CLINICAL STUDY PROTOCOL

Protocol Title	**An Intrapatient Single Dose and Multiple Ascending Dose Study to Evaluate the Pharmacokinetics, Safety, Tolerability, and Pharmacodynamics of GBT021601, a Hemoglobin S Polymerization Inhibitor, in Participants with Sickle Cell Disease (SCD)**
Protocol Number	GBT021601-012
Version/Amendment	Version 6.0, Amendment 5
Date	08 March 2022
Sponsor	Global Blood Therapeutics, Inc. PPD PPD
Sponsor's Responsible Medical Officer/ Medical Monitor and Study Director	PPD Clinical Science Global Blood Therapeutics, Inc. PPD

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2. SYNOPSIS

Study Number and Title:

GBT021601-012: An Intrapatient Single Dose and Multiple Ascending Dose Study to Evaluate the Pharmacokinetics, Safety, Tolerability, and Pharmacodynamics of GBT021601, a Hemoglobin S Polymerization Inhibitor, in Participants with Sickle Cell Disease (SCD).

Study Short Title:

GBT021601-012 Single Dose and Multiple Ascending Dose in Participants with SCD.

Estimated Number of Study Centers and Countries or Regions:

Up to 3 sites in the United States of America.

Study Rationale:

This study will evaluate the pharmacokinetics (PK), safety, tolerability, and pharmacodynamics (PD) with a single dose followed by ascending, intrapatient doses of GBT021601, a hemoglobin S (HbS) polymerization inhibitor, in participants with SCD.

Objectives:

Primary

- To evaluate the safety and tolerability of a single dose and multiple ascending doses of GBT021601 in participants with SCD.

Secondary

- To evaluate the PK of a single dose and multiple ascending doses of GBT021601 in participants with SCD.
- To evaluate the PD properties (effect on Hb oxygen equilibrium curves (OEC) as measured by % Hb modification and p50) of a single dose and multiple ascending doses of GBT021601 in participants with SCD.
- To confirm the relationship between time matched GBT021601 concentrations and the change from baseline or % change from baseline of clinical measures of anemia and hemolysis.

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- [redacted]
- [redacted]

Study Design:

This is an open-label, intrapatient, single dose followed by a multiple dose escalation study in at least six (6) participants with SCD.

Single-dose Period (Part A)

After eligibility has been confirmed and the informed consent form signed, participants will be admitted into the clinical research unit (CRU) on the day prior to study drug administration (Day -1). On Day 1 a single oral dose of GBT021601 will be administered following an overnight fast of at least 10 hours and no food will be allowed for at least 4 hours postdose. A dose of 100 mg is planned but the decision regarding the actual study dose will depend on the findings in the single ascending dose

portion of the "first-in-human" (FIH) Study GBT021601-011. The dose will be no higher than a dose that has been well tolerated by the healthy participants in the FIH study. Participants will remain confined to the CRU until 72 hours after dosing (Day 4) and return for brief visits on Days 7, 14, 21, 28, and 42 (as outlined in the Schedule of Assessments).

Safety, tolerability, and PK data collected from Day 1 through Day 42 from a minimum of 4 participants will be required for the Safety Monitoring Committee (SMC) to make the decision to proceed to multiple ascending doses (Part B).

Multiple Ascending-dose Period (Part B)

Following a minimum of a 56-day washout from the single dose in Part A, participants will start the multiple ascending dosing (Part B). Depending on the observed half-life of GBT021601 in the FIH study, participants will receive a maintenance dose regimen which may or may not be preceded by a loading dose. The % Hb occupancy by GBT021601 will be calculated from the PK as the ratio of GBT021601 concentration to the Hb (estimated at 5mM) in RBCs. The Hb% modification will be based on hemoximetry data. The mg dose and dosing frequency will be determined by the PK results of GBT021601-011 and PK and hemoximetry results (occupancy/modification) from Part A. The predicted target for the first multiple dose regimen is ~20% to 30% hemoglobin (Hb) occupancy/modification. Participants will receive a maintenance dose through Week 10.

After the first multiple dose period, if the % Hb occupancy/modification is higher than 30 percent, the participant will remain on the same maintenance dose or have a dose increase that maintains the % Hb occupancy/modification at > 30%. If the % Hb occupancy is less than 30%, the participant will dose escalate at Week 13.

At the Week 13 Visit, eligible participants may be dose escalated to receive a loading dose and subsequent maintenance dose based on a predicted target of > 30% occupancy/modification. The mg dose and frequency will be determined by the PK results of GBT021601-011 and PK and hemoximetry results from Part A and Part B. Participants will receive maintenance doses through Week 16. Week 16 will be the end of treatment (EOT) Visit and participants will return to the clinical site for the end of Part B Safety Follow-up Visit approximately 5 half-lives (maximum of 120 days) after the final dose at the Week 16 Visit. The half-life will be determined from the PK results from the GBT021601-011 study and the PK results from Day 42 following the single dose (Part A) in this study.

Participants will not be confined in the CRU during the Multiple Ascending-dose Period.

Extended Treatment Period (Part C)

As of Protocol Amendment 5, eligible participants may proceed with an Extended Treatment Period of at least 6 weeks, with a 300 mg loading dose twice daily over 4 days and subsequent maintenance dose of 150 mg once daily starting from Part C Day 1 and continuing through Part C Week 6. CCI [redacted]

Duration of Study Participation:

The maximum duration of the study is dependent on the half-life of GBT021601. At a minimum, the study duration will include a 28-day Screening period, an 8-week Single-dose Period, and a 6-week Multiple Ascending-dose Period for a total of 18 weeks. This will be followed by an EOB Visit 5 half-lives after the final dose of GBT021601. It is anticipated that 5 half-lives will not exceed 120 days after the final dose. Therefore, the maximum duration for a participant will be approximately 218 days or approximately 31 weeks.

As of Protocol Amendment 5, the maximum duration of the study will be approximately 53 Weeks, which includes the approximately 6-week Extended Treatment Period, and a 4- and 8-week follow up.

Number of Participants:

At least six (6) participants with SCD. Participants in Part A (single dose) will continue to Part B (multiple ascending-dose). As of Protocol Amendment 5, all eligible participants will proceed with the extended treatment period (Part C).

Participant Selection Criteria:

Participants with SCD ages 18 to 60 years, inclusive.

Test Product, Dose, Route of Administration, and Duration of Treatment:

Single-dose Period (Part A)

- GBT021601 will be provided as a single dose, orally administered, 100 mg tablet.

Multiple Ascending-dose Period (Part B) and Extended Treatment Period (Part C)

- GBT021601 will be provided as orally administered multiple dose tablets and/or capsules for approximately 6 to 8 weeks (Part B) and for the approximately 6-week Extended Treatment Period (Part C).
- Loading and maintenance doses and frequency will be determined based on PK results from GBT021601-011 and on PK and /or hemoximetry results from Part A. Dose escalations will not exceed 2-fold the previous dose. For the Extended Treatment Period, the loading dose will be 300 mg, twice daily, for 4 days followed by a once daily maintenance dose of 150 mg.

Criteria for Evaluation:

Safety:

Participant safety and tolerability will be monitored during the study using standard measures, including physical examination, vital signs, 12-lead electrocardiogram, safety laboratory assessments (hematology measurements, chemistry measurements [including measures of hemolysis]), urinalysis, concomitant medication usage and adverse event monitoring.

Pharmacokinetics:

Plasma and whole blood concentrations of GBT021601 will be determined using validated assay methods. Red blood cell (RBC) concentrations will be calculated. The following whole blood, plasma, and RBC PK parameters of GBT021601 will be calculated, if appropriate. See below for PK parameters to be collected during each phase.

Single-dose Period (Part A): Maximum plasma/whole blood concentration (C_{max}), time of maximum serum concentration (t_{max}), area under the concentration vs time curve from time zero to 24 hours (AUC_{0-24}), area under the concentration vs time curve from zero to last quantifiable concentration (AUC_{0-t}), area under the concentration vs time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$), apparent clearance (CL/F), apparent volume of distribution during the terminal phase (Vz/F), half-life ($t_{1/2}$) and % Hb occupancy.

Multiple Dose (Part B and Part C): Plasma/whole blood C_{max}, plasma/whole blood C_{min}, plasma/whole blood AUC at steady-state, half-life ($t_{½}$) and % Hb occupancy.

Pharmacodynamics (Parts A, B, and C):

Hemoximetry (the partial pressure of oxygen at which the hemoglobin protein is 20% and 50% saturated [p20 and p50, respectively]), RBC deformability, and serum erythropoietin will be measured. The relationship between time matched GBT021601 concentrations and the change from baseline or % change from baseline of clinical measures of anemia and hemolysis will be evaluated.

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Planned Sample Size:

Due to the exploratory nature of this study, no formal power or sample size calculations were used to determine cohort size. A sample size of at least 6 participants with SCD are expected to provide adequate characterization of PK and safety for both the Single-dose Period and the Multiple Ascending-dose Period.

Statistical Analysis:

Adverse events will be coded to system-organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized. Vital signs and laboratory safety assessments will be presented with identification of clinically significant values and those outside of normal range. CCI Electrocardiogram data will be presented with any clinically relevant abnormal findings or changes highlighted. The PK and PD parameters will be listed and summarized using appropriate descriptive statistics.

SCHEDULES OF ASSESSMENTS AND PROCEDURES

Table 1: Schedule of Assessments for Single-dose Period (Part A)

	Screen	Confinement					Outpatient				
Study Day	**-30 to -2**	**-1**	**1**	**2**	**3**	**4**	**7**	**14**	**21**	**28**	**42**
Informed consent	X										
Eligibility assessment	X	X									
Medical history[a]	X										
Physical examination[b]	X	X				X					
Height	X										
Weight	X	X				X	X	X	X	X	X
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (triple tracing)[d]	X	X	X	X	X	X		X		X	
Study drug administration			X								
Serology (hepatitis A, B, C) HIV, SARS-CoV-2	X										
Alcohol (breath or blood) and urine drugs of abuse screen	X	X									
Hematology, Serum chemistry, and Lipid Panel[e]	X	X		X		X		X		X	
aPTT, INR, PT	X										
Serum erythropoietin		X	X			X		X		X	
SCD documentation or Hemoglobin Electrophoresis	X										
eGFR[f]	X	X									
Urinalysis	X	X				X					
Pregnancy test (women only)[g]	X	X						X		X	
FSH (postmenopausal women only)	X										
Pharmacokinetic assessment (whole blood and plasma)			X	X	X	X	X	X	X	X	X
Hemoximetry			X	X		X	X		X		X
RBC deformability, dense cells[h]			X								

	Screen	Confinement					Outpatient				
Study Day	**-30 to -2**	**-1**	**1**	**2**	**3**	**4**	**7**	**14**	**21**	**28**	**42**
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: aPTT, activated partial thromboplastin time; CoV, coronavirus; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EOS, end of study; ET, early termination; FSH, follicle-stimulating hormone; HIV, human immunodeficiency virus; INR, International Normalized Ratio; PCR, polymerase chain reaction; PT, prothrombin time; RBC, red blood cell; SARs, severe acute respiratory syndrome; SCD, sickle cell disease.

[a] History update, if any, will be obtained.

[b] A full physical examination should be conducted at Screening. All subsequent physical examinations should be signs and symptoms driven.

[c] Vital Signs include blood pressure, heart rate, respiration rate, body temperature while the participant is in a supine position. See Table 2.

[d] 12-Lead ECG on Day 1 should be performed within 30 minutes prior to dose, and 4 and 8 hours after dosing, then in the morning of each day of confinement and at any time at other clinic visits. See Table 2.

[e] The Lipid Panel is done at the Screening Visit only.

[f] The eGFR will be calculated at Screening and confirmed on Day -1 using the Cockcroft-Gault formula.

[g] A serum pregnancy test will be conducted at Screening and ET and urine pregnancy test at all other visits. A serum pregnancy test will also be conducted when a positive urinary pregnancy test occurs for confirmation.

[h] RBC deformability and dense cells will be tested on Day 1 predose and 12 hours postdose.

Table 2: Schedule of Select Study Procedures (First 48 hours)

Procedure	Sampling Timepoint										
	Pre dose	Postdose (hours)									
		0.25 hr	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	12 hr	24 hr (Day 2)	36 hr	48 hr (Day 3)
HR and BP[a, b]	X				X	X	X	X	X	X		X
RR and Body Temperature[a, b]	X									X		X
12-lead safety ECGs[b, c]	X			X		X		x		X		X
PK Sampling[d]	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BP, blood pressure; ECG, electrocardiogram; HR, heart rate; PK, pharmacokinetic; RR, respiratory rate; SAD, single ascending dose.
Note: For procedures scheduled to be performed at the same time, priority is to be given to collection of the PK samples at the designated time.
ECGs, followed by vital signs, are to be taken before PK sampling, unless PK samples will be late as a result. If times are delayed due to technical difficulties, this will be noted, but not considered a protocol deviation.

