STATISTICAL ANALYSIS PLAN

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)

SAP Version 3.0
FINAL
Date: 24 MAR 2023

for

Protocol No. GBT021601-012

Submitted to:
GBT Inc., a wholly owned subsidiary of Pfizer

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Prepared by:

PPD

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
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
BLQ	Below Quantifiable Limit
BMI	Body Mass Index
BP	Blood Pressure
BPM	Beats Per Minute
CCI	[redacted]
CI	Confidence Interval
CL/F	Apparent Clearance
Cmax	Maximum Blood Concentration
Cmin	Minimum Blood Concentration
CCI	[redacted]
CoV	Coronavirus
CRA	Clinical Research Associate
CSR	Clinical Study Report
CV	Coefficient of Variation
CYP	Cytochrome P450
DMP	Data Management Plan
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EOS	End Of Study
EOT	End Of Treatment
EPO	Erythropoietin
FIH	First In Human
FSH	Follicle Stimulating Hormone
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICH	International Conference on Harmonisation
IgM	Immunoglobulin M
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
N	Number
CCI	[redacted]
CCI	[redacted]
[redacted]	[redacted]

p20	Hemoglobin protein is 20% saturated
p50	Hemoglobin protein is 50% saturated
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred Term
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAD	Single Ascending Dose
SCD	Sickle Cell Disease
SD	Standard Deviation
SMC	Safety Monitoring Committee
SOC	System Organ Class
SSP	Study-Specific Procedure
$t_{1/2}$	Half-life
TEAE	Treatment-Emergent Adverse Event
tmax	Time of maximum serum concentration
Vz/F	Apparent volume of distribution during the terminal phase
VOC	Vaso-Occlusive Crisis
WHO	World Health Organization

REVISION HISTORY

Version Number	Effective Date	Changes since previous version
Final 1.0	28 APR 2022	Original version, Not Applicable
CCI [redacted]	[redacted]	[redacted] 2) Addition of MAD PK TLFs presentation 3) Typo errors
Final 3.0	24 MAR 2023	1) TEAE definition updated 2) Section 7.17.2: criteria for character values for quantitative laboratory parameters added.

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1. INTRODUCTION

This statistical analysis plan (SAP) is consistent with the statistical methods section of the final study protocol (Version 6.0, Amendment 5 dated 08 March 2022) and includes additional detail of pharmacokinetics (PK), pharmacodynamics (PD) and safety summaries to be included in the clinical study report (CSR).

2. STUDY OBJECTIVES

2.1 Objective

The following are the study objectives:

2.1.1 Primary Objective

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

2.1.2 Secondary Objectives

- To evaluate the PK of a single dose and multiple ascending doses of GBT021601 in participants with SCD.
- CCI [redacted]
- 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.

CCI [redacted]

- [redacted]
- [redacted]

3. STUDY DESIGN

3.1 General

This is an open-label intra-patient single dose and multiple ascending dose study in at least 6 participants with SCD. The study schematic is presented in Figure 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.

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 intra-patient 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% Hb 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. After the first multiple dose period, if the % Hb occupancy is higher than 30%, the participant will remain on a maintenance dose that maintains the % Hb occupancy at >30% and will not dose escalate, based on 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 be dose escalated to receive a loading dose and subsequent maintenance dose based on a predicted target of >30% occupancy/modification as determined by the PK results of GBT021601-011 and Part A of this study. 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 after the final dose at Week 16. The elimination 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 Dose Period.

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

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 CCI

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

Figure 3-1: Study Schematic for GBT021601-012:

