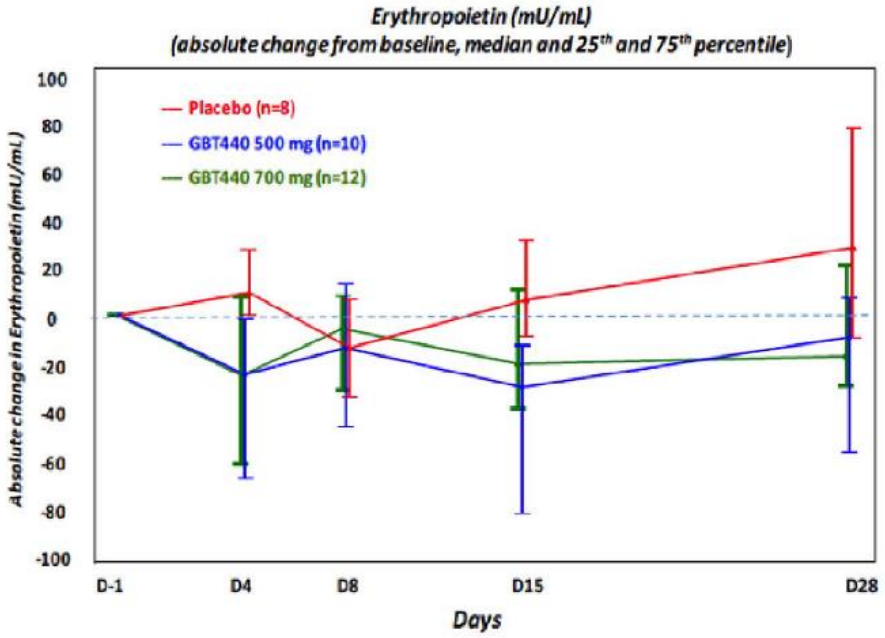


Figure 3 Changes in Erythropoietin Levels



5.2.2 Additional Phase 1 Data

A total of 156 healthy subjects have been enrolled in the 8 Phase 1 clinical pharmacology studies (GBT440-002, GBT440-003, GBT440-004, GBT440-005, GBT440-008, GBT440-017, GBT440-018, and GBT440-019). Results are available for GBT440-003 (cocktail drug interaction) and GBT440-004 (relative bioavailability), and preliminary results are available for GBT440-005 (food effect) and GBT440-008 (CYP2C8 interaction study) and GBT440-019 (PPI interaction study). Studies GBT440-017 (CYP2D6 interaction study) and GBT440-018 (bioavailability study [tablet compared to capsule formulation]) are ongoing.

5.3 Rationale

To date GBT440 has been generally well tolerated in patients with SCD for up to 90 days. There have not been any drug related SAEs and no unexpected AEs.

In addition preliminary pharmacodynamic data from patients with SCD treated with GBT440 for 28 days indicate a significant reduction in the number of the sickled RBCs, improvement in haemolysis markers as evidenced by declines in reticulocyte counts, unconjugated bilirubin and lactate dehydrogenase (LDH) levels and an improvement in anemia are encouraging. The initial impression of blinded data reviewed by the SMC suggests emerging data from GBT440-001 suggest that these improvements are sustained over 90 days of treatment.

Given the significant unmet need in SCD, there is an interest in determining the potential for further development of GBT440 by generating safety and efficacy data with longer term dosing (greater than 90 days) as quickly as possible while still safeguarding the safety of subjects. To do this safely and efficiently subjects in ongoing cohorts 17 and 15 in the GBT440-001 study will be enrolled in this proposed extension study. Additionally, SCD subjects from earlier Cohorts (i.e. Cohorts 7, 11, 12, 14 or 16) from GBT440-001 will be approached for enrollment into this study. Because of delays in initiating the GBT440-024 study, several subjects from Cohort 17 of GBT440-001 completed dosing and were unable to participate in this study. Many subjects from earlier cohorts expressed interest in longer term dosing with GBT440. The inclusion criteria have been expanded to allow enrolment of subjects with SCD who have completed the GBT440-001 study however total enrollment into this study will be limited to a total of 16 subjects. To continue to ensure the safety of subjects, regular safety monitoring and additional periodic SMC review during the total 6 month treatment period will be implemented. In particular, haemoglobin levels, reticulocyte count and erythropoietin levels will be monitored for evidence of tissue hypoxia/hyperviscosity. GBT440 treatment will be discontinued for excessive Hb increase or dose reduced for evidence of hyperviscosity based on increasing Hb, erythropoietin and reticulocyte levels.

5.3.1 Rationale for Dose Titration

Dose titration has been added because data from the GBT440-001 study has shown a linear and highly significant relationship between GBT440 blood level and improvement in hemolysis and no plateau effect has been reached. This suggests that subjects may derive greater benefit at higher doses achieving higher haemoglobin occupancy. Furthermore the target for optimal efficacy based on individuals with HbS/Hereditary persistence of fetal haemoglobin is 20-30% haemoglobin occupancy (Ngo 2011) and the preliminary PK data from Cohort 17 showed that the majority of subjects did not maintain haemoglobin occupancy >20% at 900 mg daily dosing. In addition, no dose limiting toxicities or concerning dose-or exposure related toxicities pose a safety concern with higher doses. Doses of 1000 mg for 28 days and 900 mg for 90 days have been well tolerated, with the majority of AEs were Grade 1 or 2 in severity. At 1500 mg, the predicted C_{max} is 167 µg/mL, which is less than the C_{max} already observed and found to be well-tolerated in healthy volunteerrs in GBT440-001 (294 µg/mL at 900 mg [Cohort 10]).

To assess the higher dose of 1500 mg, subjects will be dose escalated by 300 mg over 2-week intervals. The principal investigator will determine if the 600 mg or the 900 mg dose is well tolerated (after at least 28 days of prior dosing), and that the subject may receive further benefit from higher dosing (further improvement in haemoglobin, reticulocyte count or unconjugated bilirubin) the dose may be increase by one capsule (300 mg) every two weeks up to a maximum of 1500 mg.

This study will be performed in compliance with the protocol, ICH GCP and applicable regulatory requirements. Aspects of the study concerned with the investigational medicinal product(s) (IMPs) will meet the requirements of EU GMP.

5.4 Risk Assessment

Based on the mechanism of action of GBT440 and findings in the nonclinical safety toxicology studies, GBT440 could cause tissue hypoxia. In GLP toxicology studies, rats dosed for 28 days with ≥250 mg/kg/day demonstrated increased erythropoietin and red cell mass (Hct, RBC, or Hb) with extramedullary hematopoiesis and bone marrow hypercellularity. These findings are consistent with expected physiologic compensation to hypoxia, were not considered adverse, and were reversible.

In prior clinical experience with other agents, no adverse reactions related to tissue hypoxia were reported at the highest tested doses of tucaresol administered in either healthy subjects (maximum 40% Hb-modification) or subjects with SCD (maximum 24% Hb modification), or BW12C infusions in either healthy subjects (maximum 40% Hb-modification) or subjects with SCD (23% Hb modification) (Arya 1996, Keidan 1986, Nicholls 1989, Rolan 1995). Appropriate acute and chronic compensatory physiologic responses to tissue hypoxia were observed, including an increase in heart rate during

moderate exercise and a slight increase in reticulocyte counts at high doses (Nicholls 1989, Rolan 1995, Rolan 1993). Importantly, healthy subjects were well compensated-both at rest and at near maximal exercise with little change in resting heart rate (Nicholls 1989). Potential tissue hypoxia can be monitored by hematology laboratory studies, erythropoietin levels, and cardiovascular parameters.