[a] HR, BP, RR, and body temperature will be measured after a participant has rested for at least 5 minutes in the supine position.
[b] Window for collection: up to 3 hours predose, ± 15 minutes up to 12 hours post, ± 30 minutes if ≥ 24 hours postdose.
[c] ECGs (12-lead) will be collected in triplicate within 5 minutes after a participant has rested at least 5 minutes in the supine position. Pre-dose ECGs and vital signs on Day 1 may be performed within 3 hours prior to dosing.
[d] Predose blood PK sample to be collected within 60 minutes prior to dosing. Postdose collection windows are: 0.25, 0.5 and 1 hour ± 2 mins, 2 to 24 hours ± 5 mins, 36 and 48 hours ± 10 mins.

Table 3: Schedule of Assessments for Multiple Ascending-dose Period (Part B)

Study Week	**Week 8 (Day 56 + 4 weeks)[a]**	**Week 9 (Day 63 ± 3 days)**	**Week 10 (Day 70 ± 3 days)**	**Week 11 (Day 77 + 3 days**	**Week 12 (Day 84 ± 3 days)**	**Week 13 (Day 91 ±3 days)**	**Week 14 (Day 98) ± 3 days)**	**Week 15 (Day 105) ±3 days**	**Week 16 (Day 112)** EOT	**Every 4 weeks through EOB ± 7 days**	**Day 218 (EOB/ET)**
Physical examination	X					X			X		X
Height											
Weight	X		X								
Vital signs[c]	X	X	X	X	X	X	X	X	X		X
12-lead ECG (triple tracing)[d]	X					X			X		X
Study drug administration	X[e]	X	X	X	X	X[f]	X	X	X		
Dispense patient diary[g]	X	X	X	X	X	X	X	X			
Collect patient diaryg[g]		X	X	X	X	X	X	X	X		
Hematology and serum chemistry	X		X		X	X		X	X	X	X
Blood smear[h]	X								X		X
Serum erythropoietin	X					X	X		X		
eGFR[i]	X					X					X
Urinalysis	X					X					X
Pregnancy test (women only)[j]	X					X					
Pharmacokinetic assessment (whole blood and plasma)[k]	X	X	X	X	X	X	X	X	X	X	X

Study Week	**Week 8 (Day 56 + 4 weeks)[a]**	**Week 9 (Day 63 ± 3 days)**	**Week 10 (Day 70 ± 3 days)**	**Week 11 (Day 77 + 3 days**	**Week 12 (Day 84 ± 3 days)**	**Week 13 (Day 91 ±3 days)**	**Week 14 (Day 98) ± 3 days)**	**Week 15 (Day 105) ±3 days**	**Week 16 (Day 112)** EOT	**Every 4 weeks through EOB ± 7 days**	**Day 218 (EOB/ET)**
Hemoximetry[k]	X	X	X			X		X	X		X
RBC deformability, dense cells (if feasible)[k]	X	X	X			X		X	X		X
Concomitant medications	X	X	X	X	X	X	X		X		X
Adverse events	X	X	X	X	X	X	X		X		X
Clinic visit	X	X	X	X	X	X	X		X		X

Abbreviations: ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EOB, end of Part B; ET, early termination; RBC, red blood cell.
Note: For procedures scheduled to be performed at the same time, priority is to be given to collection of the PK samples at the designated time.
ECGs, followed by vital signs, are to be taken before PK sampling unless PK samples will be late as a result

[a] Week 8 (Day 56) is the first visit in the Multiple-Ascending-dose Period.
[b] The Day 218 Visit will occur approximately 5 half-lives after the dose at Week 16.
[c] HR, BP, RR, and body temperature will be measured after a participant has rested for at least 5 minutes in the supine position. Assessment of vital signs may be performed up to 3 hours predose.
[d] 12-Lead ECG should be performed within 30 minutes prior to dose and will be collected in triplicate within 5 minutes after a participant has rested at least 5 minutes in the supine position.
[e] Study drug will be administered as a loading dose of TBD mg and a maintenance dose of TBD mg every TBD (Dose 1) beginning at the Week 8 (Day 56) Visit. Participants will receive maintenance Dose 1 through Week 10. At the Week 8 Visit, the participant will remain in the clinic for 4 hours postdose for vitals, 12-lead ECG and AE assessment.
[f] Study drug will be administered as a loading dose of TBD mg and a maintenance dose of TBD mg every TBD (Dose 2) beginning at the Week 13 (Day 91) Visit. Participants will receive maintenance Dose 2 through Week 16. At the Week 13 Visit, the participant will remain in the clinic for 4 hours postdose for vitals, 12-lead ECG and AE assessment
[g] Site to dispense a new diary and collect the previous diary from the patient, when applicable. Diary to be collected only during the maintenance dosing when the participant is self-administering study drug at home. Participants should be instructed to complete the diary each week and return it at the next visit for site review.
[h] A blood smear is to be performed before the Multiple Ascending Dosing Period Day 56 and Day 112 visits.
[i] The eGFR will be calculated using the Cockcroft-Gault formula.
[j] A urine pregnancy test will be conducted. A serum pregnancy test will also be conducted when a positive urinary pregnancy test occurs for confirmation.
[k] Samples for PK will be collected: predose, 0.25 to 1 hours postdose and 2 to 4 hours postdose. Sample collection times for hemoximetry and RBC deformability should be aligned with the predose PK sample and the 2 to 4 hour postdose PK sample. No 0.25 to 1 hour postdose sample shall be collected for hemoximetry or RBC deformability. The predose blood sample for PK and PD assessments should be collected within 30 minutes prior to dosing.

Table 4: Schedule of Assessments for Extended Treatment Period (Part C)

Study Day/Week	**Part C Screening Visit (Day -28 to Day -1)**	**Part C Day 1**	**Part C Week 2 (Day 14 ± 3 days)**	**Part C Week 4 (Day 28 ± 3 days)**	**Part C Week 6 (Day 42) ± 3 days)** EOET	**Part C Week 10 (Day 70 ± 3 days)**	**Part C Week 14 (Day 98 ± 3 days)**	**Final Visit** (EOS/CCI
Informed Consent	X							
Eligibility confirmation[a]	X							
Physical examination	X				X		X	X
Weight	X	X			X		X	X
Vital signs[b]	X	X	X	X	X	X	X	X
12-lead ECG (triple tracing)[c]	X	X	X	X	X		X	X
Study drug administration[d]		X	X	X	X			
Dispense participant diary[e]		X	X	X				
Collect participant diary[e]			X	X	X			
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hematology and serum chemistry	X	X	X	X	X	X	X	X
Serum erythropoietin	X	X			X		X	X
eGFR[f]	X	X			X		X	X
Urinalysis	X	X			X		X	X
Pregnancy test (women only)[g]	X	X			X		X	X
Pharmacokinetic assessment (whole blood and plasma)[h]		X	X	X	X	X	X	X
Hemoximetry[h]		X		X	X		X	X

Study Day/Week	Part C Screening Visit (Day -28 to Day -1)	Part C Day 1	Part C Week 2 (Day 14 ± 3 days)	Part C Week 4 (Day 28 ± 3 days)	Part C Week 6 (Day 42) ± 3 days) EOET	Part C Week 10 (Day 70 ± 3 days)	Part C Week 14 (Day 98 ± 3 days)	Final Visit (EOS CCI
RBC deformability, dense cells (if feasible)[h]		X		X	X		X	X
Blood smear		X			X		X	X
CCI		[redacted]			[redacted]			
Concomitant medications		X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X

Abbreviations: CCI ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EOET, End of Extended Treatment; EOS, end of study; ET, early termination; CCI RBC, red blood cell.
Note: For procedures scheduled to be performed at the same time, priority is to be given to collection of the PK samples at the designated time.
ECGs, followed by vital signs, are to be taken before PK sampling unless PK samples will be late as a result

[a] For newly enrolled participants, the Screening Visit will be the same as that in Table 1.

[b] HR, BP, RR, and body temperature will be measured after a participant has rested for at least 5 minutes in the supine position. Assessment of vital signs may be performed up to 3 hours predose.

[c] 12-Lead ECG should be performed within 30 minutes prior to dose at Part C Day 1, Part C Week 2, and 4hrs post dose at Part C Weeks 4 and 6. All ECGs will be collected in triplicate within 5 minutes after a participant has rested at least 5 minutes in the supine position.

[d] Study drug will be administered beginning at the Day 1 Visit as a loading dose of 300 mg twice daily for four days followed by a maintenance dose of 150 mg once daily through at least Part C Week 6 (if treatment will be extended beyond 6-weeks, additional study drug administration and Visits will be added). At the Part C Week 4 and Part C Week 6 Visits, the participant will remain in the clinic for 4 hours postdose for vitals, 12-lead ECG and AE assessment.

[e] Site to dispense a new diary and collect the previous diary from the participant, per above. Diary to be completed throughout the study, except for the first loading dose and any maintenance doses administered in the clinic. The actual time of every dose administration should be recorded in the diary or at the clinic to enable PK calculations. CCI [redacted]

[f] The eGFR will be calculated using the Cockcroft-Gault formula.

[g] A urine pregnancy test will be conducted. A serum pregnancy test will also be conducted when a positive urinary pregnancy test occurs for confirmation.

[h] Samples for PK will be collected: prior to the first dose at Part C Day 1, Part C Week 2, Part C Week 4, Part C Week 6 as well as at 0.25 to 1 hours post-dose and 2 to 4 hours post dose on the Week 4 and Week 6 visits. Sample collection times for hemoximetry and RBC deformability should be aligned with the pre-dose PK sample and the 2 to 4-hour post-dose PK sample (for Week 4 and Week 6 visits). Refer to Table 12 for specifics. No 0.25 to 1 hour post-dose samples shall be collected for hemoximetry or RBC deformability. The predose blood sample for PK and PD assessments should be collected within 30 minutes prior to dosing.

LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
ADLs	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the concentration vs time curve from time zero to 24 hours
AUC_{0-t}	Area under the concentration vs time curve from zero to last quantifiable concentration
$AUC_{0-\infty}$	Area under the concentration vs time curve from time zero extrapolated to infinity
BP	Blood pressure
BPM	Beats per minute
CCI	[redacted]
CL/F	Apparent clearance
C_{max}	Maximum plasma/whole blood concentration
C_{min}	Minimum plasma/whole blood concentration
CCI	[redacted]
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CRU	Clinical research unit
CYP	Cytochrome P450
°C	Degrees Celsius
CCI	[redacted]
DILI	Drug-induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of Study
EOT	End of Treatment
EPO	Erythropoietin
ET	Early Termination
FDA	(United States) Food and Drug Administration
CCI	[redacted]

Abbreviation or Specialist Term	Explanation
FIH	First-in-human
FSH	Follicle-stimulating hormone
GBT	Global Blood Therapeutics, Inc.
GCP	Good Clinical Practice
Hb	Hemoglobin
Hb-O_2	Hemoglobin-oxygen
HbS	Sickle hemoglobin
HbSB	Double heterozygote for HbS and b-0 thalassemia
HbSS	Homozygous for sickle cell allele
HIV	Human immunodeficiency virus
HR	Heart rate
HU	Hydroxyurea
IgM	Immunoglobulin M
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No-observed-adverse-effect level
CCI	[redacted]
CCI	[redacted]
OxyHb	Oxy-hemoglobin
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Prothrombin time
p20	Hemoglobin protein is 20% saturated
p50	Hemoglobin protein is 50% saturated
RBC	Red blood cell
RR	Respiratory rate
SAD	Single ascending dose
SAE	Serious adverse event
SARS	Severe acute respiratory syndrome
SCD	Sickle cell disease
SMC	Safety Monitoring Committee

Abbreviation or Specialist Term	Explanation
t_{max}	Time of maximum serum concentration
$t_{½}$	Half-life
ULN	Upper limit of normal
US	United States
Vz/F	Apparent volume of distribution during the terminal phase

3. INTRODUCTION AND BACKGROUND

3.1. Introduction

Global Blood Therapeutics, Inc. (GBT; the Sponsor) intends to develop GBT021601, a sickle hemoglobin (HbS) polymerization inhibitor for the treatment of sickle cell disease (SCD).

Sickle cell disease is an inherited disorder caused by a point mutation in the β-globin gene leading to formation of HbS. A primary and obligatory event in the molecular pathogenesis of SCD is the polymerization of intracellular HbS following deoxygenation in the microvasculature. HbS polymerization leads to decreased red blood cells (RBC) deformability, morphologic sickling of RBCs, decreased RBC survival, and microvascular obstruction (Bunn, 1997). Clinically, SCD is a devastating and debilitating disease marked by the pathophysiologic features of hemolytic anemia, vaso-occlusion, and progressive end-organ damage. Despite current standards of care, including hydroxyurea (HU), blood transfusion, and supportive care with analgesia, patients with SCD continue to suffer serious morbidity and premature mortality.