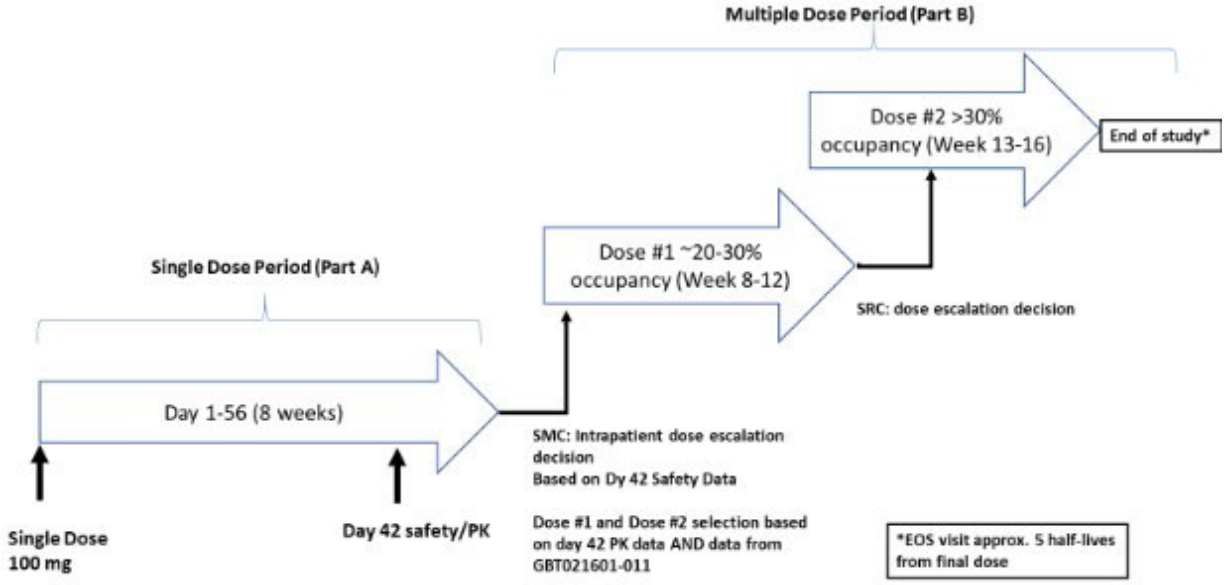

Table3-1: Schedule of Assessments for Single-dose Period (Part A)

	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								
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

Abbrevia tions: a PTT, 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.
[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.

[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 3-2: Schedule of Select Study Procedures (First 48 hours)

		Sampling Timepoint (hours postdose)										
Procedure	**Predose**	**Postdose**										
		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 violation.

[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. Predose 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 3-3: 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[f]	X	X[f]	X	X	X		
Dispense patient diary[g]	X	X	X	X	X	X	X	X			
Collect patient diary[g]		X	X	X	X	X	X	X	X		
Hematology and serum chemistry	X		X	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
Hemoximetry[k]	X	X	X			X		X			X
RBC deformability, dense cells (if feasible)[k]	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 12. 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 21 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 postdosesample 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 3-4: 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/ OLE)
Informed Consent	X							
Eligibility confirmation[a]	X							
Physical	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			X	X	X			
CCI	■	■	■	■	■	■		
			■	■	■	■	■	■
y and serum chemistry	X	X	X	X	X	X	X	X
Serum	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		X	X	X	X	X	X	X
Hemoximetry[h]		X		X	X		X	X
RBC deformability, dense cells (if feasible)[h]		X		X	X		X	X
Blood smear		X			X		X	X
		CCI			■			
Concomitant medications		X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X

Abbreviations: [redacted] ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; EOET, End of Extended Treatment; EOS, end of study; ET, early termination; [redacted]

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 3-1.

[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 4 hours 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, a dditional study drug administration and Visits will be added). At the Part C Week 4 and [redacted] 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. Participants should be instructed to complete the diary as well as the Bristol stool chart. [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 hour 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 3-9 for specifics. No 0.25 to 1-hour post-dose samples shall be collectedfor hemoximetry or RBC deformability. The predose blood sample for PK and PD assessments should be collected within 30 minutes prior to dosing.

3.2 Study Population

At least 6 participants with SCD ages 18 to 60 years, inclusive will be enrolled (dosed) in this study. Participants in Part A (single dose) will be continued to Part B (multiple ascending-dose) based on SMC review of data. All eligible participants will proceed with the extended treatment period (Part C).