Gastrointestinal effects (primarily emesis, and soft or liquid feces) were observed in all species and were dose-limiting in dogs and monkeys. Gastrointestinal erosions, ulcers, or epithelial hyperplasia were observed at high doses in rats.

Preliminary results from Study GBT440-001 evaluating GBT440 in adult subjects suggest that GBT440 is well tolerated in healthy subjects at single doses from 100 to 2800 mg and in subjects with SCD at a single dose of 1000 mg. The results also suggest that GBT440 is well tolerated in healthy subjects following repeat administration at dosages up to 900 mg once daily for 15 days, and in subjects with SCD following administration at dosages up to 1000 mg once daily for 28 days. The Safety Monitoring Committee (SMC) review of ongoing dosing in a 90 day treatment cohort at 700 mg and 900 mg per day has found GBT440 to be generally safe and well tolerated (as of 06 June 2016). The most commonly reported AEs across all subjects principally included diarrhea and headache; these events were often considered by the Investigator to be treatment-related. In addition, the decline in erythropoietin levels suggest an improvement in oxygen delivery either by increase in hemoglobin or improvement in microvascular blood flow, or both.

5.5 Urgent safety measures

In accordance with UK Law [Medicines for Human Use (Clinical Trials) as amended: SI 1031 Part 4 Section 30] the Sponsor and Investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical trial against any immediate hazard to their health or safety. If such measures are taken the Sponsor shall immediately (no later than 3 days from the date the measures are taken) give written notice to the licensing authority and the relevant ethics committee of the measures taken and the circumstances giving rise to those measures.

6.0 STUDY OBJECTIVES

6.1 Primary Objective

- To evaluate the safety and tolerability of up to a total of 6 months dosing in subjects with sickle cell disease (SCD) who participated in the GBT440-001 study.

6.2 Secondary Objectives

- To observe the pharmacokinetics (PK) of GBT440 in plasma and whole blood in subjects with SCD.
- To characterize the effect on biomarkers of hemolysis in subjects with SCD.

6.3 Exploratory Objectives

- To obtain data on exploratory markers of sickle cell disease activity.
- To obtain data on sickle cell disease symptoms.

7.0 INVESTIGATIONAL PLAN

7.1 Overall Study Design

This is an open label, single arm study.

Up to 16 subjects with SCD who were enrolled in the GBT440-001 study (Cohorts 7, 11, 12, 14, 15, 16 or 17 will be eligible to participate.. On attendance to the clinic, subjects in Cohorts 15 or 17 will be asked whether they want to be considered for study GBT440-024. If the subject is interested in study GBT440-024 all consent activities will be completed before the samples/procedures for GBT440-024 are collected/performed. For subjects who were enrolled in Cohorts 7, 11, 12, 14, 16 or 17 who are interested in participating in study GBT440-024, all consent activities will be completed before the samples/procedures for GBT440-024 are collected/performed. Prior to enrolment into this study the individual subject treatment allocations for eligible subjects from the GBT440-001 (Cohorts 15 or 17) will be unblinded and subjects will be assigned to the following treatment groups:

Group 1

Subjects from Cohort 17 in the GBT440-001 study who have received GBT440 900 mg per day for 4 months will continue receiving GBT440 900 mg per day for a further 2 months in this study.

Group 2

Subjects from Cohort 17 in the GBT440-001 study who have received placebo for 2 months will receive GBT440 900 mg per day for 6 months in this study.

Group 3

Subjects from Cohort 15 in the GBT440-001 study who have received GBT440 600 mg per day for 2 months will continue receiving GBT440 600 mg for a further 4 months in this study or the dose may be increased if the subject has tolerated 600 mg in GBT440-001.

Group 4

Subjects from Cohort 15 in the GBT440-001 study who have received placebo for 2 months will receive GBT440 900 mg per day for 6 months in this study.

Group 5

Subjects from Cohort 7, 11, 12, 14, 16 or 17 who received either GBT440 or placebo will receive a total of continuous 6 months of treatment with GBT440 in this study (GBT440 024) at a dose of 900 mg per day.

Subjects enrolled on this study will be numbered based on the subject number that were assigned in Study GBT440-001 with the addition of 24 to the beginning of the subject number. eg, Subject 17001 in study GBT440-001 will be assigned number 2417-1001 in study this study.

Subject numbering in this study will be as follows:

GBT440-001 Cohort	GBT440-001 Subject Number	GBT440-024 Group	GBT440-024 Subject Number
17	17001-17008	1 and 2	2417-1001 to 2417-1008
15	15001-15008	3 and 4	2415-1001 to 2415-1008
7	07001-07008	5	2407-1001 to 2407-1008
11	11001-11016		2411-1001 to 2411-1016
12	12001-12014		2412-1001to 2412-1014
14	14001-14008		2414-1001 to2414-1008
16	16001-16008		2416-1001 to 2416-1008

If a subject from GBT440-001 elects not to participate in this protocol, their corresponding identification number would remain unused.

All Subjects will receive a total of 6 months treatment with GBT440 which will include treatment with GBT440 in the GBT440-001 study for subjects in Cohort 15 or 17. Subjects from Cohort 7, 11, 12, 14, 16 or 17 who received either GBT440 or placebo will receive a total of 6 months of treatment with GBT440 in this study.

A Safety Monitoring Committee (SMC) consisting of the Principal Investigator, Sponsor Medical Monitor, and Independent Safety Physician will have overall responsibility for assessing safety and tolerability. The SMC will review cumulative data at least monthly to determine whether continued dosing may proceed. The responsibilities of the SMC will be described in a separate charter.

7.1.1 Stopping Rules

Individual subject stopping rule

- Dosing for any individual subject will be stopped if the subject experiences a serious adverse event (SAE) or a clinically significant non serious AE, which in

the opinion of the Principal Investigator or Sponsor's Medical Monitor, warrants discontinuation of the study for that subject's wellbeing.

7.2 Study Population

Male/female patients with sickle cell disease will be entered into this study provided that they satisfy the following inclusion/exclusion criteria.

7.2.1 Subject Inclusion Criteria

1. Male or female subjects with HbSS, HbS/β^0thalassemia, HbS/β^+thalassemia, or HbSC aged 18 to 60 years inclusive and >50 kg who have enrolled in cohorts 15 or 17 of the GBT440-001 study and will not experience interruption in dosing for greater than 7 days prior to commencing continuation of dosing in this extension study protocol.

2. Male or female subjects who were enrolled in Cohorts 7, 11, 12, 14, 16 or 17 in the GBT440-001 study (and are currently off-study) are eligible to enroll into this study.

3. Subjects who if female and of child bearing potential, agree to continue to use highly effective methods of contraception prior to enrolment in this study and for 3 months after the last dose of IMP.

4. Subjects whose clinical laboratory test results are not clinically relevant and continue to be acceptable to the Investigator at the final visit of the GBT440-001 study for subjects enrolled in Cohort 15 or 17.

5. Subjects who if male are willing to continue to use barrier methods of contraception, prior to enrolment in this study to 3 months after the last dose of IMP.