A drug that inhibits HbS polymerization in all RBCs has the potential to provide superior efficacy to available treatments. GBT021601 is an HbS polymerization inhibitor being developed by GBT for the treatment of SCD. GBT021601 increases hemoglobin-oxygen (Hb-O_2) affinity and stabilizes hemoglobin (Hb) in the oxy-hemoglobin (oxyHb) state thereby inhibiting polymerization of HbS in RBCs. By addressing this underlying mechanism of SCD, GBT021601 has the potential to be a disease-modifying therapy, leading to improved anemia, reduced hemolysis and the potential to reduce the end-organ damage resulting from chronic hemolytic anemia. Proof of concept for this Hb modification approach has been provided with voxelotor, an orally administered small molecule inhibitor of HbS polymerization.

Voxelotor is an allosteric modifier of Hb-O2 affinity and following binding to Hb, stabilizes the oxyhemoglobin state (Metcalf, 2017; Oksenberg 2016), thereby inhibiting polymerization of HbS in RBCs and in patients with SCD.

Data from the Phase 3 study of voxelotor in patients with SCD showed a dose-dependent improvement in hemolytic anemia, with an increase in Hb and concomitant decrease in clinical measures of hemolysis (including indirect bilirubin, reticulocytes, and lactate dehydrogenase) (Vichinsky, 2019).

The % Hb occupancy approximates the percentage of high-affinity anti-polymerizing oxyHb molecules per RBC and is calculated as a percentage of the molar ratio of drug concentration in RBCs to the estimated Hb concentration (5000 μM) in RBCs (Howard, 2019; Hutchaleelaha, 2019).

Clinical studies with voxelotor in patients with SCD showed that daily doses of 1500 mg (the FDA-approved dose), which achieved a mean Hb occupancy of ~27%, was well tolerated and resulted in a clinically meaningful increase in Hb by > 1 g/dL in > 50% patients with concurrent reductions in clinical measures of hemolysis (Vichinsky, 2019). Additionally, the highest Hb occupancy achieved in that study with 1500 mg was 45%. In SCD mice treated with GBT021601, a Hb occupancy of ~6% resulted in a > 1 g/dL increase in Hb concentration in all animals. Moreover, at a GBT021601 Hb occupancy of ~29% (similar to the mean achieved by the 1500 mg dose of voxelotor in SCD patients), GBT021601 caused a sustained and almost complete elimination of circulating sickled RBCs, reduced reticulocyte counts by > 50%,

increased RBC half-life by 6.1 days, and normalized Hb with a 6.7 g/dL increase from baseline in SCD mice. These data indicate that at similar Hb occupancies, GBT021601 is expected to be more potent than voxelotor in patients with SCD.

Voxelotor was recently approved by the United States (US) Food and Drug Administration (FDA), under the tradename OXBRYTA®, for the treatment of SCD in adults and pediatric patients 12 years of age and older.

As stated above, GBT021601 shares the same mechanism of action as voxelotor and thus is designed to optimize the potential for clinical benefit derived from stabilizing oxyHb.

Erythropoiesis increases in response to tissue hypoxia, and this increase is mediated by tissue sensing of hypoxia resulting in an increase in erythropoietin production, which in turn causes an increase in reticulocyte production. Because increased erythropoiesis is the compensatory response for decreased tissue oxygen extraction, treatment effects on these markers were assessed in the Phase 3 voxelotor study. No evidence of a compensatory erythropoietic response was seen with voxelotor at 900 mg and 1500 mg: erythropoietin did not increase and reticulocytes decreased.

The safety related to pharmacology of GBT021601 is also supported by the safety findings for voxelotor, which was found to be well tolerated without demonstrated safety concerns in studies on both healthy participants and patients with SCD (Hutchaleelaha, 2019; Vichinsky, 2019).

3.2. Study Drug Background

GBT021601 increases Hb-O_2 affinity and stabilizes Hb in the oxyHb state thereby inhibiting polymerization of HbS in RBCs. In preclinical animal studies, GBT021601 partitioned preferentially to the RBC compartment with a mean blood/plasma ratio of 48–122:1. Thus, similar to voxelotor, GBT021601 is expected to partition preferentially into RBCs, where it specifically binds to Hb, and therefore minimizes plasma exposures.

3.3. Summary of Findings to Date

3.3.1. Nonclinical Experience

Nonclinical studies have been conducted to characterize GBT021601, including primary and secondary pharmacodynamics (PD), safety, pharmacology, pharmacokinetics (PK), and toxicology. The results from these studies support planned clinical studies with GBT021601 and are described in detail in the GBT021601 Investigator's Brochure.

3.3.2. Clinical Experience

A first-in-human (FIH) single ascending and multiple ascending dose (SAD/MAD) study in healthy participants (Study GBT021601-011) is ongoing. Safety and PK data on single doses from 50 mg to 2200 mg in healthy participants has demonstrated that GBT021601 is well tolerated with a linear dose-dependent increase in percent Hb occupancy. Safety and PK assessments for multi-day loading doses and daily maintenance doses of 15, 25, and 50 mg for 14 days has been completed in three cohorts of the MAD.

For the current Study GBT021601-012, in Part A, six adults with SCD have received a single 100 mg dose of GBT021601, and the dose has been well tolerated. After an 8-week washout,

participants received a GBT021601 loading dose of 300 mg on day 1, 200 mg on Day 2, followed by a maintenance dose of 50 mg/day for 5 weeks (Part B). Dose escalation occurred at Week 13 with participants receiving a 500 mg loading dose on Day 91, 400 mg loading dose on day 92 followed by a maintenance dose of 100 mg/day for approximately 3 weeks. Dosing in Part B is now complete with follow-up ongoing.

3.4. Study Rationale

This Phase 1b study is designed to investigate GBT021601, administered orally as a single dose and multiple ascending doses in participants with SCD.

3.4.1. Rationale for Study Design

This is the first study with GBT021601 in SCD participants; this study will evaluate the safety, tolerability, PK, and PD following a single dose and multiple ascending doses of GBT021601. Since the objectives of this study are to determine the safety and tolerability of the single dose and multiple ascending doses of GBT021601, it is designed as an open-label study. The addition of the multiple-ascending dose period may also provide SCD participants with a biologically and clinically active dose as well as provide the Sponsor with information on intrapatient variability.

3.4.2. Rationale for Dose Selection

3.4.2.1. Rationale for Single Dose Selection

A single dose of 100 mg GBT021601 was selected based on all available nonclinical toxicology data (these data are described in detail in the GBT021601 Investigator's Brochure).
Key GBT021601-related effects in the 28-day oral toxicity studies in rats and cynomolgus monkeys included increases in red cell mass (RBCs, Hb, and hematocrit) which were accompanied with increases in reticulocyte counts and other RBC parameters. These changes were indicative of increased erythropoiesis associated with pharmacologic activity of

GBT021601 and correlated with reversible microscopic changes of increased hematopoiesis in the bone marrow (rats and monkeys) and spleen (rats). The no-observed-adverse-effect level (NOAEL) was 30 mg/kg/day in cynomolgus monkeys and 50 mg/kg/day in rats following oral administration of GBT021601 for 13 weeks (Table 5).

Table 5: Thirteen-Week Oral Toxicity Studies in Rats and Cynomolgus Monkeys: Whole Blood and Plasma Exposures and Hemoglobin Occupancies Achieved at the No-Observed-Adverse-Effect Levels

Species	Day 91: Mean Exposures to GBT021601[a]				GBT021601 NOAEL (mg/kg/day)	% Hb Occupancy[b]
	C_{max} (µg/mL)		AUC_{0-t} (µg•h/mL)			
	Whole Blood	Plasma	Whole Blood	Plasma		
Rat	832	33.2	15,750	482	50	60
Cynomolgus monkey	902	23.3	18,600	290	30	83

Abbreviations: AUC_{0-t}, area under the concentration-time curve from the start of dose administration to the time at which the last quantifiable concentration was observed; C_{max}, maximum blood or plasma concentration; NOAEL, no-observed-adverse-effect level.

[a] Mean of males and females.

[b] Estimated by comparing the molar ratio of GBT021601 to hemoglobin in erythrocytes.

In rats, while pharmacologically mediated increased erythropoiesis was observed at this 60% Hb occupancy (and in turn, led to the designation of 50 mg/kg/day as the NOAEL), these effects are monitorable, reversible, and were not associated with adverse findings. Additionally, in a post-hoc analysis of the pivotal HOPE study, 8 of 81 participants (9.9%) taking 1500 mg of voxelotor daily exceeded 50% Hb occupancy during treatment (GBT data on file). Therefore, for these reasons, attaining 60% occupancy in a clinical study does not raise specific safety concerns.

A dose of 100 mg GBT021601 was estimated using:

1. A human equivalent dose of 8 mg/kg/day, derived using the 28-day rat NOAEL of 50 mg/kg/day and a body surface area conversion factor of 6.2 (Table 5);
2. A human body weight of 60 kg;
3. A safety factor of 5.

This estimation method is consistent with that described in the United States Food and Drug Administration Guidance for Industry: *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* (FDA, 2005).

For the initial clinical evaluation in participants with SCD, the recommended starting dose of 100 mg GBT021601 will be administered as a single dose. This 2-fold higher starting dose, derived using a safety factor of 5 for participants relative to that (50 mg using a safety factor of 10) for healthy participants, is based on risk-benefit considerations. Furthermore, key GBT021601-related effects in the 28-day oral studies in rats and monkeys were consistent with exaggerated pharmacological effects at high Hb occupancies and were generally reversible, indicating a low risk to participants at a dose of 100 mg.

3.4.2.2. Rationale for Multiple Dose Selection

The starting multiple ascending dose is predicted to achieve a C_{max} at steady-state no higher than 2-fold the C_{max} already achieved and well tolerated following a single ascending dose or multiple ascending dose in healthy participants (Study GBT021601-011). The starting multiple ascending dose is also predicted to achieve ~ 20% to 30% Hb occupancy, a level of Hb occupancy/modification which has been well tolerated with voxelotor (Hutchaleelaha, 2019 and Vichinsky, 2019). If needed, dose escalation will proceed at up to 2-fold until > 30% occupancy/modification (40% Hb occupancy has been well tolerated without tissue hypoxia in healthy participants with voxelotor [Hutchaleelaha, 2019]) has been reached and by less than 1.3-fold, thereafter.

The doses and frequency for the multiple ascending dose period of this study will be determined based on the results from the FIH Study GBT021601-011 in healthy participants and the single-dose, Day 42 PK and hemoximetry analysis in participants with SCD in this study. At the time of the first administration of GBT021601 to participants with SCD, safety data from the first 5 cohorts (50, 100, 200, 400, and 800 mg) and PK data from the first 3 cohorts from the SAD FIH Study GBT021601 will be available. A Safety Monitoring Committee (SMC, Section 7.6) will convene to review the safety, tolerability, and PK data when a minimum of 4 participants with SCD who have received a single dose of GBT021601 have reached Week 6 (Day 42). If the SMC agrees to initiate the intrapatient multiple-dose portion of the study, participants will receive a maintenance dose (possibly preceded by a loading dose) at Week 8 (+ 4 weeks).

The maintenance dose will be administered for the following 9 weeks (Week 8 to Week 16). After the first multiple dose period (Week 8 through Week 10), if the % Hb occupancy is higher than 30%, the participant may remain on the same maintenance dose or have a dose increase that maintains the % Hb occupancy/modification at > 30%.

If the % Hb occupancy is less than 30%, the participant will dose escalate at Week 13. At Week 13, eligible participants will be dose escalated to receive a maintenance dose (possibly preceded by a loading dose) based on a predicted target of > 30% Hb occupancy as determined by the PK results of GBT021601-011 and Day 42 PK and/or hemoximetry from the Single-dose Period.

At the proposed starting dose of 100 mg in SCD participants and subsequent, intrapatient multiple dose escalation, there may be sufficient Hb occupancies (after multiple dosing) to provide potentially beneficial pharmacological effects.

3.4.2.3. Rationale for Evaluation of Higher Dose of GBT021601

As of Protocol Amendment 5, after a total of 8 weeks of treatment, all participants in this study demonstrated improvements in hematologic parameters, including reticulocytes and absolute reticulocytes, lactate dehydrogenase, and indirect bilirubin (Brown, 2021). Preliminary findings indicate a dose-related mean increase from about 15% to 32% in Hb occupancy after dosing with 50 mg daily and 100 mg daily respectively. Preliminary clinical safety data show that GBT021601 has been well tolerated with no significant treatment-related safety findings reported. An extended treatment period evaluating a dose escalation to 150 mg once daily for at least 6 weeks preceded by a loading dose of 300 mg, given twice daily over 4 days (the loading dose is being administered twice daily to minimize the potential for any gastrointestinal effect

that could theoretically occur with a higher once daily loading dose) is targeted to increase the Hb occupancy to approximately 54%. These projections were obtained from a population pharmacokinetic (PPK) model using the data from all 6 participants who have been enrolled in this study.