3.3 Evaluations at Screening and Check-in

Screening procedures will be conducted within 30 days prior to Day 1 dosing (Day -30 to Day -2). Screening and check-in evaluations for the single dose period each period are presented in Table 3-1 and screening activities for Part C are found in Table 3-4.

3.4 Randomization and Treatment Assignments

Participants will be enrolled sequentially into this open-label, fixed-sequence study. Randomization will not be performed in the study.

3.5 Determination of Sample Size

No sample size estimation was performed to determine the cohort size. The sample size is based on practical considerations, and not on a formal statistical power calculation. Six participants with SCD are expected to provide adequate characterization of PK and safety.

3.6 Study Drug 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.

Part A: Single oral dose of GBT021601 100 mg on Day 1.

Part B: The starting multiple ascending doses will be chosen to achieve ~20% to 30% Hb occupancy with once daily treatment (Dose 1) proceeded by loading doses. In addition, this dose level is predicted to achieve a Cmax at steady-state no higher than 2-fold the Cmax observed and well tolerated following single dose or multiple doses in study GBT021601-011. For the second dose level (Dose 2), the target of >30% Hb occupancy will be used as determined by the PK results found in GBT021601-011 and results from Part A of this study given at Weeks 8-13.

Part C: 300 mg loading dose twice daily over 4 days subsequent maintenance dose of 150 mg once daily starting from Day 5 and continuing through Week 6.

3.7 Concomitant Medications and Procedures

Study participants will be allowed to take other medications as needed as described in protocol. 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) procedures along with start and stop date, type and reason for procedures will be captured on eCRF.

3.8 Drug Administration and Compliance

Study drug will be administered orally with approximately 240 mL non-carbonated room temperature water. Both tablets and capsules will be provided by sponsor.

Table 3-5: Identity of Study Drugs

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

Study drug will be provided as a tablet or capsule as per below table:

Table 3-6: Study Drug for Extended Treatment Period

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

The first dose of the study drug will be administered by delegated and trained staff at the CRU. 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 initial 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.

For Extended Treatment Period of at least 6 weeks, loading dose will be 300 mg 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.

3.9 Evaluation of Efficacy

This section is not applicable for this study.

3.10 Evaluation of Pharmacokinetic Sampling Schedule

The PK samples for GBT021601 will be collected at time points specified in the PK/PD sampling schedules (Table 3-1, Table 3-2, Table 3-3 and Table 3-4).

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

Table 3-7: Windows for PK Sample Collection – Single-dose Period

Sample Collection Time	Allowed Deviation
0.0 – 1.0 hour	± 2 minutes

Sample Collection Time	Allowed Deviation
> 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

Multiple Ascending-dose Period: Plasma and whole blood predose and postdose PK samples will be collected in the Multiple Ascending-dose period as listed in below table:

Table 3-8: PK and PD Sample Collection Times – Multiple Ascending-dose Period

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

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

Table 3-9: PK and PD Sample Collection Times –Extended Treatment Period (Part C)

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 at 4 hours
6	43	1 PK sample	1 PK sample between 0.25 hour to 1 hour 1 PK sample at 2 hours
10	71	1 PK sample	
14	98	1 PK sample	
Final Visit	Anytime during visit		

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

3.11 Evaluation of Pharmacodynamics Sampling Schedule

Single dose-period: Blood samples for hemoximetry, RBC deformability and dense cells will be collected at the same time as the PK samples (refer Table 3-7) at predose and 12 hours postdose on Day 1. In addition, hemoximetry samples will be collected on Days 2, 4, 7, 21, and 42.

Multiple ascending dose-period: Whole blood samples for hemoximetry, RBC deformability and dense cells will be collected at the same time as the PK samples (refer Table 3-8).

Extended Treatment Period: Whole blood samples for hemoximetry, RBC deformability and dense cells will be collected on Day 1 and Day 15 (refer Table 3-9).

CCI [redacted]

3.12 Evaluation of Treatment Safety

3.12.1 Adverse Events

An adverse event (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. A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE.

A treatment-emergent AE (TEAE) is an AE that occurs or worsens during the on-treatment period defined as the time from the first dose of study drug through minimum of 56 days + last dose of study treatment, date of study completion/discontinuation.