7.2.2 Subject Exclusion Criteria

1. Subjects requiring chronic transfusion therapy.

2. Subjects receiving a blood transfusion within 30 days of enrolment in this study.

3. Subjects with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5x upper limit of normal reference range (ULN)

4. Subjects with moderate or severe renal dysfunction (calculated modification of diet in renal disease estimated glomerular filtration rate (MDRD eGFR) <60mL/min/1.73 m^2 appropriately corrected for race and gender).

5. Subjects with any history of congestive heart failure requiring hospitalisation or whose 12 lead ECG prior to enrolment has a confirmed QTcF interval of >450 msec for male subjects or >470 msec for female subjects.
6. Subjects who do not conform to the above inclusion criteria.
7. Female subjects who are pregnant, trying to become pregnant or lactating.
8. Subjects who have a clinically relevant history or presence of respiratory, gastrointestinal, renal, hepatic, haematological, lymphatic, neurological, cardiovascular, psychiatric, musculoskeletal, genitourinary, immunological, dermatological, connective tissue diseases or disorders, or additional risk factors for torsades de pointe (e.g., heart failure, hypokalemia, personal or family history of long QTc interval).
9. Subjects who have a history of relevant atopy.
10. Subjects who have a history of relevant drug hypersensitivity.
11. Subjects who have a history of alcoholism.
12. Subjects who have a history of drug abuse (N.B. occasional recreational cannabis use is not an exclusion).
13. Subjects who consume more than 14 (female subjects) or 21 (male subjects) units of alcohol a week.
14. Subjects who have a significant infection or known inflammatory process on admission to this study.
15. Subjects who have acute gastrointestinal symptoms at the time of admission (e.g. nausea, vomiting, diarrhoea, heartburn).
16. Subjects who have an acute infection such as influenza at the time of admission.
17. Subjects (females of child-bearing potential and males) who do not agree to use contraception (as defined in Section 7.2.3.2).
18. Subjects who are vegans.
19. Subjects who cannot communicate reliably with the Investigator.
20. Subjects who are unlikely to co-operate with the requirements of the study.

7.2.3 Restrictions

- Since GBT440 is a weak inhibitor of cytochrome P450 (CYP3A4), GBT440 should be used with caution with CYP3A4 substrates with a narrow therapeutic index (refer to Table 1).
- In vitro data suggest that GBT440 could be metabolized by CYP1A1, 1B1, 2B6, 2C9, 2C19, 3A4, and 3A5. Thus strong inducers of CYP2B6, CYP2C9, CYP2C19, and CYP3A4/CYP3A5 should be prohibited (Table 2). The use of herbal medications (e.g., St. John's Wort) are not allowed.

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
CYP2C8	None

*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.

Table 2: Strong CYP Inducers

CYP	Strong Inducers
CYP3A4/3A5	Aavasimibe, 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.

- During the study, male subjects should continue to avoid consuming more than 3 units of alcohol per day and female subjects should continue to avoid consuming more than 2 units of alcohol per day.
- Subjects will be required to abstain from blood or plasma donation until 3 months after the final medical examination at the study clinic follow up.

If a subject does not comply with these restrictions or tests positive to any laboratory tests (e.g. drug, alcohol) they may be excluded or withdrawn from the study.

7.2.3.1 Avoidance of Pregnancy

Women of Child Bearing Potential

Pregnancy should be avoided by either true abstinence or the use of highly effective means of contraception (see Section 7.2.3.2) for the duration of the study and a total period of 3 months after the subject has taken the last dose of GBT440.

In order to include women of child bearing potential in any clinical trial, certain precautions pertaining to pregnancy must be taken. These will include serum pregnancy testing at enrollment and urine pregnancy test at the times indicated in Table 4, Table 5 and Table 6.

Female subjects who become pregnant during a study will be withdrawn.

Women of Non-Child Bearing Potential

Female subjects of non-child bearing potential are defined as; bilateral oopherectomy / hysterectomy/ post-menopausal females being amenorrhoeic for greater than 2 years with an appropriate clinical profile, e.g. age appropriate, history of vasomotor symptoms.

Instructions for Male Subjects

There is no information about effects that GBT440 could have on the development of the foetus in humans. Therefore, it is important that the partners of male subjects do not become pregnant during the study and for a total period of 3 months after the male subject has taken the last dose of GBT440.

As a precaution, all male subjects should avoid fathering a child by either true abstinence or the use of barrier methods of contraception (see Section 7.2.3.2).

As there is no information for GBT440 being secreted in the ejaculate, male subjects (including men who have had vasectomies) whose partners are currently pregnant should use barrier methods for the duration of the study and for 3 months afterwards. This is to ensure that the foetus is not exposed to the IMP in the ejaculate.

7.2.3.2 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

Hormonal contraception must be supplemented with a barrier method (preferably male condom).

- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable

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:

- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:

7.2.3.3 Time Period for the Collection of Pregnancy Information

All pregnancies in female subjects and the female partners of male subjects receiving at least one dose of IMP will be recorded from first dose to 3 months after the final dose.

7.2.3.4 Follow-up in the Event of a Pregnancy

If a female subject, or the female partner of a male subject, who has received IMP becomes pregnant, the pregnancy will be recorded. The ethics committee and the Sponsor will be informed. The subject will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise.

Spontaneous miscarriage and congenital abnormalities will be reported as SAEs.

The follow-up period will be deemed to have ended when the health status of the child has been determined at birth.

7.2.4 Subject Withdrawals

The Principal Investigator will make every reasonable attempt to complete the study. A subject may withdraw for any reason. The Principal Investigator will advise the Sponsor of the withdrawal of any subject.

A subject may be withdrawn in any of the following circumstances:

- AEs;
- Protocol violation;
- Withdrawal of consent;
- Termination of the study by the Principal Investigator or Sponsor.

Subjects who voluntarily withdraw are termed dropouts. Dropouts and subjects withdrawn due to protocol violations may be replaced following discussion with the Principal Investigator and Sponsor.

Subjects withdrawn due to an adverse event will not be replaced.

Should a subject request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Subjects withdrawing due to an AE should be followed up according to follow-up visit.

7.2.5 Study Termination

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the incidence or severity of adverse events in this or other studies indicating a potential health hazard to subjects.

8.0 STUDY TREATMENT

8.1 Investigational Product(s)

GBT440 oral capsules 300 mg capsules.

8.1.1 Supply, Packaging and Labelling

GBT440 oral capsules will be supplied to the Investigational Site by GBT or their representative.

Individual subject treatments will be dispensed by the Investigational Site Pharmacist.

A release document signed by Investigational Site Pharmacist or designee at the Investigational Site will be placed in the appropriate section of the Trial Master File to document labelling and dispensing of the study drug to the subject. A Pharmacy Manual (detailing IMP handling instructions) will be in place to cover all pharmacy related activities, and IMP accountability. .

8.1.2 Storage and Handling Procedures

All study medication will be stored at 25°C protected from light in the storage area of the Investigational Site Pharmacy, which is a secure, temperature controlled, locked environment with restricted access.

No special procedures for the safe handling of GBT440 are required. The Sponsor will be permitted upon request to audit the supplies, storage, dispensing procedures and records provided that the blind of the study is not compromised.

8.1.3 Accountability

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

All unused supplies of GBT440 will either be destroyed by the Investigational Site or returned to the study Sponsor at the end of the study in accordance with instruction by the Sponsor.

8.2 Dosage and Administration

GBT440 will be administered as oral capsule formulations with water as follows.

During the outpatient dosing period and in between study visits, subjects will not be required to fast and should take their study drug in the morning.