The Extended Treatment Period is being added to explore the safety and tolerability of these loading and maintenance dose levels. It is believed that higher Hb occupancy will translate to clinical benefits such as improved signs and symptoms of anemia, potentially reduced VOCs, and improved overall well-being in participants with SCD. To assess the full potential of this new agent, a formal multicenter dose-ranging study is being planned to evaluate higher doses of GBT021601, and it is critical to determine to safety/tolerability and effects on Hb occupancy and other hematological parameters at this proposed regiment (300 mg bid x 4 days plus 150 mg QD for 81 days).

CCI [redacted]

4. TRIAL OBJECTIVES AND PURPOSE

4.1. Primary Objective

- To evaluate the safety and tolerability of a single dose and multiple ascending doses of GBT021601 in participants with SCD.

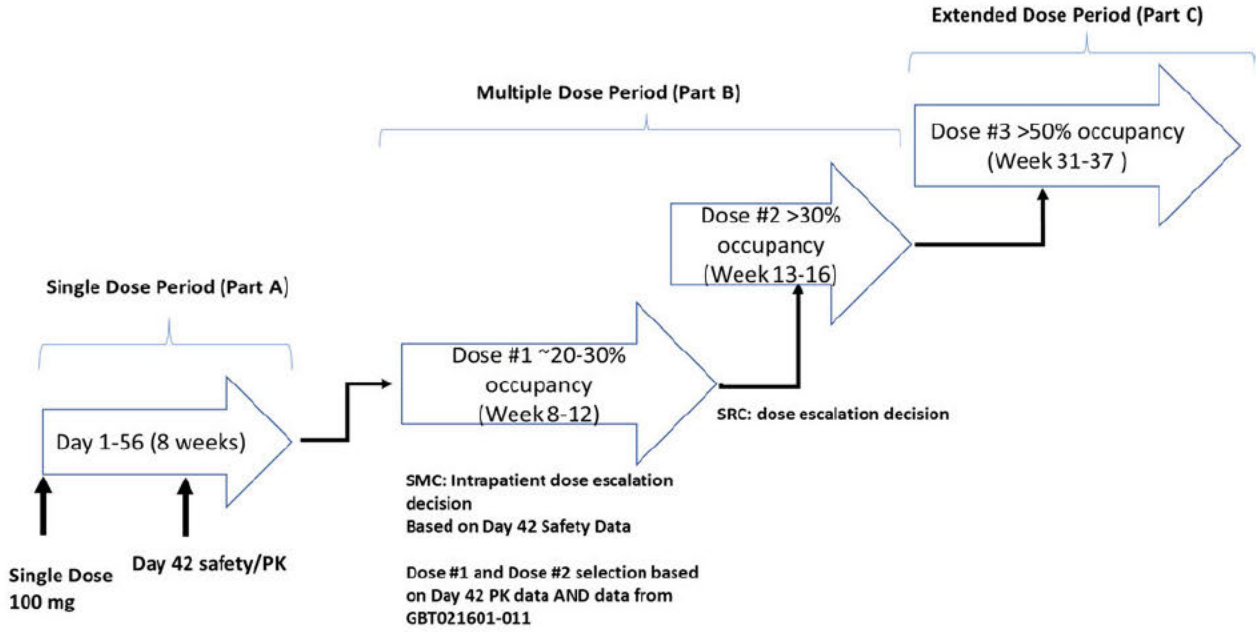
4.2. Secondary Objectives

- To evaluate the PK of a single dose and multiple ascending doses of GBT021601 in participants with SCD.
- CCI
- To confirm the relationship between time matched GBT021601 concentrations and the change from baseline or % change from baseline of clinical measures of anemia and hemolysis.

4.3. Overall Study Design

This is an open-label intrapatient single dose and multiple ascending dose study in at least six (6) participants with SCD. A diagram of the study is shown in Figure 1.

Figure 1: Study Schema for GBT021601-012



4.3.1. Single-dose Period (Part A)

After eligibility has been confirmed and the informed consent form signed, participants will be admitted into the clinical research unit (CRU) on the day prior to study drug administration (Day -1). A single oral dose of 100 mg of GBT021601 will be administered following an overnight fast of at least 10 hours and no food will be allowed for at least 4 hours postdose. The dose will be no higher than a dose that has been well tolerated by the healthy participants in the FIH study. Participants will remain confined to the CRU until 72 hours after dosing (Day 4) and return for brief visits on Days 7, 14, 21, 28, and 42, (as outlined in the Schedule of Assessments, Table 1 and Table 2).

4.3.2. Multiple Ascending-dose Period (Part B)

After a sufficient washout period (minimum of 56 days) and completion of a minimum of 4 participants in the Single-dose Period, the SMC will convene to review the safety, tolerability, and PK data from Day 42. If the SMC agrees to initiate the intrapatient multiple ascending dose portion of the study, participants will receive a maintenance dose regimen which may or may not be preceded by a loading dose at Week 8 (± 4 weeks). The initial loading dose and maintenance dose and frequency will be based on a predicted target of ~20% to 30% occupancy as determined by the PK results from the SAD part of Study GBT021601-011 in healthy participants and PK and hemoximetry results (occupancy/modification) from Part A. The maintenance dose will be administered through Week 10. Pharmacokinetics and % Hb occupancy will be evaluated following multiple dosing (first intrapatient dose escalation) in order to determine a dosing regimen for the second intrapatient dose escalation via modeling and simulation.

After the first multiple dose period, if the % Hb occupancy is higher than 30%, the participant may remain on the same maintenance dose or have a dose increase that exceeds the % Hb occupancy/modification of 30% based on the SMC recommendation. If the % Hb occupancy is less than 30%, the participant will dose escalate at Week 13.

At the Week 13 Visit, participants may receive a loading dose and subsequent maintenance dose based on a predicted target of > 30% occupancy/modification as determined by the PK and/or hemoximetry results of GBT021601-011 and Part A of this study. The maintenance dose will then be given Week 14 through Week 16 up to the end of treatment (EOT) Visit. Week 16 will be the EOT Visit and participants will return to the clinical site for the end of study (EOS) Visit approximately 5 half-lives after the final dose at Week 16. The half-life will be determined from the PK results from the GBT021601-011 study and Day 42 following a single dose of 100 mg. It is anticipated that 5 half-lives will not exceed 120 days after the final dose.

Participants will not be confined at the CRU during the Multiple Ascending-dose Period.

4.3.3. Extended Treatment Period (Part C)

As of Protocol Amendment 5, eligible participants may proceed with an Extended Treatment Period of at least 6 weeks, with a 300 mg loading dose twice daily over 4 days and subsequent maintenance dose of 150 mg daily per the Schedule of Assessments in Table 4. CCI

[redacted]

4.4. Number of Participants

At least 6 participants will participate in both the Single-dose Period and the intrapatient Multiple Ascending-dose Period. As of Protocol Amendment 5, all eligible participants will proceed with the extended treatment period.

4.5. Duration of Study

The maximum duration of the study is dependent on the half-life of GBT021601. At a minimum, study duration will include a 28-day Screening period, an 8-week Single-dose Period, and a 6-week Multiple Ascending-dose Period for a total of 18 weeks. This will be followed by an EOS Visit 5 half-lives after the final dose of GBT021601. It is anticipated that the EOS will not exceed 120 days after the final dose. As of Protocol Amendment 5, the maximum duration of the study will be approximately 53 weeks, which includes the approximately 6-week Extended Treatment Period, and an 8-week follow up.

4.6. Definition of Study Completion

The EOB Visit will occur after completion of the Multiple Ascending-dose Periods as presented in Table 3 and the EOS Visit will occur after completion of the Extended Treatment Period as presented in Table 4.

Participants who terminate from the study early will have Early Termination (ET) Visit procedures performed at the time of discontinuation. Participants with ongoing clinically significant clinical or laboratory findings will be followed until the finding is resolved or medically stable; reasonable attempts will be made to follow-up with participants. All serious and nonserious adverse events (AEs) must be followed until they are resolved or stabilized, or until reasonable attempts to determine resolution of the event are exhausted. The Investigator should use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events. Participation in the study will end once all study assessments and visits have been completed.

4.7. End of Study

The EOS is defined as the date when the last participant has completed all study procedures up to and including EOS or ET visits, as specified in Table 4.

5. SELECTION AND WITHDRAWAL OF PARTICIPANTS

5.1. Participant Inclusion Criteria

Participants must meet all inclusion criteria to be eligible for study participation.

1. Male or female with SCD.
2. Documentation of SCD genotype homozygous for sickle cell allele (HbSS) or double heterozygote for HbS and β-0 thalassemia (HbSB).
3. Age 18 to ≤ 60 years, inclusive.
4. Hb ≥ 5.5 and ≤ 10.5 g/dL during Screening and considered stable and close to Baseline by the Investigator.
5. For participants taking HU, the dose in mg/kg must be stable for at least 90 days prior to signing the informed consent form (ICF) and with no anticipated need for dose adjustments during the study in the opinion of the Investigator.
6. Female participants of child-bearing potential, must agree to use highly effective methods of contraception or practice abstinence from study start to 165 days after the last dose of study drug. Males who are not surgically sterile with partners of childbearing potential must agree to use a highly effective method of birth control during the study and for 165 days after the last dose of study drug. A highly effective method of contraception is defined as one that results in a low documented failure rate when used consistently and correctly such as: condom plus use of an intrauterine device; intrauterine system or hormonal method of contraception (oral, injected, implanted, or transdermal) for their female partner; or sexual abstinence. In addition, males who are not surgically sterile with a partner who is pregnant must agree to condom use or maintain sexual abstinence during the study and for 165 days after the last dose of study drug.
7. Males must agree to not donate sperm from study start through 165 days after the final dose.
8. Participant has provided documented informed consent.

5.2. Participant Exclusion Criteria

Participants meeting any of the following exclusion criteria will not be eligible for study enrollment:

1. More than 10 vaso-occlusive crises within 12 months of Screening that required a telemedicine, hospital, emergency room, or clinic visit.
2. Female participant who is breastfeeding or pregnant.
3. Receiving regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventive transfusion) or have received an RBC transfusion for any reason within 60 days of signing the ICF or at any time during the Screening period.
4. Hospitalized for sickle cell crisis or other vaso-occlusive event within 14 days of signing the ICF or within 28 days prior to the start of study treatment (ie, participants with a vaso-occlusive event must wait at least 14 days before signing an ICF and Screening period must be at least 14 days before the start of study treatment).

5. Screening laboratory test of alanine aminotransferase (ALT) > 4 × upper limit of normal (ULN).
6. Acute illness or clinically significant bacterial, fungal, parasitic, or viral infection which requires therapy, including acute bacterial infection requiring antibiotics within 14 days prior to the start of study drug administration.
7. Participants with positive Screening tests for hepatitis (A, B, or C) or human immunodeficiency virus (HIV) or who are known to have active hepatitis infection or to be HIV positive or hepatitis C antibody positive.
8. Participants with symptomatic coronavirus disease 2019 (COVID-19) infection, temporary exclusion.
9. Estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73 m^2 at the Screening Visit, calculated by the central laboratory, or is on chronic dialysis.
10. History of malignancy within the past 2 years prior to treatment Day 1 requiring chemotherapy and/or radiation (with the exception of local therapy for non-melanoma skin malignancy).
11. History of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to consent including but not limited to the following:
    a. Unstable angina pectoris or myocardial infarction or elective coronary intervention
    b. Congestive heart failure requiring hospitalization
    c. Uncontrolled clinically significant arrhythmias, high grade atrioventricular block (ie, Mobitz II or 3rd degree), pacemaker, or implantable cardioverter-defibrillator.
    d. Pulmonary hypertension
12. Abnormal and clinically significant 12-lead ECG, including QT interval corrected for heart rate according to Fridericia's formula (QTcF) > 450 ms, QRS interval ≥ 120 ms, PR interval > 220 ms, based on the average of triplicated ECG, assessed at Screening and the day prior to start of study treatment. If any of these test results are out of range the test can be repeated once (in triplicate).
13. Any condition affecting drug absorption, such as major surgery involving the stomach or small intestine (prior cholecystectomy is acceptable).
14. Has received an investigational drug (including vaccines, except COVID-19 vaccine) within 5 times the elimination half-life (if known) or within 30 days (if the elimination half-life is unknown) prior to study drug administration or is concurrently enrolled in any research judged not to be scientifically or medically compatible with this study.
15. Difficulty with venous access or unsuitable or unwilling to undergo intravenous catheter insertion.
16. Medical, psychological, or behavioral conditions, which, in the opinion of the Investigator, may preclude safe participation, confound study interpretation, interfere with compliance, or preclude informed consent.