A Serious Adverse Event (SAE) is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect or important medical events.

All AEs will be recorded from the time the study participant signs the Informed Consent Form (ICF) 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. All serious and non-serious AEs must be followed until they are resolved or stabilized, or until reasonable attempts to determine resolution of the event are exhausted. 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.

The following details will be collected: description of the AE, onset date/time, action taken with study drug, outcome, severity (grade 1, grade 2, grade 3, grade 4 or grade 5), seriousness (yes, no) and relationship to study drug administration (not related or related).

3.12.1.1 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 (e.g., acute viral hepatitis; alcoholic and autoimmune hepatitis; hepatobiliary disorders; nonalcoholic steatohepatitis; cardiovascular causes; concomitant treatments)

Potential events of DILI will be reported as SAEs. 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.

3.12.2 Clinical Laboratory Assessments

Laboratory evaluations will be collected for hematology, coagulation, chemistry, urinalysis and other parameters. Refer to Table 3-10.

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

Table 3-10: 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 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

[a] Using the using the Cockcroft-Gault formula.
[b] Tests will be conducted at the clinic.

3.12.3 Vital Signs

Vital signs assessments will include respiratory rate (breaths per minute), systolic and diastolic blood pressure (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. 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.

3.12.4 Electrocardiogram

Electrocardiogram (ECG) (12-lead) will be collected in triplicate within 5 minutes. The following ECG parameters will be recorded: HR, PR, QRS, QT, and QTcF intervals. ECGs will be collected at the time points in the schedules of assessments/procedures in Table 3-1 to Table 3-4.

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

3.12.5 Physical Examinations

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 3-1 to Table 3-4).

An abnormal physical examination finding during the on-study period (i.e., 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.

3.12.6 Medical and Surgical History

Medical and surgical history will be collected at Screening and again at CRU admission to determine if any changes have occurred since screening.

3.13 Protocol Deviation Reporting

Procedural deviations found by the Clinical Research Associate (CRA) during monitoring visits and data deviations captured on the case report form (CRF) and found through programming and examining the database will be listed by participant.

4. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

All analyses specified in this SAP are consistent with the final study protocol (Version 6.0, Amendment 5 dated 08 March 2022). Any changes in this analysis provided or any additional analysis performed will be documented in CSR.

5. QUALITY CONTROL AND QUALITY ASSURANCE METHODS FOR DATA ANALYSIS

Case report forms will be monitored and processed according to the ICON Study Specific Procedure (SSP) DM-35070052.01 Data Management Plan (DMP). The DMP describes CRF data processing, edit checks, data query management, medical dictionary coding, SAE reconciliation, data transfers, and data quality review through database lock or any necessary reopening of the database. After database lock, the data will be retrieved from the database using SAS GRID Linux/SAS Studio - SAS® 9.4 version (or higher).

6. PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS

6.1 Pharmacokinetic Analysis

Pharmacokinetic variables will be calculated from the RBC, plasma and whole blood concentration data for GBT021601 using non-compartmental methods[redacted] and actual sampling times for single dose part only.

The following PK parameters will be determined for RBC, plasma and whole blood concentrations of GBT021601:

Single-dose parameter:

Term	Parameter	Description
C_{max}	Maximum observed concentration	Observed peak concentration obtained directly from the experimental data without interpolation.
t_{max}	Time to maximum observed concentration	Time corresponding to C_{max}.
AUC_{0-24}	AUC from time 0 to 24 hr	Calculated by linear/log trapezoid rule. At 24 hr the last quantifiable concentration
AUC_{0-t}	Area under the concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration	Calculated by linear/log trapezoid rule.
$AUC_{0-\infty}$	AUC from time 0 to infinity	AUC_{0-t} + the area extrapolated from the last quantifiable concentration to infinity (i.e., $C_{last}/\lambda z$).
CL/F Apparent Oral Clearance	$Dose/AUC_{0-\infty}$	$Dose/AUC_{0-\infty}$
V_z/F	Apparent volume of distribution	$Dose/(AUC_{0-\infty} * \lambda z)$
$t_{1/2}$	Terminal phase (apparent elimination) half-life	$\ln(2)/\lambda z$

The concentrations of GBT021601 in RBC will be derived using the following equation:

$$RBC\ Conc = \frac{Blood\ Conc - [(1 - Hematocrit) * Plasma\ Conc]}{Hematocrit}$$

The RBC concentration will be determined using individual hematocrit data collected on the day of PK sample collection. If hematocrit data are not available, the RBC value will be set to missing.