On study visits during the dosing period when PK samples are collected, subjects should have an overnight fast prior to taking study drug in clinic.

Additionally, during the outpatient dosing period in between study visits, subjects may be contacted weekly phone by clinic staff to confirm study drug administration.

Dosing will be stopped if the Hb is >12.8 g/dL but may restart at a reduced dose once the Hb is <12 g/dl following consultation and agreement of the referring SCD NHS haematologist.

8.2.1 Dose Titration

Provided the Principal Investigator determines that the 600mg dose (in Cohort 15), 900 mg dose (in Cohort 17), and 900 mg dose in the Cohorts 7, 11, 12, 14, 16 or 17 is well tolerated (after at least 28 days of dosing), and that the subject may receive further benefit from higher dosing (further improvement in haemoglobin, reticulocyte count or unconjugated bilirubin) the dose may be increase by one capsule (300 mg) every two weeks up to a maximum of 1500 mg dose.

When increasing the dose, the subject should return to clinical every 2 weeks for Laboratory and AE assessments

8.3 Dose Modification

Dose modification may be considered if warranted and as outlined below. All instances of study drug modification (change in dosing frequency, dose reduction or discontinuation) are to be captured in the subject research record and on the CRF and will require prompt notification of the medical monitor (i.e., typically within 48 hours). If the conditions/event leading to the dose modification have resolved, the original dose level and once a day dosing frequency should be resumed, unless in the judgement of the investigator, this cannot be done safely. Dose reductions will be made in 300 mg increments.

Dose level may be reduced for:

- Mild or moderate (Grade ≤2) adverse events that persist for ≥72.
- Moderate (Grade ≥2) adverse events that require intervention (excluding over the counter symptomatic treatment such as acetaminophen, NSAIDs, antacids, antihistamines), that in the Investigator's judgement are deemed study drug related.
- Severe (Grade ≥3) adverse events that are not serious and that in the Investigator's judgement are deemed study drug related.

Study drug may be suspended for:

- Any AE that, in the opinion of the Investigator is drug related and warrants suspension of dosing.

- Re-initiation of dosing will be based on the Investigator's clinical assessment in consultation with the sponsor.
- If the conditions/event leading to the dose suspension have improved or resolved, dosing should be resumed at the original dose level and once a day dosing frequency, unless in the judgement of the investigator, this cannot be done safely.

Study drug may be discontinued for:

- Grade ≥ 3 drug-related SAE
- Any AE that, at the discretion of the Investigator, warrants discontinuation of study drug.

8.4 Warnings and Precautions

The preclinical data suggest an acceptable safety margin. The clinical data to date suggests that GBT440 is well tolerated. However GBT440 is in early clinical development. Facilities and staff for resuscitation and the treatment of other medical emergencies will be provided during clinic visits. During outpatient dosing periods, subjects will be provided with emergency numbers and contacted on a regular basis (weekly) by clinic staff to monitor their wellbeing.

8.5 Prior and Concomitant Medication

The SCD subjects will be allowed to take the medications as needed with the exception of those described listed in Section 7.2.3. All concomitant medication will be documented.

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. All treatments must be recorded in the subjects' case report form (CRF) (medication, dose, treatment duration and indication).

Subjects will be provided with a diary card for completion during outpatient periods and will be instructed to document in the diary all details of AEs, and details of any medication taken

8.6 Method of Assigning Subjects to Treatment Groups

Following confirmation of continued eligibility subjects will be assigned to the following treatment groups:

Group 1

Subjects from Cohort 17 in the GBT440-001 study who have received GBT440 900 mg per day for 4 months will continue receiving GBT440 900 mg per day for a further 2 months in this study.

Group 2

Subjects from Cohort 17 in the GBT440-001 study who have received placebo for 4 months will receive GBT440 900 mg per day for 6 months in this study.

Group 3

Subjects from Cohort 15 in the GBT440-001 study who have received GBT440 600 mg per day for 2 months will continue receiving GBT440 600 mg for a further 4 months in this study or the dose may be increased if the subject has tolerated 600 mg in GBT440-001.

Group 4

Subjects from Cohort 15 in the GBT440-001 study who have received placebo for 2 months will receive GBT440 900mg per day for 6 months in this study.

Group 5

Subjects from Cohort 7, 11, 12, 14, 16 or 17 who received either GBT440 or placebo who are enrolled into this study will receive GBT440 at a dose of 900 mg per day for a total of 6 months in this study.

All Subjects will receive a total of 6 months treatment with GBT440 which will include treatment with GBT440 in the GBT440-001 study for subjects in Cohort 15 or 17. Subjects from Cohort 7, 11, 12, 14, 16 or 17 who received either GBT440 or placebo will receive a total of 6 months of treatment with GBT440 in this study.

8.7 Randomisation Procedures

Not Applicable – this is an open label single arm study in which all subjects will receive GBT440.

9.0 STUDY PROCEDURES

Table 2 Estimated Blood Volumes:

Assessment	Sample Volume (mL)	No. of Samples	Total Volume (mL)
Sickle Cell Disease Subjects: Multiple Dose			
Safety			
Serum Biochemistry	3.5	Up to 10	35.0
Coagulation	1.8	Up to 8	14.4
Haematology	2.0	Up to 10	20.0
Pregnancy	3.5	8	28.0
Hba1c	3.5	7	24.5
Pharmacokinetic			
GBT440	2.0	11	22.0
Pharmacodynamic			
Serum erythropoietin (EPO)	3.5	Up to 8	28.0

Assessment	Sample Volume (mL)	No. of Samples	Total Volume (mL)
Frozen Plasma Reserved for immunology/inflammation ELISAs and exploratory markers	5.0	Up to 8	40.0
Haemoglobin electrophoresis	2.0	Up to 4	8.0
Carboxyhaemoglobin	2.0	Up to 7	14.0
Disease Related			
Dense Cells	2.0	Up to 8	16.0
NT pro-BNP	2.0	Up to 8	16.0
Total [b]			335.9

Sample volumes are based on direct venipuncture.

9.1 Pharmacokinetic Assessments

Serial whole blood samples will be obtained from all and SCD subjects at the times shown in the schedule of events (see Section 17.0) for the determination of GBT440 concentrations in whole blood and plasma.

Blood and plasma samples will be analyzed for GBT440 using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

9.2 Pharmacodynamic/Treatment Response Assessments

Sample collection and assessment times are included in the schedule of events (see Section 17.0).

9.2.1 Haemolysis markers:

Haemoglobin, unconjugated bilirubin, LDH, absolute and % reticulocyte counts and % dense cells will be measured.

9.2.2 Disease Related Assessments:

Inflammatory markers and exploratory biomarkers related to SCD disease severity will be assessed and may include, but are not limited to:

- Serum erythropoietin
- Urine microalbumin
- Plasma cytokines or other exploratory markers of SCD
- Haemoglobin F levels
- Immune and Inflammatory plasma biomarkers (e.g. inflammatory cytokines)

9.3 Safety Assessments

9.3.1 Adverse Events

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any clinically significant sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Drug Reaction (ADR)

Any untoward and unintended response in a subject to an IMP which is related to any dose administered to that subject.

Serious Adverse Event (SAE)

An adverse reaction is ‘serious’ if it:

- Results in death;
- Is life-threatening;
- Requires hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect;
- Is a medically important event.

Unexpected Adverse Reactions

An adverse reaction is ‘unexpected’ if its nature and severity are not consistent with the information about the medicinal product in question set out:

- 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 (Investigator's Brochure Version 3, 2016).