17. Received erythropoietin or other hematopoietic growth factor treatment within 28 days of signing ICF or is anticipated to require such agents during the study.
18. Ongoing or recent (within 2 years) substance abuse or positive alcohol/drugs of abuse results at Screening or the day prior to the start of GBT021601 treatment.
19. Known allergy to GBT021601 or other Hb polymerization inhibitors.
20. Current or recent use of voxelotor, crizanlizumab or L-glutamine. Recent use is defined as within the past 3 months prior to the start of GBT021601 treatment.
21. Ongoing or recent use of strong inducers of CYP (cytochrome P450) 3A4/CYP3A5. Recent is defined as within 5 half-lives or 30 days, whichever is longer prior to the start of GBT021601 treatment.
22. Ongoing or recent use of strong inhibitors of CYP3A4/CYP3A5. Recent is defined as within 5 half-lives prior to the start of GBT021601 treatment.
23. Ongoing or recent use of the P-glycoprotein substrates digoxin and dabigatran. Recent is defined as within 5 half-lives prior to the start of GBT021601 treatment.
24. Use of a prohibited prescription or nonprescription drugs and dietary supplements (including herbal and alternative medications), as specified in Section 6.5.2.
25. Consumption of grapefruit and/or grapefruit juice within 14 days prior to Day -1 and is unwilling to abstain from consumption of grapefruit and/or grapefruit juice until the EOS/ET.
26. Any other condition or prior therapy that, in the Investigator's opinion, would confound or interfere with the evaluation of or PK, safety, tolerability, and PD of the study drug, interfere with study compliance, or preclude informed consent.
27. History of severe allergic reaction (including anaphylaxis) to any substance, or previous status asthmaticus.

5.2.1. Additional Exclusion Criteria (Part C):

28. More than 10 VOCs within 10 months of Screening.
29. For Part C of the study recent use of voxelotor is defined as within 10 days prior to the start of GBT021601 treatment.
30. Ongoing or recent use of strong or moderate inducers of CYP3A4/CYP3A5. Recent is defined as withing 5 elimination half-lives or 14 days, whichever is longer prior to the start of GBT021601 treatment.
31. Ongoing or recent use of strong or moderate inhibitors of CYP3A4/CYP3A5. Recent is defined as within 5 elimination half-lives prior to the start of GBT021601 treatment.
32. Consumption of Seville oranges within 14 days prior to the start of GBT021601 treatment and is unwilling to abstain from consumption of Seville oranges until the EOS/ET Visit.

33. History of overt stroke including hemorrhagic stroke or transient ischemic attack (TIA) or spinal cord injury, magnetic resonance angiography (MRA)-defined vasculopathy, or magnetic resonance imaging (MRI)/transcranial doppler (TCD)-documented silent cerebral infarcts within 2 years of screening.
34. Ongoing or recent (within 2 years) substance abuse (alcohol).
35. Has received COVID-19 vaccine (first dose, second dose, or booster dose), authorized by regional regulatory authority, within 7 days prior to start of GBT021601 treatment.
36. Has received an exchange transfusion for any reason within 90 days prior to the start of GBT021601 treatment.

5.3. Participant Re-Screening

Participants who screen fail may be rescreened as long as the participant was not a screen fail due to noncompliance with the protocol (ie, positive urine drugs of abuse screen, etc). If the participant is re-screened, the participant must again consent to participate in the study and a new Screening number must be used. All Screening assessments will be repeated.

5.4. Participant Withdrawal

Participants are free to discontinue the study at any time, for any reason, and without prejudice to further treatment. The Investigator may remove a participant if, in the Investigator's judgment, continued participation would pose unacceptable risk to the participant or to the integrity of the study data. All procedures for the ET Visit must be completed. Reasons for removal or withdrawal may include:

- Withdrawal of consent
- Discretion of the Investigator/Sponsor
- Participant noncompliance
- Safety concern by the Investigator or the Sponsor

Once dosed, participants who discontinue the study due to an AE will not be replaced. Participants who discontinue the study due to reasons other than an AE or who have non-evaluable PK samples may be replaced at the discretion of the Sponsor.

In the event of a participant's withdrawal, the Investigator will promptly notify the Medical Monitor and Study Director and will make every effort to complete the Early Termination (ET) assessments. All withdrawn participants with ongoing clinically significant AEs/serious adverse events (SAEs) or laboratory findings will be followed until the finding is resolved or medically stable; reasonable attempts will be made to follow-up with participants.

5.5. Early Termination of Study

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, (1) the incidence or severity of AEs in this or other studies indicating a potential health hazard to participants, and (2) in the Sponsor's judgment, there are no further benefits to be achieved from the study.

If the study is terminated early, the Sponsor shall inform all Investigators/institutions, regulatory authorities, and the Institutional Review Board (IRB).

5.5.1. Stopping Rules

All participants will be closely monitored for any AEs by the site Investigator and the Sponsor's Medical Monitor. The SMC will meet to review the Day 42 PK data as well as safety and tolerability data prior to the first and second dose escalations in the multiple ascending dose period of the study. Additionally, the SMC will meet on an ad hoc basis under any condition(s) where decisions about ongoing participant dosing in the study is in question and participant safety may be at risk. Criteria that may warrant an ad hoc SMC meeting include, but are not limited to the following:

1. A participant experiences any AE Grade ≥ 2 or SAE.
2. A participant experiences worsening of an ongoing AE by ≥ 1 grade.
3. A participant experiences any other finding (symptoms, physical examination, laboratory) whose severity may preclude dosing new participants in the study.

AEs will be graded based on National Cancer Institute's Common Toxicity Criteria Scale (NCI CTCAE v5). The individual participant's tolerability to the study drug will be determined based on the criteria provided below. Individual Dose Stopping Rules

Dosing for any individual participant will be stopped if the participant experiences a SAE or a clinically significant nonserious AE, which in the opinion of the Principal Investigator or Sponsor's Medical Monitor, warrants discontinuation of the study for that participant's well-being.

5.6. Safety Monitoring Committee

The sites' Principal Investigators and the Sponsor's Medical Monitor will closely monitor the safety of the study participants throughout the duration of study. The SMC will review the totality of safety, tolerability, and available PK and PD data to monitor safety.

The SMC will be composed of the Principal Investigators from each site, or designee, and Sponsor representatives, including the Medical Monitor, Clinical Pharmacologist, Biostatistician, and Product Safety Officer and/or Product Safety Medical Scientist. The SMC will have overall responsibility for any safety and tolerability decisions and for proceeding with dose escalation. Details of the scope including decision, responsibilities, action taken, and frequency of the SMC will be provided in the SMC charter.

In the Multiple Ascending-dose Period of the study, the SMC will review safety, tolerability, PK, and PD data through Day 42 after the single dose from at least 4 participants. The Sponsor will inform the SMC in writing regarding the GBT021601 half-life, and dosing interval of steady-state multiple dosing for the participants of this study.

For the Extended treatment period (Part C), the SMC will meet on an ad hoc basis under any condition(s) where decisions about ongoing participant dosing in the study is in question and participant safety may be at risk.

This is an open label study, so the data reviewed to make dose escalation decisions will not be blinded.

5.7. Dose Escalation Criteria

The % Hb occupancy by GBT021601 will be calculated from the PK as the ratio of GBT021601 concentration to the Hb (estimated at 5mM) in RBCs. The Hb% modification will be based on hemoximetry data. The Hb% occupancy/modification will be utilized as a PD marker because it is a measure of target engagement that has been employed in prior clinical studies of hemoglobin modifying agents.

Dose escalation will be pharmacologically guided (based on PK and PD target levels, Table 6). Dose escalation will proceed after review of safety, tolerability, PK, and PD data through Day 42. Dose escalation will stop according to the stopping rules (Section 5.5.1). Dose escalation will proceed (no more than 2-fold increments) beginning with the Dose 1 with a predicted target of ~20% to 30% Hb occupancy/modification and Dose 2 with a predicted target of > 30% Hb occupancy/modification.

Concerns over potential acute mechanism-related toxicities (tissue hypoxia) are related to the peak achieved % Hb occupancy and therefore to the maximum plasma concentration (C_{max}). For this reason, prior to initiating multiple doses, safety, tolerability, PK, and PD data will be reviewed by the SMC. Prior to dose escalation, dose levels may be revised if indicated, based on PK/PD data.

Progression to the next higher dose will only occur if the previous dose level was deemed by the SMC to be safe and well tolerated.

When it is not appropriate to escalate the dose, then the same dose or a titrated dose may also be investigated depending upon the results of the safety data from the previous dose levels.

Table 6: Target % Hb Occupancy/Modification for Multiple Ascending-dose Period, Intrapatient Dose Escalation

Dose Escalation Level	Predicted % Hb Occupancy/Modification	Anticipated Loading Dose (mg)[a]	Anticipated Maintenance Dose (mg)[a]
Dose 1	~20% to 30%	TBD	TBD every TBD
Dose 2	> 30%	TBD	TBD every TBD

[a] The GBT021601 dose levels and frequency to be evaluated will be determined based on PK/PD evaluation of single doses in healthy volunteers and Day 42 PK in adults with SCD.

Based on the findings from Dose Levels 1 and 2, there were no significant safety concerns related to GBT021601 and based on PPK modeling, the planned doses are expected to result in Hb occupancy of approximately 54%.

Table 7: Model-Predicted Dose Planned for Extended Treatment Period

Loading Dose	Maintenance Dose	Mean Targeted % Hb Occupancy
300 mg BID x 4 days	150 mg QD	~54%

6. TREATMENT OF PARTICIPANTS

6.1. Description of Study Drug

Study drug details are presented in Table 8.

Table 8: Identity of Study Drugs

Study Drug	Dosage Form	Strength
GBT021601	Tablet	100 mg
GBT021601	Capsule	5 mg, 25 mg

As of Protocol Amendment 5, study drug will be provided as a tablet or capsule as per Table 9.

Table 9: Study Drug for Extended Treatment Period

Study Drug	Dosage Form	Dose Strength
GBT021601	Tablet	100 mg
GBT021601	Capsule	25 mg

GBT021601 tablets and capsules will be provided by the Sponsor.

6.2. Treatments Administered

Study drug will be administered orally with approximately 240 mL non-carbonated room temperature water.

6.3. Method of Assigning Participants to Treatment Groups

This is an open-label, single-arm, intrapatient, single dose and multiple dose escalation study. Participants will be assigned a study identification number during Screening and a separate number assigned at enrollment.

6.4. Measurements of Treatment Compliance

The first dose of the study drug will be administered by delegated and trained staff at the clinical research unit (CRU). Details regarding dosing, including the dose administered and the date and time of dosing, will be recorded in a dosing diary during the maintenance doses. Additionally, a hand and mouth check will be performed to verify that the administered dose was swallowed.

For the Multiple Ascending-dose Period of this trial, at Week 8 and Week 13 Visits, the loading dose (as applicable) will be administered by delegated and trained staff at the CRU. Details regarding dosing, including the dose administered and the date and time of dosing, will be recorded. Maintenance doses will be administered either by the CRU staff during visits or by the participant based on the to be determined frequency of dosing. Recording of dosing to monitor compliance will also be based on the dosing frequency.

6.5. Concomitant Medications, Procedures, Other Restrictions and Requirements

6.5.1. Concomitant Medications and Procedures

Study participants will be allowed to take other medications as needed with the exception of those described listed in Section 6.5.2. All concomitant medications will be documented.

In the interests of participant 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 participants' electronic case report form (eCRF) (medication, dose, treatment duration and indication).

6.5.2. Other Restrictions

Participants will be instructed to adhere to the following restrictions:

- Participants are not permitted to use drugs of abuse from Screening through EOS/ET Visit.
- Participants are not permitted to use herbal preparations or dietary supplements, or any drugs that induce or inhibit study drug-specific CYP(s) within 14 days or 5 half-lives, whichever is longer, prior to Day -1.
- Participants are not permitted to use voxelotor, crizanlizumab, or L-glutamine while participating in this clinical study.
- Participants are not permitted to consume grapefruit and/or grapefruit juice from 14 days prior to Day -1 through the EOS/ET Visit.
- During the Single-dose Period, participants are not permitted to consume any food and drink from outside of the CRU while residing at the CRU.
- Participants are not permitted to participate in any other interventional clinical study or donate blood or plasma while participating in this clinical study.

6.5.3. Fertility and Contraceptive Requirements

6.5.3.1. Female Participants of Childbearing Potential

Refer to Inclusion Criterion 6.

Female participants who are of child-bearing potential are required to use highly effective methods of contraception.

Highly effective contraception methods are defined as the following:

a. Estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation OR progestogen only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration
b. An intrauterine device (IUD)
c. An intrauterine hormone-releasing system (IUS)

d. Females with bilateral tubal occlusion

e. Surgically sterile male partner (eg, vasectomy)

f. True sexual abstinence, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Periodic abstinence (eg, calendar, ovulation, symptom-thermal, post-ovulation methods), and withdrawal are not acceptable methods of contraception.