Only data points that describe the terminal elimination log-linear decline will be used in the regression equation for calculation of λ_z; C_{max} and any data point in the distribution phase are not included in the calculation. A minimum of 3 points will be used for determination of λ_z. A general rule of adjusted $R^2 \geq 0.80$ will be considered as acceptable for calculation of λ_z. If adjusted R^2 falls below 0.80, then λ_z will be reported as Not Determined (ND) and that participant's values for λ_z, $t_{1/2}$, CL/F, V_z/F and $AUC_{0-\infty}$ will reported in the appropriate listings but will be flagged and excluded from descriptive summaries and statistical analysis. If the extrapolated AUC_{inf} is more than 20%, then AUC_{inf}, CL/F and V_z/F will be listed but flagged and excluded from descriptive summaries and statistical analysis.

Blood to plasma ratios and RBC to plasma ratios for C_{max} and AUC will also be determined.

Multiple Dosing Period

Concentrations of GBT021601 in whole blood, plasma, and RBC will be listed for apparent C_{min} (minimum concentration from predose to 4 hours postdose) and C_{max} (maximum concentration from predose to 4 hours postdose) for each subject by visit and dose level. Descriptive statistics [n, arithmetic mean, SD, coefficient of variation (CV) %, geometric mean, and geometric mean CV%] will be summarized. For Part C, concentration data till Week 2 will not be summarized.

%Hb Occupancy

For both the SAD and MAD portions of the study the C_{max} (SAD) and apparent C_{min} and C_{max} (MAD) values will be used to calculate Hb occupancy with the following equation.

$$\%\ Hb\ occupancy = \frac{[GBT021601]_{RBC}}{MCHC}$$

MCHC = mean corpuscular hemoglobin concentration; the MCHC value on the day of PK sample collection will be used. If MCHC value is not available, the % Hb occupancy value will be set to missing.

The % Hb occupancy of GBT021601 will be listed and summarized for each visit by treatment group, including n, arithmetic mean, SD, CV %, and in graphical format (linear scale [MAD only]).

6.2 Treatment of Outliers

Individual concentration-time points, if considered anomalous, may be excluded from the analysis at the discretion of the pharmacokineticist following a review of the available documentation. Any such exclusion will be discussed with the sponsor and clearly outlined in the study report.

Entire individual treatment profiles for a participant may be excluded following review of the available documentation and discussion with the sponsor. However, results of analysis with and without the excluded profiles may be presented in the study report. Any such exclusion will be clearly listed in the study report along with justification for exclusion.

Any anomalous concentration values observed at predose will be identified and discussed in the CSR. Participants who experience emesis during the course of the study will be excluded from the PK summaries and statistical analysis if vomiting occurs at or before 2 times median T_{max}.

6.3 Non-Quantifiable Concentrations

All concentration values reported as no results (not collected or ND) will be treated as missing. For the calculation of concentration summaries, plotting mean and individual concentration time profiles, all concentrations below quantifiable limit (BLQ) will be treated as zero. For the purpose of calculating PK parameters, BLQ values will be treated as zero prior to the first measurable concentration. After the first measurable concentration, subsequent BLQ values will be treated as missing.

6.4 Pharmacodynamic Analysis

CCI [redacted]

A separate report will be prepared for rest of the PD parameters analysis (hemoximetry and RBC deformability).

7. STATISTICAL METHODS

7.1 General

The statistical analysis will be conducted following the principles specified in the International Conference on Harmonisation (ICH) Topic E9 Statistical Principles for Clinical Trials (CPMP/ICH/363/96).