9.3.2 Reporting of Adverse Events

All AEs must be fully recorded in the AE book throughout the entire study period and will be transcribed into the subjects’ CRF, whether or not they are considered to be drug-related. Signs and symptoms of each AE should be described in detail: onset time and

date, offset time and date, description of event, severity and relationship to IMP, action taken and outcome.

Adverse events ongoing from study GBT440-001 will be recorded and identified in the CRF as being ongoing from study GBT440-001 for Cohorts 15 or 17.

Adverse events will be recorded beginning with administration of study drug in GBT440-024.

All adverse events should be followed until recovery to the normal state has been achieved. In the event of a subject not returning to the clinical unit, the outcome of this event will be recorded as lost at follow up.

Diagnosis versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF 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 CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

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 CRF.

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

Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the CRF unless their severity increases. If a persistent AE becomes more severe, it should be recorded again on the CRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on the CRF.

Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (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. alkaline phosphatase and bilirubin 5× the ULN associated with cholecystitis), only the diagnosis (e.g. cholecystitis) needs to be recorded on the CRF.

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 CRF. If the laboratory abnormality can be characterised 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 CRF, unless their severity, seriousness, or etiology changes.

Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be recorded on the CRF.

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g. "more frequent headaches").

Worsening of Sickle Cell Disease

Complications related to SCD should be recorded as an AE or SAE only if judged by the investigator to have unexpectedly worsened in severity and/or frequency or changed in nature any time during the study. When recording an unanticipated worsening of SCD on the CRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g. "expansion of nonhealing leg ulcer"). Specific SCD- related AEs will be tabulated and reported (see assessment of safety section).

Protocol-Defined Events of Special Interest

The following events are events of special interest and will need to be reported to the Sponsor's medical representative Josh Lehrer-Graiwer, MPhil, MD, FACC within 24 hours, irrespective of regulatory seriousness criteria: any suspected drug

hypersensitivity reactions. Suspected drug hypersensitivity includes but is not limited to any occurrence of two or more of the following: fever, rash or lymphadenopathy.

Reporting of SAEs and SUSARs

SAEs occurring on this study will be reported to the Sponsor's medical representative Josh Lehrer-Graiwer, MPhil, MD, FACC within 24 hours. The Principal Investigator will be requested to complete a separate SAE reporting form in addition to the information on the CRF and in the AE book.

The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 1031) and subsequent amendments define the following terms:

A suspected unexpected serious adverse reaction (SUSAR) which is fatal or life-threatening must be reported to the competent authority and ethics committee immediately (within 7 days) after the Sponsor became aware of the event. Any additional information must be reported within 8 days of sending the first report.

A SUSAR which is not fatal or life-threatening must be reported to the competent authority and ethics committee as soon as possible (within 15 days) after the Sponsor becomes aware of the event.

If a clinical trial is being conducted at a trial site in a third country in addition to sites in the United Kingdom, the Sponsor of that trial shall ensure that all SUSARs occurring at that site are entered into the European database established in accordance with Article 11 of the EU Clinical Trials Directive.

As soon as practicable after the end of the reporting year, a Sponsor shall, in relation to each IMP tested in clinical trials in the United Kingdom for which he is the Sponsor provide the licensing authority and the relevant ethics committees with -

- A list of all the suspected serious adverse reactions which have occurred during that year in relation to:
    - those trials, whether at trial sites in the United Kingdom or elsewhere;
    - or any other trials relating to that product which are conducted outside the United Kingdom and for which he is the Sponsor;
- including those reactions relating to any investigational medicinal product used as a placebo or as a reference in those trials; and
- A report on the safety of the subjects of those trials.

9.3.3 Categorisation of Adverse Events

General AE grading scale:

- Grade 1: Transient or mild discomfort (<48 hours); no interference with daily activities; no medical intervention required.
- Grade 2: Mild to moderate interference with daily activity; no or minimal medical intervention required.
- Grade 3: Considerable interference with daily activity; medical intervention required; hospitalization possible.

9.3.4 Causal Relationship Assessment

Causal relationship assessment to drug treatments is required for purposes of reporting AEs. To promote consistency, the following guidelines should be taken into considerations along with good clinical and scientific judgment when determining the relationship of drug treatments to an AE:

Definitely Related: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to the medication administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible.

Possibly Related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to the medication administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on the drug withdrawal may be lacking or unclear.

Unlikely Related: A clinical event, including laboratory test abnormality, with little or no temporal relationship to medication administration, and which other drugs, chemicals or underlying disease provide plausible explanations.

Not Related: A clinical event, including laboratory test abnormality that has no temporal relationship to the medication or has more likely alternative etiology.

9.3.5 Action Taken

Action taken will be defined as:

- None;
- Dose reduced;
- Dosing interrupted;

- Dosing stopped.

9.3.6 Outcome

Outcome will be defined as:

- Resolved;
- Ongoing;
- Lost to follow up.

9.3.7 Coding of Adverse Events

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

9.4 Clinical Laboratory Safety Tests

Sample collection times are included in the schedule of events (see Section 17.0).

9.5 Clinical Laboratory Safety Tests

Sample collection times are included in the schedule of events (see Section 17.0).

Table 3 Laboratory Parameters

Panel	Parameters	
Haematology	Red blood cell count Haemoglobin Haematocrit Platelet count Mean cell volume White blood cell count (total leucocytes) Red cell distribution width-SD Red cell distribution width-CV	Neutrophils (absolute and %) Lymphocytes (absolute and %) Monocytes (absolute and %) Eosinophils (absolute and %) Basophils (absolute and %) Mean corpuscular haemoglobin Mean corpuscular haemoglobin concentration Reticulocyte count
Coagulation	Prothrombin time Activated partial thrombin time	International normalised ratio
Serum biochemistry	Aspartate transaminase Alanine transaminase Alkaline phosphatase Total bilirubin [direct and indirect] Lactate dehydrogenase (LDH) Creatine kinase [a] C-reactive protein	Sodium Potassium Chloride Urea Creatinine Albumin Calcium Phosphate Glucose Bicarbonate Iron studies (serum ferritin, iron and transferrin calculated [% transferrin saturation])
Urinalysis	Leucocytes Protein Bilirubin Urobilinogen Glucose	Ketones Blood pH Nitrite Specific gravity microalbumin creatinine
Urine microscopy	To be performed where clinically indicated	
Serum/urine pregnancy test [b]		

[a] Creatine kinase MB fraction will be performed if clinically indicated.

[b] The pregnancy test will be conducted in urine for subjects enrolling from Cohort 17 and 15. The pregnancy test will be conducted on a serum sample at baseline visit for subjects from Cohort 7, 11, 12, 14 or 16 and in urine at the other times.

[c] At the physicians discretion when clinically indicated.

Additional and repeat testing may be performed at the discretion of the Investigator.

Unless otherwise specified all clinical laboratory tests will be performed by Viapath.

Details of all methodology and reference ranges are provided in the Trial Master File.

9.6 Clinical Safety Assessments

Assessment times are included in the schedule of events (see Section 17.0).

Vital Signs

Blood pressure, heart rate, respiration rate and oral temperature will be measured using an automated instrument after the subject has rested comfortably for 2 minutes in the supine position. Additional vital signs may be added for safety of the subjects at the discretion of the Investigator.

12 Lead ECG

Computerised 12-lead ECG recordings will be obtained as a single measurement. Each lead shall be recorded for at least 3 beats at a speed of 25 mm/sec. Subjects should be lying quietly in a fully supine position for at least 5 minutes prior to each 12-lead ECG.