6.5.3.2. Instructions for Male Participants Capable of Fathering a Child

There is no information about effects that GBT021601 could have on male sperm and on the development of the fetus in humans. Therefore, it is important that the female partners of male participants do not become pregnant during the study and for a total period of 165 days after the male participant has taken the last dose of GBT021601.

As a precaution, all male participants who are sexually active and not surgically sterile should avoid fathering a child by either true abstinence or the use of barrier methods of contraception plus highly effective contraception for their female partner if of childbearing potential.

6.5.3.3. Acceptable Forms of Contraception for Male Participants with Female Partners Capable of Reproduction

Refer to Inclusion Criterion 6.

Male participants who are not surgically sterile with partners of childbearing potential must agree to use a highly effective method of birth control during the study and for 165 days after the last dose of study drug. A highly effective method of contraception is defined as one that results in a low documented failure rate when used consistently and correctly such as: condom plus use of an intrauterine device; intrauterine system or hormonal method of contraception (oral, injected, implanted, or transdermal) for their female partner; or sexual abstinence.

Male participants who are not surgically sterile with a partner who is pregnant must agree to condom use or maintain sexual abstinence during the study and for 165 days after the last dose of study drug.

7. STUDY DRUG MATERIALS AND MANAGEMENT

7.1. Study Drug

GBT021601 will be provided as a tablet formulation in the strength of 100 mg and a capsule formulation in strengths of 5 mg and 25 mg. All excipients used are compendial grade and are listed in the FDA's Inactive Ingredients Database. As of Protocol Amendment 5, GBT021601 will be provided as a 100 mg tablet or a 25 mg capsule.

7.2. Study Drug Packaging and Labeling

GBT021601 will be provided in high density polyethylene (HDPE) bottles of 30 tablets and in separate HDPE bottles of 30 capsules with child resistant caps with induction seal and labeled according to local regulations.

7.3. Study Drug Storage

Study drug will be stored at controlled room temperature between 15°C to 25°C in the storage area of the investigational site pharmacy, which is a secure, temperature controlled, locked environment with restricted access.

No special considerations for safe handling of GBT021601 are required.

7.4. Blinding of Treatment Assignment

Not applicable since this is an open-label study.

7.5. Administration

GBT021601 will be administered orally. For the single-dose period, participants will fast at least 10 hours before and for at least 4 hours after study drug administration. Water will be allowed as desired except for 1 hour before and 1 hour after study drug administration.

For the multiple ascending-dose period of the study, GBT021601 can be taken with or without food.

Each dose will be administered orally with approximately 240 mL of water (additional water to complete dosing is allowed). Participants will be instructed to swallow the tablets or capsules within 5 minutes. If the participant vomits, the dose should not be repeated.

7.6. Study Drug Accountability and Disposal

The Investigator must ensure that all study drug supplies are kept in a secure locked area with access limited to those authorized by the Investigator. The Investigator must maintain accurate records of the receipt of all study drug shipped by the Sponsor or their representative, including but not limited to the date received, lot number, amount received, and the disposition of all study drug. Current dispensing records will also be maintained including the date and amount of study drug dispensed and the participant receiving the study drug. All remaining study drug not required by regulations to be held by the CRU must be reconciled prior to destruction. Drug may be returned to the Sponsor's representative immediately after the study is completed or destroyed on-site with Sponsor approval.

8. PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

8.1. Blood Sample Collection

The PK/PD samples for GBT021601 will be collected at time points specified in the PK/PD sampling schedules (Table 1, Table 2, Table 3, and Table 4). Sample collection, processing, and shipping details will be outlined in a separate study reference manual.

For procedures scheduled to be performed at the same time, priority is to be given to collection of the PK samples at the designated time. ECGs, followed by vital signs, are to be performed before PK sampling unless PK samples will be delayed as a result.

8.1.1. Single-dose Period

During the Single-dose Period, plasma and whole blood PK samples will be collected at the following times:

Pre-dose (within 60 minutes of dosing) and postdose at 0.25, 0.5, 1, 2, 4, 6, 8, 12 hours; 24 hours (Day 2), 36 hours, 48 hours (Day 3), and 72 hours (Day 4); Days 7, 14, 21, 28, and 42.
The windows for sample collection are provided in Table 10.

Table 10: Windows for PK Sample Collection – Single-dose Period

Sample Collection Time	Allowed Deviation
0.0 – 1.0 hour	± 2 minutes
> 1.0 – 24.0 hours	± 5 minutes
> 24.0 – 72.0 hours	± 10 minutes
> 72.0 – 144.0 hours	± 15 minutes
> 144.0 hours	± 24 hours

Blood samples for hemoximetry and RBC deformability, dense cells will be collected at the same time as the PK samples at pre-dose and 12 hours postdose on Day 1. In addition, hemoximetry samples will be collected on Days 2, 4, 7, 21, and 42.

8.1.2. Multiple Ascending-dose Period

Plasma and whole blood pre-dose and postdose PK samples will be collected in the Multiple Ascending-dose period as listed in Table 11. Whole blood samples for hemoximetry and RBC deformability, dense cells will be collected at the same time as the PK samples.

Table 11: PK and PD Sample Collection Times – Multiple Ascending-dose Period

Week	Pre-dose[a]	Postdose
8	1 PK/PD sample Pre-dose	1 PK sample between 0.25 hour to 1 hour 1 PK/PD sample between 2 to 4 hours
9	1 PK/PD sample Pre-dose	1 PK sample between 0.25 hour to 1 hour 1 PK/PD sample between 2 to 4 hours
10	1 PK/PD sample Pre-dose	1 PK sample between 0.25 hour to 1 hour 1 PK/PD sample between 2 to 4 hours
11	1 PK sample Pre-dose	1 PK sample between 0.25 hour to 1 hour, 1 PK/ sample between 2 to 4 hours
12	1 PK sample Pre-dose	1 PK sample between 0.25 hour to 1 hour 1 PK sample between 2 to 4 hours
13	1 PK/PD sample Pre-dose	1 PK sample between 0.25 hour to 1 hour 1 PK/PD sample between 2 to 4 hours
14	1 PK sample Pre-dose	1 PK sample between 0.25 hour to 1 hour 1 PK sample between 2 to 4 hours
15	1 PK sample Pre-dose	1 PK sample between 0.25 hour to 1 hour 1 PK sample between 2 to 4 hours
16 EOT	1 PK/PD sample Pre-dose	1 PK sample between 0.25 hour to 1 hour 1 PK/PD sample between 2 to 4 hours
EOS/ET	Anytime during visit	

Abbreviations: PD, pharmacodynamics; PK, pharmacokinetics.
[a] The pre-dose blood sample for PK and PD assessments should be collected within 30 minutes prior to dosing.

Table 12: PK and PD Sample Collection Times –Extended Treatment Period CCI

Extended Treatment Period		Pre-dose[a]	Postdose
Week	Day		
1	1	1 PK/PD sample	1 PK sample between 0.25 hour to 1 hour 1 PK/PD sample between 2 to 4 hours
2	15	1 PK/PD sample	1 PK sample between 0.25 hour to 1 hour 1 PK/PD sample between 2 to 4 hours
4	29	1 PK sample	1 PK sample between 0.25 hour to 1 hour 1 PK sample between 2 to 4 hours
6	43	1 PK sample	1 PK sample between 0.25 hour to 1 hour 1 PK sample between 2 to 4 hours
10	71	1 PK sample	
14	98	1 PK sample	
Final Visit	Anytime during visit		

Abbreviations: PD, pharmacodynamics; PK, pharmacokinetics.
[a] The pre-dose blood sample for PK and PD assessments should be collected within 30 minutes prior to dosing.

8.2. Pharmacokinetic Analysis

Plasma and whole blood concentrations will be determined using a validated assay.

For the single-dose period, the following whole blood, plasma, and PK parameters of GBT021601 will be calculated, if appropriate: maximum observed plasma/whole blood concentration (C_{max}), time of maximum serum concentration (t_{max}), area under the concentration vs time curve from zero to 24 hours (AUC_{0-24}), area under the concentration vs time curve from time zero to last quantifiable concentration (AUC_{0-t}), area under the concentration vs time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$), apparent clearance (CL/F), apparent volume of distribution during the terminal phase (Vz/F), and half-life ($t_{1/2}$).

For the multiple ascending-dose period, the following whole blood and plasma PK parameters of GBT021601 will be calculated using nonlinear mixed effects modeling: plasma/whole blood C_{max}, plasma/whole blood C_{min}, plasma/whole blood AUC at steady-state and half-life. The % Hb occupancy will be estimated based on C_{min} and C_{max} as well as hemoximetry data.

8.3. Pharmacodynamic Analysis

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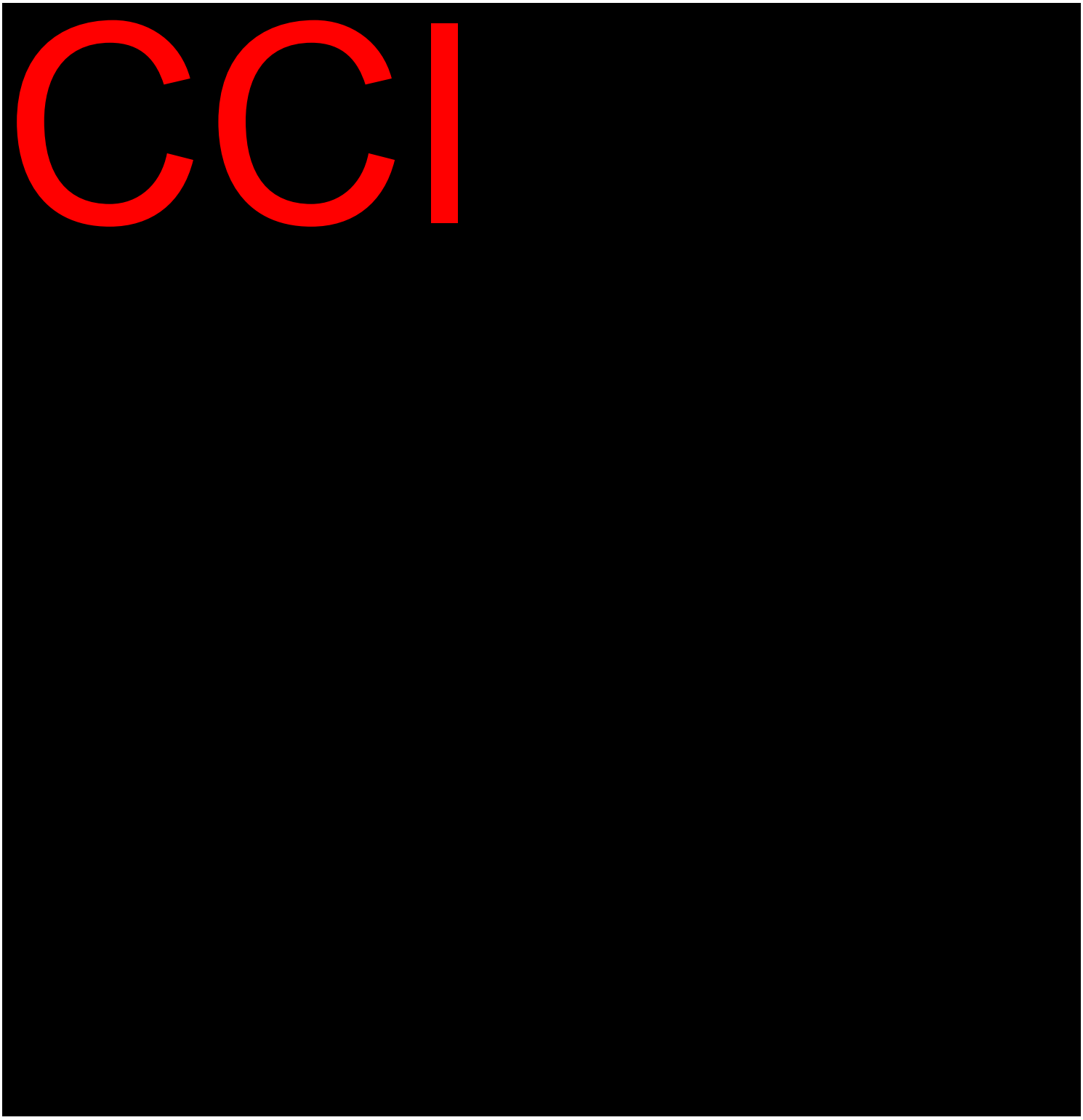
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9. ASSESSMENT OF SAFETY

9.1. Safety Parameters

9.1.1. Demographic/Medical History

The Investigator or designee will collect a complete medical and surgical history at Screening and again at CRU admission to determine if any changes have occurred since Screening.

9.1.2. Vital Signs

Vital signs assessments will include respiratory rate (breaths per minute), systolic and diastolic BP (mmHg), and heart rate (HR) (beats per minute [bpm]) and body temperature, which will be measured after a participant has rested for at least 5 minutes in the supine position as per Table 1, Table 2, Table 3, and Table 4.

Any clinically significant abnormal vital sign assessment requires at least 1 repeat measurement.

Vital signs abnormalities that are (1) considered clinically significant initially and on confirmation, (2) require a participant to be discontinued from the study, (3) require a participant to receive treatment, or (4) require a change or discontinuation from the study drug (if applicable) will be recorded as AEs.

9.1.3. Weight and Height

Height will be completed at Screening only and weight as per Table 1,Table 3, and Table 4.

9.1.4. Physical Examination

A full physical examination will be conducted at Screening. All subsequent physical examinations should be signs and symptoms driven. Full physical examination will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system (Table 1,Table 3, and Table 4).

An abnormal physical examination finding during the on-study period (ie, following dose administration) that is considered clinically significant and (1) requires the participant to be discontinued from the study, or (2) requires the participant to receive treatment will be recorded as an AE.

9.1.5. Electrocardiogram

Electrocardiograms (ECG) (12-lead) will be collected in triplicate within 5 minutes as per Table 1, Table 2, Table 3, and Table 4.

ECGs will be recorded after a participant has rested at least 5 minutes in the supine position. The following ECG parameters will be recorded: HR, PR, QRS, QT, and QTcF intervals.

ECG assessment will include interpretation of the tracings (eg, rhythm, presence of arrhythmia or conduction defects, any evidence of myocardial ischemia/infarction, or ST segment, T-wave, and U-wave abnormalities). The Investigator or designee is responsible for reviewing and over-reading the ECG interpretation, for assessing whether the ECG machine interpretation findings

are accurate, appropriate, normal, or abnormal, and for providing corrected interpretations as appropriate. In addition, any abnormal ECGs will be assessed for clinical significance.

Additional ECGs may be obtained if clinically indicated and must be obtained if abnormal and clinically significant or thought to be an error (eg, lead placement error, movement artifact, etc.). Any additional relevant data obtained by the Investigator during the course of this study will be supplied to the Sponsor.

For any ECG that the Investigator considers clinically significant, the Investigator will:

- Repeat the ECG.
- Follow-up ECG(s) will be obtained if any significant abnormalities are detected after dose administration to document resolution and as clinically indicated.
- Record as an AE any ECG that is 1) confirmed by the Investigator as clinically significant, 2) requires a participant to be discontinued from the study, or 3) requires a participant to receive treatment.

9.1.6. Laboratory Assessments

9.1.6.1. Standard Clinical Laboratory Assessments

Clinical laboratories described in Table 13 will be collected as outlined in Table 1 and Table 3, and Table 4. A certified laboratory will be utilized to process and provide results for the clinical laboratory tests. The Baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the first dose of study drug.

During Screening, if a participant has an out-of-range value for a clinical laboratory parameter that the Investigator believes is not clinically significant or that the Investigator does not believe is correct (eg, laboratory or specimen processing error), but the Investigator wants to confirm with a repeat laboratory test, a single repeat is allowed to confirm the initial result.

All out of-range values will be assessed by the Investigator as clinically significant or not clinically significant. For any laboratory test value outside the reference range that the Investigator considers clinically significant during the on-study period (ie, following dose administration), the Investigator will repeat the test to verify the out-of-range value and clinical significance.

Additional safety laboratory tests may be conducted as needed by the Investigator to evaluate participant safety.

9.1.6.2. Other Laboratory Assessments

Assessments of p50 and p20 will be conducted by hemoximetry as indicated in Table 1, Table 3, and Table 4 . Assessments of RBC deformability and dense cells will be conducted as indicated in Table 1, Table 3, and Table 4.

Assessments of serum erythropoietin (EPO) will be conducted as indicated in Table 1 and Table 3, and Table 4.

Table 13: Clinical Laboratory Tests

Hematology	Coagulation	Chemistry	Urinalysis	Other
Hematocrit Hb RBC count Mean corpuscular volume Mean corpuscular Hb Mean corpuscular Hb concentration Reticulocyte count (absolute and %) Platelet count (estimate not acceptable) White blood cell count including differential count (percent and absolute): • Neutrophils • Lymphocytes • Monocytes • Basophils • Eosinophils	International normalized ratio Prothrombin time aPTT	ALT Albumin Alkaline phosphatase AST Bicarbonate Blood urea nitrogen Calcium Chloride Creatine phosphokinase Creatinine Fasting glucose Lactate dehydrogenase Magnesium Phosphorous Potassium Sodium Total bilirubin (direct and indirect) Total protein Uric acid eGFR[a]	Bilirubin Blood Glucose Ketones Leukocytes Microscopic analysis of sediment if clinically indicated Nitrite pH Protein Specific gravity Urobilinogen **Urine Drug screen** Cannabinoids Amphetamines Methamphetamines Opiates Methadone Cocaine Benzodiazepines Phencyclidine, if clinical suspicion Barbiturates Alcohol breath test	EPO FSH (post-menopausal females only) Pregnancy - serum and urine (females only) [b] Lipid Panel Amylase Lipase Hemoximetry RBC deformability and dense cells **Serology Panel:** HIV 1/2 antibody Hepatitis A virus IgM antibody Hepatitis B virus surface antigen Hepatitis C virus antibody SARS CoV-2

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; EPO, erythropoietin; FSH, follicle stimulating hormone; Hb, hemoglobin; HIV, human immunodeficiency virus; IgM, immunoglobulin M; PCR, polymerase chain reaction, RBC, red blood cells.
Note: Not all of these clinical laboratory tests are performed for safety purposes.
[a] Using the using the Cockcroft-Gault formula.
[b] Tests will be conducted at the clinic.

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10. ASSESSMENT OF SAFETY — ADVERSE EVENTS

10.1. Adverse and Serious Adverse Events

10.1.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered related to the study drug. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a study drug. An AE may also constitute complications occurring as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies), including the period prior to receiving the first dose of the study drug (eg, medication washout). In addition to new events, any increase in the severity or frequency of a pre-existing condition occurring after the participant signs the ICF is considered to be an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

A life-threatening AE or life-threatening suspected adverse reaction is an AE or suspected adverse reaction that, in the view of either the Investigator or Sponsor, places the study participant at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

An AE or suspected adverse reaction is considered to be "unexpected" if it is not listed in the Reference Safety Information section of the current IB or is not listed at the specificity or severity that has been observed.

10.1.2. Serious Adverse Event

A SAE or serious suspected adverse reaction is an AE or suspected adverse reaction that, at any dose, in the view of either the Investigator or Sponsor, results in any of the following outcomes:

- Death;
- A life-threatening AE;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant incapacity or disability (substantial disruption of the ability to conduct normal life functions);
- A congenital anomaly/birth defect; or
- Important medical events that may not result in death, be immediately life-threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the study participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Note: Hospitalization planned prior to study enrollment (eg, for elective surgeries) is not considered to be an SAE. Hospitalizations that occur for pre-existing conditions that are scheduled after study enrollment are considered SAEs.

10.2. Severity

Whenever possible, the severity of all AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0.

For AEs not adequately addressed in the NCI CTCAE, Version 5.0, the following criteria should be used.

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

To make sure that there is no confusion or misunderstanding between the terms “serious” and “severe”, which are not synonymous, the following note of clarification is provided. The term “severe” is often used to describe the intensity (severity) of a specific event (ie, mild, moderate, or severe); the event itself, however, may be of relatively minor medical significance (eg, severe headache). This is not the same as “serious”, which is based on the study participant/event outcome or action criteria associated with events that pose a threat to a participant’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.3. Relationship to Study Drug

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

- **Not Related**: Evidence exists that the AE has an etiology other than the study drug and/or the temporal relationship of the AE/SAE to the study drug administration makes the relationship unlikely. If an SAE is not considered to be related to study drug, then an alternative explanation should be provided.
- **Related**: A temporal relationship exists between the event onset and the administration of the study drug and makes a causal relationship possible or probable. It cannot be readily explained by the participant’s clinical state or concomitant therapies and may appear, with some degree of certainty, to be related based on the known therapeutic and pharmacologic actions of the drug. Good clinical judgment should be used for determining causal assessment.

10.4. Unexpected Adverse Reactions

An AE is "unexpected" if its nature and severity are not consistent with the information about the study drug provided in the Reference Safety Information in the IB.

10.5. Recording Adverse Events

10.5.1. General

All AEs will be recorded from the time the study participant signs the ICF form until the EOS Visit or ET Visit, whichever comes first. All AEs must be reported on the AE electronic case report form (eCRF) via the electronic data capture system. The Investigator is responsible for evaluating all AEs, obtaining supporting documents, and ensuring that documentation of the event is complete. Details of each reported AE must include at a minimum severity, relationship to study treatment, duration, and outcome. All serious and nonserious AEs must be followed until they are resolved or stabilized, or until reasonable attempts to determine resolution of the event are exhausted.

Any participant who experiences an AE may be discontinued from study treatment at any time at the discretion of the Investigator. The Sponsor/Medical Monitor(s) must be notified of the study participant discontinuation.

10.5.2. Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded in the eCRF rather than individual signs and symptoms (eg, 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 separately in the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

10.5.3. Abnormal Laboratory Values

Clinically significant laboratory abnormalities will be recorded in the AE eCRF (eg, abnormalities that have clinical sequelae, more frequent follow-up assessments, or further diagnostic investigation). If the clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (eg, cholecystitis) should be recorded in the eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded. For example, a 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 on the AE eCRF, unless their severity, seriousness, or etiology changes.

10.6. Reporting Adverse Events

10.6.1. Serious Adverse Events

All SAEs, regardless of causal attribution, must be reported by the Investigator or designee or site personnel within 24 hours of awareness by completing the paper SAE report forms and submit via fax or email to Sponsor's Pharmacovigilance or designated CRO.

The Sponsor or designee may request additional source documentation pertaining to the SAE from the investigational site. Follow-up reports must be submitted within 24 hours of awareness, and participant identifier information (eg, name, medical record number) must be redacted in the hospital discharge summaries, autopsy reports, and/or death certificates.

Follow-up SAE information must be submitted within 24 hours of awareness as additional information becomes available. All SAEs regardless of causal attribution must be followed to resolution or stabilization, or until reasonable attempts to determine resolution of the SAE are performed.

Investigators are not obligated to actively seek SAE information from participants that complete the study, but investigators are encouraged to notify the Sponsor, or designee, of any SAEs of which they become aware occurring at any time after a participant has discontinued or completed the study that they judge may be reasonably related to treatment with study drug or study participation.

10.6.2. Reporting Suspected Unexpected Serious Adverse Reactions and Urgent Safety Issues

The Sponsor or designee is responsible for reporting suspected unexpected serious adverse reactions (SUSARs) to regulatory agencies, competent authorities, IRB, and Investigators as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than 7 calendar days of the Sponsor's or designee's first knowledge of the event and follow-up information submitted within an additional 8 calendar days, or as otherwise required per local laws and regulations. All other SUSARs will be submitted within 15 calendar days of the Sponsor's or designee's first knowledge of the event. The Investigator is responsible for notifying the local IRB of all SAEs that occur at his or her site as required by local regulations or IRB policies, if this responsibility resides with the site.

Investigators are required to report any urgent safety matters to the Sponsor or designee within 24 hours of awareness. The Sponsor or designee will inform regulatory authorities, IRBs, and Investigators, as applicable, of any events (eg, change to the safety profile of GBT021601, major safety findings that may place study participants at risk) that may occur during the clinical study that do not fall within the definition of a SUSAR but may adversely affect the safety of study participants.

10.7. Pregnancy

If a participant becomes pregnant while on study, the pregnancy must be reported to the Sponsor or designee within 24 hours of awareness. The Investigator will discuss the risks and concerns of study drug exposure to a developing fetus and counsel the participant and/or pregnant partner (or ensure such counseling is provided).

Reported pregnancy of a participant while participating in this study will be monitored for the full duration of the pregnancy, and/or followed through a definitive outcome (ie, birth or spontaneous or elective abortion). Pregnancies in partners of male study participants will similarly be monitored for the full duration of the pregnancy and/or followed through a definitive outcome (ie, birth or spontaneous or elective abortion).

An uncomplicated pregnancy will not be considered an AE or SAE. Pregnancy complications such as spontaneous abortion/miscarriage and congenital anomalies are considered SAEs and must be reported as described in Section 10.6.1. Note that an elective abortion is not considered an SAE. Pregnancy and pregnancy outcomes must be reported on a Pregnancy Notification Form or Pregnancy Outcome Form, respectively, and sent to the Sponsor or designee within 24 hours of the Investigator site personnel learning of the pregnancy or pregnancy outcome.

The child born to a female participant or partner of a male participant exposed to study drug will be followed for 3 months after delivery. The outcome of any pregnancy and the presence or absence of any congenital abnormality will be recorded in the Pregnancy Outcome Form and reported to the Sponsor or designee. Any congenital abnormalities in the offspring will be reported as an SAE and must be reported as described in Section 10.6.1.