The following parameters will be recorded: rhythm, ventricular rate, PR interval, QRS duration, QT and QTcF.

Medical History

A complete medical history will include evaluation (past or present) of the following: general, head and neck, eyes, ears, nose throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, gynecological/urogenital, musculoskeletal/extremities, skin, neurological/psychiatric, endocrine/metabolic, haematologic/lymphatic, allergies/drug sensitivities, past surgeries, substance abuse or any other diseases or disorders.

Physical Examination

Physical examinations will be performed by a physician and will include the examination of the following: general appearance, eyes, ears, nose, throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, musculoskeletal/extremities, dermatological/skin, thyroid/neck, lymph nodes, neurological/psychiatric. The physical examinations will include specific surveillance for skin rashes and lymphadenopathy.

In addition a directed physical examination may be conducted if there are any previously identified or new signs or symptoms including any adverse events or diagnoses the subject has experienced since the last visit. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate.

Height and Body Weight

Height will only be measured at baseline visit The subjects will be required to remove footwear and will wear normal indoor clothing during the measurement of height and weight.

10.0 DATA COLLECTION

Paper CRFs will be produced by Quintiles. Study data including laboratory safety data will be recorded in the CRF by the Investigational Site Staff. Laboratory safety data will be recorded in the CRF only if the lab cannot provide an electronic transfer.

Study data will be recorded on source documents provided by Quintiles when direct data entry into CRFs is inappropriate or impractical. Data from source documents will be transcribed, where necessary, into CRFs by the Investigational Site staff. All source documents will be retained by the investigational site. Photocopies of completed source documents will be provided only if essential (i.e. for regulatory purposes) at the request of the Sponsor.

The CRFs must be kept in order and up-to-date so that they always reflect the latest observations on the enrolled subjects.

Safety laboratory data may be integrated with the consolidated clinical data by Quintiles before database lock.

All records should be kept in conformance to applicable national laws and regulations.

Adverse events will be coded using the current MedDRA thesaurus; concomitant medication will be coded using WHO DD (if required).

CRFs must be completed legibly for each subject enrolled in the study and signed-off by the Investigator.

11.0 EVALUATION OF STUDY DATA

11.1 Evaluation of Pharmacokinetic Parameters

Whole blood and plasma levels of GBT440 as indicated in the schedule of assessments in section 17.

11.2 Evaluation of Pharmacodynamic Measures

11.2.1 Haemolysis markers:

Haemoglobin, unconjugated bilirubin, LDH, absolute and % reticulocyte counts and % dense cells will be measured as indicated in the SOA.

11.2.2 Disease Related Assessments:

Inflammatory markers and exploratory biomarkers related to SCD disease severity will be assessed as indicated in the SOA.

11.3 Evaluation of Safety

The safety evaluation will include blood pressure, pulse rate, body temperature, respiratory rate, ECG parameters, clinical laboratory tests (haematology, serum biochemistry (including erythropoietin), coagulation, urinalysis and urine microscopy) and adverse events.

12.0 STATISTICAL METHODS

Statistical programming and analyses will be performed using established statistical methods. 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.

12.1 Sample Size Determination

This is an extension study following on from GBT440-001. The sample size has therefore not been subject to any statistical considerations.

12.2 Subject Population for Analyses

The PK population will consist of all subjects who receive active study drug and have at least 1 measured concentration at a scheduled PK time point after start of dosing for at least 1 PK analyte. If any subjects are found to be noncompliant with respect to dosing or have incomplete data, protocol violations, or clinical events that affect PK, a decision will be made on a case-by-case basis as to their inclusion in the analysis. Subjects in this population will be used for all PK summaries.

The PD population will consist of all subjects who receive active study drug, and have at least 1 measured value at a scheduled PD time point after start of dosing for at least 1 PD analyte. If any subjects are found to be noncompliant with respect to dosing or have incomplete data, or protocol violations, 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 PD summaries.

The safety population will include all subjects who receive at least 1 dose of the study drug. Subjects in this population will be used for all demographic and safety summaries.

12.3 Pharmacokinetic Analysis

A listing of PK sample collection times will be provided. Whole blood and plasma levels of GBT440 will be listed and summarised using appropriate descriptive statistics by dose and study day. Where appropriate an estimate of apparent elimination half -life ($t_{½}$) will be computed and presented in tabular form with appropriate descriptive statistics

12.4 Pharmacodynamic/Efficacy Analysis

Haemolysis and Disease related assessments will be listed and summarised at each time point using appropriate descriptive statistics.

12.5 Safety Data Analysis

Individual and summary blood pressures, heart rate, body temperature, respiratory rate, ECG parameters and clinical laboratory data (haematology, serum biochemistry and coagulation) will be presented in tabular form with appropriate descriptive statistics. Adverse events will be tabulated and summarized.

13.0 STUDY REPORT

A clinical study report, compliant with the requirements of ICH E3, will be prepared by Quintiles.

14.0 REGULATORY AND ETHICAL ISSUES

14.1 Regulatory and Ethics Review and Approval

The study will be submitted for to the Medicines and Healthcare products Regulatory Agency (MHRA-UK) for review and approval and to an Ethics Committee for ethical review and approval.

14.2 Informed Consent

Informed consent will be given freely after the subject has been informed of the nature, significance, implications and risks of the trial; and consent is evidenced in writing, dated and signed, or otherwise marked, by that person so as to indicate his/her consent, prior to the start of the study. The nature of the informed consent will comply with the current version of the Declaration of Helsinki, the current requirements of GCP (Committee for Proprietary Medicinal Products/ICH/135/95 and local regulation (The requirements are set out in Schedule 1 of Statutory Instrument 1031 and amendments) which ever provides the greater subject protection.

14.3 Indemnity and Compensation

In accordance with Statutory Instrument 1031 and amendments section 15 (5i, j) and the EU Clinical Trials Directive 2000/20/EC Article 3 (2f), provision is to be made for:

- The indemnity or compensation in the event of injury or death attributable to the clinical trial; and
- Insurance or indemnity to cover the liability of the Investigator or Sponsor.

Therefore the Sponsor Global Blood Therapeutics Inc will indemnify the Investigators, The BRC Clinical Research facility (KCL and GSTT) from all and any claims arising out of this study except for their negligence or malpractice and providing that the study is conducted according to the standards established by the protocol.

In the event that it can be demonstrated that a subject suffers any significant deterioration in health or well-being or any harmful susceptibility or toxicity as a direct result of their participation in this study then Global Blood Therapeutics, Inc will agree to abide by the current ABPI and FDA with regard to compensation payable to the subject. The amount of compensation will be calculated by reference to the level of damages commonly awarded in law for UK for similar injuries at the time when such injury occurred.

The Investigators, The BRC Clinical Research facility (KCL and GSTT) declare to having insurance cover for the malpractice and/or negligence of their employees and agents.

15.0 STUDY MANAGEMENT

15.1 Quality Assurance and Quality Control

In accordance with the guideline for ICH GCP, the Sponsor has responsibility for implementing and maintaining quality assurance and quality control systems, and the ultimate responsibility for the quality integrity of the trial data resides with the Sponsor.

15.2 Protocol Adherence

The protocol must be read thoroughly and the instructions followed exactly. Any deviations should be agreed by both the Sponsor and the Investigator, with the appropriate written and approved protocol amendments made to reflect the changes agreed upon. Where the deviation occurs for the well-being of the subject, the Sponsor must be informed of the action agreed upon.