Information regarding pregnancy testing (including definition of females of childbearing potential) is provided in Section 6.5.3. Highly effective means of contraception are listed in Section 6.5.3.3.

10.8. Drug-induced Liver Injury

Participants will be monitored for signs of drug-induced liver injury (DILI).

Potential events of DILI will be defined as meeting all the following criteria (as specified in the FDA Guidance for Industry: *Drug-Induced Liver Injury: Premarketing Clinical Evaluation*. [FDA, 2009]):

- ALT > 4 × ULN or aspartate aminotransferase > 3 × ULN
- No other reason can be found to explain the combination of laboratory value increases (eg, acute viral hepatitis; alcoholic and autoimmune hepatitis; hepatobiliary disorders; nonalcoholic steatohepatitis; cardiovascular causes; concomitant treatments)

Potential events of DILI will be reported as SAEs (Section 10.6.1). All participants with potential DILI will be closely followed until abnormalities return to normal or baseline or until all attempts to determine resolution of the event are exhausted.

11. STATISTICS

Study data will be reported using summary tables, figures, and listings. Study analyses will be descriptive in nature and no formal statistical tests are planned.

11.1. Sample Size Calculation

Due to the exploratory nature of this study, no formal power or sample size calculations were used to determine cohort size. A sample size of up to 6 participants with SCD are expected to provide adequate characterization of PK and safety.

11.2. Analysis Populations

Safety Population: All participants who received study drug.

Pharmacokinetic Full Population: All participants who received study drug and have at least 1 concentration data point (plasma or whole blood).

Pharmacokinetic Evaluable Population: All participants who received study drug and have a sufficient PK profile to derive at least 1 PK parameter.

11.3. Interim Analysis

There is no formal planned interim analysis.

11.4. Safety Analysis

AEs will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized. Vital signs and laboratory safety assessments will be presented with identification of values outside of normal range. Electrocardiogram data will be presented, with any clinically relevant abnormal findings or changes highlighted.

11.5. Pharmacokinetic Analysis

Noncompartmental PK analysis or population PK analysis using nonlinear mixed-effect modeling will be performed to characterize GBT021601 PK in plasma, and whole blood following single and multiple doses.

11.6. Pharmacodynamic Analysis

Pharmacodynamic markers and computed PD parameters will be listed. Individual and mean PD marker data will be presented graphically.

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11.7. Pharmacokinetic/Pharmacodynamic Relationships

The relationships between PK and PD may be explored by PK/PD modeling, if appropriate. Results of these analyses will be presented in a separate report.

12. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will permit study-related monitoring, audits, IRB review, and regulatory inspection, as appropriate, by providing direct access to source data/documents.

12.1. Source Data

Original documents, data, records (eg, clinic records, laboratory notes, memoranda, participant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, participant files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical study), and all relevant sections of the participant's medical records and all other data collection made specific to this study constitute source documents.

Before an investigational site can enter a participant into the study, a representative of Sponsor and/or designee will visit the CRU to:

- Determine the adequacy of the facilities; and
- Discuss with the Investigator and other personnel their responsibilities with respect to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from the Sponsor or representative will have regular contact with the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol that data are being accurately recorded in the eCRF, and that study drug accountability checks are being performed and dosing diaries reviewed.
- Perform source data verification. This includes a comparison of the data in the eCRF with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the Sponsor or safety designee and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator or other staff needs information.

12.2. Data Collection

The Investigator will be responsible for maintaining accurate and adequate source documents. All relevant observations and data related to the study will be recorded. This will include medical and medication history, physical examinations, a review of inclusion and exclusion criteria, investigational treatment administration and record of sample collection, clinical assessments, AEs, and final evaluation(s).

Data for each participant will be recorded on the eCRF. An eCRF must be completed for every participant enrolled in the study. When data are complete, the Investigator or medically qualified sub-Investigator listed on FDA Form 1572 will apply his/her signature on the eCRF indicating he/she has reviewed and approves of the data collected on the eCRF. The monitor will review all eCRFs and compare data to those contained in clinic notes and participants' source documents/medical records.

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1. Monitoring

Site personnel will be provided with training on how to collect quality data for the study, and a Sponsor monitor or designee will be contacting the site periodically to review study conduct and data recorded at the site. At the Sponsor's discretion, on-site monitoring visits may be conducted prestudy, during the study, and following study completion. These visits are to provide the Sponsor with the opportunity to evaluate study progress; verify the accuracy and completeness of source data and eCRFs; and ensure that all protocol and Good Clinical Practice (GCP) requirements, applicable country-specific regulations, and Investigator obligations are being fulfilled. The Sponsor may terminate study participation if study-site personnel do not follow the protocol or GCP. Additionally, individual participants may be excluded if a medical record review indicates protocol deviations or if other factors appear to jeopardize the validity of the study.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected during the monitoring visits are resolved.

13.2. Quality Control and Quality Assurance

The Sponsor may conduct quality assurance audits of this study. If such an audit occurs, the Investigator agrees to allow the auditor direct access to all relevant documents (eg, all participant records, medical records, and eCRFs) and access to all corresponding portions of the office, clinic, laboratory, or pharmacy that may have been involved with the study. The Investigator will allocate his or her time and that of the study-site personnel to the auditor to discuss findings and any relevant issues.

In addition, regulatory agencies may conduct a regulatory inspection of this study. If such an inspection occurs, the Investigator agrees to notify the Sponsor upon notification by the regulatory agency. The Investigator agrees to allow the inspector direct access to all relevant documents and to allocate his or her time and that of the study-site personnel to the inspector to discuss findings and any relevant issues. The Investigator will allow Sponsor personnel to be present as an observer during a regulatory inspection, if requested.

13.3. Laboratory Accreditation

The laboratory facility used for analysis of clinical laboratory samples must provide evidence of adequate licensure or accreditation. Copies of laboratory certification, licensure, and reference ranges (as appropriate) will be supplied to the Sponsor prior to study initiation. The Sponsor or designee should be notified of any changes in reference range values or certification/license renewal during the study.

14. ETHICS

14.1. Ethical Conduct of the Study

The Investigator will ensure that this study is conducted in full conformity with the current revision of the 1964 Declaration of Helsinki.

The Investigator is generally not to deviate from the protocol. In medical emergencies, the Investigator will use medical judgment and will remove the participant from immediate hazard. The Investigator will immediately notify the Sponsor and IRB regarding the nature of the emergency and the course of action taken. The Investigator is to notify the Sponsor of any inadvertent protocol deviations upon discovery and is to document the deviations appropriately in the study files or on the eCRFs. The Sponsor assumes no responsibility or liability for any deviations. Major changes in the protocol initiated by the Sponsor will be provided as an amendment and must be approved by the IRB prior to implementation (refer to Section 14.4).

14.2. Good Clinical Practice

The study will be conducted according to the protocol, guidelines established by the International Council for Harmonisation (ICH) for GCP in clinical studies and country-specific requirements as applicable.

14.3. Informed Consent

Each individual will be provided with oral and written information describing the nature, purpose and duration of the study, participation/termination conditions, and risks and benefits. Prior to initiation of any study-related procedures, participants (and/or their parent or legal guardian for participants under 18 years of age) will sign and date the ICF to participate in the study. Participants under 18 years of age (and their parent or legal guardian) will review the ICF and sign a Child Assent Form, according to local institution/IRB guidelines. The parent or legal guardian for participants under 18 years of age will also sign and date an authorization form required under the Health Insurance Portability and Accountability Act (HIPAA), if applicable, that authorizes the use and disclosure of the participant's protected health information. In the event of a pregnancy in the female partner of a male participant, a pregnancy consent form will be provided to allow the follow-up of the pregnancy.

Participants unable to sign the ICF may participate in the study if a legal representative or witness provides the consent (in accordance with the procedures of ICH-GCP and local regulations) and the participant confirms his/her interest in study participation. The participant, parent, or legal guardian will be informed that he/she can freely withdraw consent and stop participation in the study at any time with no prejudice to further treatment. It is the parent or legal guardian's responsibility to communicate this decision to the Investigator.

14.4. Institutional Review Board and Regulatory Approval

The Investigator must inform and obtain approval from the IRB for the conduct of the study at named sites and for the protocol, the participant ICF, and any other written information that will be provided to the participants and any advertisements that will be used. Written approval must be obtained prior to enrollment of participants into the study and shipment of study drug.

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

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

14.5. Essential Documentation Requirements

The Sponsor or Sponsor's representative will collect from the investigational site the required essential regulatory documents per ICH guidance prior to study drug shipment to the site.

14.6. Confidentiality

The Investigator must ensure that the participant's privacy is maintained. In the eCRF and other documents submitted to the Sponsor, participants will be identified by a participant study number only. Documents that are not submitted to the Sponsor (eg, signed ICF) should be kept in a strictly confidential file by the Investigator.

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

14.7. Regulatory, Ethical, and Legal Obligations

The study will comply with the applicable local data protection regulations. Data collected will be pseudonymized.

The processing of the personal data of participants will be minimized by making use of a unique participant study number only on study documents and electronic database(s).

All study documents will be stored securely and only accessible by study staff and authorized personnel. The study staff will safeguard the privacy of participants' personal data.
The participant information sheet/informed consent for the study will inform participant of their rights.

14.8. Study Documentation and Data Storage

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

The Investigator must retain essential documents as detailed in Section 15.2. Participant files and other source data (including copies of protocols, original reports of test results, investigational agent dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be kept for the maximum period of time permitted by the institution. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

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

15. DATA HANDLING AND RECORDKEEPING

15.1. Inspection of Records

The Sponsor or Sponsor's representatives will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

The Investigator agrees to maintain a regulatory binder, paper or electronic, in a current, organized fashion; this binder will contain documentation supportive of the protocol- and GCP-compliance of the study. The contents of the binder will be organized according to the standards of ICH E6, Section 8 (Essential Documents). The Investigator agrees to make this binder accessible to the monitor, auditor, and representatives of regulatory agencies and the IRB.

15.2. Retention of Records

The Investigator will maintain adequate records, including participants' medical records, laboratory reports, signed consent forms, drug accountability records, safety reports, information regarding participants who discontinued the protocol, and any other pertinent data. All study records must be retained for at least 2 years after the last approval of a marketing application in the US or an ICH region and until (1) there are no pending or contemplated marketing applications in the US or an ICH region, or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug under study. The Investigator/institution should retain participant identifiers for at least 15 years after the completion or discontinuation of study. Study participant files and other resource data must be kept for the maximum period of time permitted by the hospital or institution but not less than 15 years. These documents should be retained for a longer period, if required by the applicable regulatory requirements or by the Sponsor. The Sponsor must be notified should the Investigator/institution be unable to continue with the maintenance of study participant files for the full 15 years. All study records must be stored in a secure and safe facility.

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

If the 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. The Investigator must notify the Sponsor immediately in the event of accidental loss or destruction of any protocol records.

15.3. Disclosure of Information

Participants' medical information obtained as a result of this study is considered confidential, and disclosure to third parties other than those noted in this protocol is prohibited. Subject to any applicable authorization(s), all reports and communications relating to participants in this study will identify participants only by initials and number.

Medical information resulting from a participant's participation in this study may be given to the participant's personal physician, other authorized parties, or appropriate medical personnel responsible for the participant's participation in this clinical study. Data generated in this study will be available for inspection on request by government regulatory agency auditors; the Sponsor, the Sponsor's Medical Monitor, and their designated representatives; the IRB; and other authorized parties. All information concerning the study drug and the Sponsor's operations (such as patent applications, formulas, manufacturing processes, basic scientific data, or other information supplied by the Sponsor and not previously published) is considered to be confidential and shall remain the sole property of the Sponsor.

The Investigator agrees to use this information only in conducting this study and not to use it for other purposes without the Sponsor's prior written consent. The information developed in this clinical study will be used by the Sponsor in the clinical development of GBT021601 and, therefore, may be disclosed by the Sponsor as required to authorized parties (including its corporate partners for the study drug, if any, and their designated representatives), other clinical Investigators, pharmaceutical companies, the US FDA, and other government agencies.
Any information, inventions, discoveries (whether patentable or not), innovations, suggestions, ideas, and reports made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor.
The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions as the Sponsor deems necessary or appropriate to obtain patents in the Sponsor's name covering any of the foregoing.

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PROTOCOL TITLE: An Intrapatient Single Dose and Multiple Ascending Dose Study to Evaluate the Pharmacokinetics, Safety, Tolerability, and Pharmacodynamics of GBT021601, a Hemoglobin S Polymerization Inhibitor, in Participants with Sickle Cell Disease (SCD)

GBT021601-012 Protocol Amendment 5

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This clinical study protocol has been reviewed and approved by **Global Blood Therapeutics, Inc.**

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