15.3 Documents Necessary for Initiation of Study

The following documents will be available prior to the first administration of the drug to the first subject:

- Regulatory authorisation;
- Copy of current Investigator's Brochure;
- Risk assessment report;
- Completed and signed investigator agreement/contract;
- Signed original of the final protocol;
- Ethics Committee approval;
- Copy of the constitution of the Research Ethics Committee;
- A list of members of the Ethics Committee;
- A copy of the consent form and subject information to be used;
- The curriculum vitae of all Investigators;
- The Qualified Person's certification for the release of each batch of IMP;
- A technical agreement between the Sponsor and The Investigational Site defining the responsibilities of the Sponsor, The Investigational Site and Quintiles Ltd. and any third parties significantly involved in the supply chain of the IMP, where applicable;

- The product specification file, where applicable; and

  A list of laboratory reference range values for parameters measured in the study.

15.4 Study Monitoring

The Investigator will allow trial-related monitoring audits, ethics committee review, and regulatory inspection allowing direct access to the source data/documents.

15.5 Study Closure

Premature termination of the study by either Principal Investigator or Sponsor will be governed under the terms of the contract between both parties.

15.6 Study Record Retention

In accordance with SI 1928, the Sponsor and the Principal Investigator shall ensure that the documents contained, or which have been contained, in the trial master file are retained for at least 5 years after the conclusion of the trial and that during that period are:

- Readily available to the licensing authority on request; and
- Complete and legible.

All data derived from the study will remain the property of the Sponsor, Global Blood Therapeutics. The study will be the subject of a final clinical study report compiled by, or by order of the Sponsor.

All correspondence (e.g. with the Sponsor, ethics committee) relating to this study should be kept in the appropriate file folders.

Records of subjects source documents, CRF's, IMP inventory, pertaining to the study must be kept on file. Records must be retained according to the current ICH Guidelines on GCP.

The Sponsor and Principal Investigator shall ensure that the medical files of trial subjects are retained for at least 5 years after the conclusion of the trial. The Sponsor shall appoint named individuals within his organization to be responsible for archiving the documents which are, or have been, contained in the trial master file. Access to those documents shall be restricted to those appointed individuals. If there is transfer of ownership of data or documents connected with the clinical trial:

- The Sponsor shall record the transfer; and
- The new owner shall be responsible for data retention and archiving in accordance Statutory Instrument 1031 and amendments.

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.

15.7 Publication Policy

After completion of the study, the Sponsor may prepare a joint publication with the Principal Investigator. The Investigator must undertake not to submit any part of the individual data from this protocol for publication without prior consent of the Sponsor at a mutually agreed time.

16.0 REFERENCES

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17.0 STUDY SCHEDULE

Table 4 Schedule of Assessments Group 1

Group 1: Subjects from Cohort 17 in the GBT440-001 study who have received GBT440 900mg per day for 4 months will continue receiving GBT440 900 mg per day for a further 2 months.

Assessments	**Enrolment**	**Outpatient Treatment Period**							
Day number	**Last treatment day GBT440-001 (+6 days) a**	**1 a**	**15 +/-3 days g**	**30 +/-3 days**	**45 +/-3 days g**	**60 +/-3 days**	**67 +/-3 days**	**74 +/-5 days**	**88 end**
Visit number	0	1		2		3	4	5	6
Informed consent	X	X							
Eligibility assessment	X	X							
Medical History	X								
Physical examination **b**	X		X	X	X	X			X
Weight	X		X	X	X	X			X
Vital signs	X	X	X	X	X	X			X
12 Lead ECG (single) **c**				X		X			X
Drug administration **d**		X	----------X						
Adverse events	X----------X								
Urinalysis **e**	X		X		X				X
Urine microalbumin/creatinine	X								X
Haematology **e**	X		X	X	X	X			X
Serum biochemistry **e**	X		X	X	X	X			X
Coagulation **e**	X		X		X				X
Pregnancy test (females only)	X			X		X			X
Haemoglobin electrophoresis									X
PK samples (plasma and whole blood) **f**	X			X		X	X	X	X
Serum erythropoietin	X[h]			X		X			X
Exploratory plasma biomarkers	X[h]			X		X			X
Dense cells	X[h]			X		X			X
Carboxyhaemoglobin	X[h]								X
HbA1c	X[h]								X
NT-proBNP	X[h]								X
Concomitant medication diary	X----------X								

Key

a: Enrolment and visit 1 may be combined. On admission to the clinic the subjects will be asked whether they want to be considered for study GBT440-024. If the subject is interested in being enrolled on study GBT440-024 all consent activities will be completed before the samples/procedures for GBT440-001 or GBT440-024 are collected/performed. Visit 0 (enrolment visit) is the last day of treatment in GBT440-001, which can be 6 days before Visit 1. If the last day of treatment in GBT440-001 (Day 118 or Day 60 for Cohort 17 and Cohort 15) – the enrolment visit is not being repeated as standalone visit.

b: Complete physical examination on enrolment, a limited physical examination on all other days. Directed physical examinations will be performed as required.

c: 12 lead ECG (single) will be performed within 30 minutes prior to dose

d: GBT440 900 mg(three capsules) will be administered daily in the morning. On days when PK samples are drawn GBT 440 should be administered after an overnight fast.

During the dosing period subjects will be contacted every week in between out-patient visits to confirm GBT440 administration and subject well -being.

e: Additional samples will be collected if clinically indicated

f: PK samples will be drawn pre dose. If the dose is increased to 1500 mg, please collect the following timepoints: pre dose, then 1-4 hours, 6-8 hours and 24 hours post dose on study visit days of Day 15 (±3 days) , Day 60 (±3 days) and Days 90 (±3 days) of receiving 1500 mg.g: Days 15 and 45 are only to be conducted if the dose is increased to 1500 mg.

h: Can be omitted if measurements were collected in the past 7 days as part of the GBT440-001 study.

Table 5 Schedule of Assessments for Groups 2, 4 and 5

Groups 2: Subjects from Cohort 17 in the GBT440-001 study who have received placebo for 4 months will receive GBT440 900mg per day for 6 months

Group 4: Subjects from Cohort 15 in the GBT440-001 study who have received placebo for 2 months will receive GBT440 900 mg per day for 6 months

Group 5: Subjects with SCD from Cohorts 7, 11, 12, 14, 16 or 17 in the GBT440-001 study will receive GBT440 900 mg per day for 6 months

Assessments	**Enrolment a**		**Outpatient Treatment Period**											
Day number	**Last treatment day GBT440-001 (+6 days) Cohorts 15 and 17**	**Baseline for Cohort 7,11,12,14, 16 or 17 (within 7 days of Day`1)**	**1 +/-3 days a**	**15 +/-3 days**	**30 +/-3 days**	**45 +/-3 days**	**60 +/-3 days**	**90 +/-3 days**	**120+/-3 days**	**150+/-3 days**	**180 +/-3 days**	**187+/-3 days**	**194 +/-5 days**	**208 End**
Visit number	0		1	2	3	4	5	6	7	8	9	10	11	12
Informed consent	X	X												
Eligibility assessment	X	X												
Medical History	X	X												
Physical examination **b**	X	X		X	X		X	X	X	X	X			X
Weight	X	X		X	X	X	X	X	X	X	X			X
Vital signs	X	X	X	X	X	X	X	X	X	X	X			X
12 Lead ECG (single) **c**	X	X			X		X	X	X	X	X			
Drug administration **d**			X----------X											
Adverse events			X----------X											
Urinalysis **e**	X	X						X	X	X	X			X
Urine microalbumin/creatinine	X	X						X			X			
Haematology **e**	X	X		X	X	X	-	X	X	X	X			X
Serum biochemistry **e**	X	X		X	X	X	X	X	X	X	X			X
Coagulation **e**	X	X		X		X		X	X	X	X			X
Pregnancy test (females only)	X	X			X		X	X	X	X	X			X
Haemoglobin electrophoresis		X						X			X			X
PK samples (plasma and whole blood) **f**	X			X	X		X	X	X	X	X	X	X	X
Serum erythropoietin	X[h]	X			X		X	X	X	X	X			X
Exploratory plasma biomarkers	X[h]	X			X		X	X	X	X	X			X

Assessments	Enrolment a		Outpatient Treatment Period											
Day number	**Last treatment day GBT440-001 (+6 days) Cohorts 15 and 17**	**Baseline for Cohort 7,11,12,14, 16 or 17 (within 7 days of Day`1)**	**1 +/-3 days a**	**15 +/-3 days**	**30 +/-3 days**	**45 +/-3 days**	**60 +/-3 days**	**90 +/-3 days**	**120+/-3 days**	**150+/-3 days**	**180 +/-3 days**	**187+/-3 days**	**194 +/-5 days**	**208 End**
Dense cells	X[h]	X			X		X	X	X	X	X			X
Carboxyhaemoglobin	X[h]	X						X			X			X
HbA1c	X	X						X			X			X
NT-proBNP	X[h]	X						X			X			X
Concomitant medication diary		X	X----------X											

Key

Note: Visit 0 is the last treatment day for subjects in GBT-440-001 (Day 118 for Cohort 17 and Day 60 for Cohort 15)

a: Enrolment and visit 1 may be combined. On admission to the clinic the subjects will be asked whether they want to be considered for study GBT440-024. If the subject is interested in being enrolled on study GBT440-024 all consent activities will be completed before the samples/procedures for GBT440-001 or GBT440-024 are collected/performed. Visit 0 (enrolment visit) is the last day of treatment in GBT440-001, which can be 6 days before Visit 1. If the last day of treatment in GBT440-001 (Day 118 or Day 60 for Cohort 17 and Cohort 15) – the enrolment visit is not being repeated as standalone visit.

b: Complete physical examination on enrolment, a limited physical examination on all other days. Directed physical examinations will be performed as required.

c: 12 lead ECG (single) will be performed within 30 minutes prior to dose

d: GBT440 900mg(three capsules) for Group 2 and GBT 440 600mg (2 capsules) for Group 4 and GBT440 900 mg (3 capsules) for Group 5 will be administered daily in the morning. On days when PK samples are drawn GBT 440 should be administered after an overnight fast.

During the dosing period, subjects will be contacted every week in between outpatient visits to confirm GBT440 administration and subject well being.

e: Additional samples will be collected if clinically indicated

f: PK samples will be drawn pre dose. If the dose is increased to 1500 mg, please collect the following timepoints: pre dose, then 1-4 hours, 6-8 hours and 24 hours post dose on study visit days of Day 15 (±3 days) , Day 60 (±3 days) and Days 90 (±3 days) of receiving 1500 mg.

h: Can be omitted if measurements were collected in the past 7 days as part of the GBT440-001 study.

Table 6 Schedule of Assessments Group 3

Group 3: Subjects from Cohort 15 in the GBT440-001 study who have received GBT440 600 mg per day for 2 months will continue receiving GBT440 600 mg per day for a further 4 months (the dose may be increased if the subject tolerated 600 mg in GBT440-001).

Assessments	**Enrolment**	**Outpatient Treatment Period**								
Day number	**Last treatment day GBT440-001 (+6 days) a**	**1 +/-3 days a**	**30 +/-3 days**	**45 +/-3 days[g]**	**60 +/-3 days**	**90 +/-3 days**	**120+/-3 days**	**127 +/-3 days**	**134+/-5 days**	**148 End**
Visit number	0	1	2		3	4	5	6	7	8
Informed consent	X	X								
Eligibility assessment	X	X								
Medical History	X									
Physical examination **b**	X		X	X	X	X	X			X
Weight	X		X	X	X	X	X			X
Vital signs	X	X	X	X	X	X	X			X
12 Lead ECG (single) **c**	X		X		X	X	X			X
Drug administration **d**	X----------X									
Adverse events	X----------X									
Urinalysis **e**	X			X		X	X			X
Urine microalbumin/creatinine	X						X			X
Haematology **e**	X		X	X	X	X	X			X
Serum biochemistry **e**	X		X	X	X	X	X			X
Coagulation **e**	X			X		X	X			X
Pregnancy test (females only)	X		X		X	X	X			X
Haemoglobin electrophoresis					X	X				X
PK samples (plasma and whole blood) **f**	X		X		X	X	X	X	X	X
Serum erythropoietin	X[g]		X		X	X	X	X		X
Exploratory plasma biomarkers	X[g]		X		X	X	X			X
Dense cells	X[g]		X		X	X	X			X
Carboxyhaemoglobin	X[g]				X					X
HbA1c	X[g]					X				X
NT-proBNP	X[g]					X				X
Modified SCD severity questionnaire	X		X		X	X	X	X		X
Concomitant medication diary	X----------X									

Key

a: Enrolment and visit 1 may be combined. On admission to the clinic the subjects will be asked whether they want to be considered for study GBT440-024. If the subject is interested in being enrolled on study GBT440-024 all consent activities will be completed before the samples/procedures for GBT440-001 or GBT440-024 are collected/performed. Visit 0 (enrolment visit) is the last day of treatment in GBT440-001, which can be 6 days before Visit 1. If the last day of treatment in GBT440-001 (Day 118 or Day 60 for Cohort 17 and Cohort 15) – the enrolment visit is not being repeated as standalone visit.

b: Complete physical examination on enrolment, a limited physical examination on all other days. Directed physical examinations will be performed as required.

c: 12 lead ECG (single) will be performed within 30 minutes prior to dose

d: GBT440 600mg (two capsules) will be administered daily in the morning. On days when PK samples are drawn GBT 440 should be administered after an overnight fast.

During the dosing period, subjects will be contacted every week in between outpatient visits to confirm GBT440 administration and subject well-being.

e: PK samples will be drawn pre dose. . If the dose is increased to 1500 mg, please collect the following timepoints: pre dose, then 1-4 hours, 6-8 hours and 24 hours post dose on study visit days of Day 15 (±3 days) , Day 60 (±3 days) and Days 90 (±3 days) of receiving 1500 mg.

f. Days 45 are only to be conducted if the dose is increased to 1500 mg.

g: Can be omitted if measurements were collected in the past 7 days as part of the GBT440-001 study.

18.0 PROTOCOL SIGNATURES

INVESTIGATOR SIGNATURE:

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

Tim Mant — 28/SEP/2016

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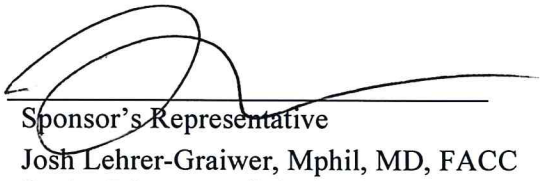

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