All statistical tabulations and analyses will be done using SAS GRID Linux/SAS Studio - SAS® 9.4 version (or higher) and any exceptions will be detailed in the CSR.

All continuous data will be listed with the same precision as presented in the database. Both observed values and change-from-baseline values for each participant will be given where applicable. Unless otherwise noted, continuous variables will be summarized using number of non-missing observations (n), mean, standard deviation (SD), median, quartile (Q1 and Q3), minimum, and maximum; categorical variables will be summarized using the frequency count and the percentage of participants in each category.

In the data listings, study day relative to first dose of study drug may be presented. Study day relative to first dose will be calculated as: event date – first dose date (+ 1 if event date ≥ first dose date).

For Part A (SAD), baseline will be the average of screening and day -1 values prior to the first study drug administration in the study.

For Part B (MAD) and Part C (Extended treatment period), baseline will be the last measurement prior to the 2nd drug administration, i.e. the value on Day 56 should be the baseline.

The change from baseline and percent change from baseline to any subsequent post-baseline visit will be calculated as the absolute difference between that post-baseline visit's value and the baseline visit value, as below:
Change from baseline = Post-baseline value – Baseline value.
Percent Change from baseline = [(Post baseline value – Baseline value) /Baseline value]*100.

For safety summaries, the unscheduled and repeat assessments will not be summarized; however, will be included in the data listing. PK, PD, and safety data will be summarized by loading and maintenance doses or overall, as applicable.

Statistical analysis will be performed separately for Part A (SAD), Part B (MAD) and Part C (Extended treatment period) for PK, PD, and safety analysis.

7.2 Handling of Dropouts or Missing Data

Missing data will not be imputed except for the way described to handle concentration in Section 6.1.2.

7.3 Handling of missing/ incomplete dates for Adverse Event

Imputation rules for missing or partial AE start date are defined below:

If only Day of AE start date is missing:

If the start date has month and year but day is missing, the first day of the month will be imputed

- If this date is earlier than the first dose date, then the first dose date will be used instead.
- If this date is later than the stop date (possibly imputed), then the stop date will be used instead.

If Day and Month of AE start date are missing:

If the start date has year, but day and month are missing, the 1st of January will be imputed

- If this date is earlier than the first dose date, then the first dose date will be used instead.
- If this date is later than the stop date (possibly imputed), then the stop date will be used instead.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing, then imputation will not be done.

If the AE end date (full or partial) is before the first dose date then the AE should be considered as a pre-treatment AE. Otherwise, the AE will be considered as TEAE.

7.4 Handling of missing or partial Prior/Concomitant Medication Dates

Missing or partial medication start date:

a. If only Day is missing, the first day of the month will be assumed.
b. If Day and Month are both missing, the first day of the year will be assumed.
c. If Day, Month and Year are all missing, the day before the first dose date will be assumed.

Missing or partial medication stop date:

a. If only Day is missing, the last day of the month will be assumed.
b. If Day and Month are both missing, the last day of the year will be assumed.
c. If Day, Month and year are all missing, 'ongoing status to stop date will be assigned.

7.4 Multiple Comparisons and Multiplicity

No multiple comparison or multiplicity adjustment will be done based on the objective of the study.

7.5 Adjustments for covariates

Not applicable

7.6 Multicenter Studies

This study will be conducted in up to 3 sites in United States of America.

7.7 Examination of Subgroups

No subgroup analyses are planned.

7.8 Coding dictionaries

Medical history, concomitant procedures and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 or higher. Medications will be coded using the World Health Organization Drug Dictionary (WHO Global B3 format - March 2021 or higher).

7.8 Analysis Sets

7.8.1 Safety Population

All participants who received any amount of study drug (GBT021601).

7.8.2 Pharmacokinetic Population

All participants who received at least 1 dose of GBT021601and have at least 1 plasma or whole blood concentration data point.

7.9 Participant Accountability

Summaries of analysis populations and subject disposition will be presented by overall and will contain the following information:

- Number and percent of subjects received any dose (Safety Population)
- Number of subjects who completed Single dose period
- Number of subjects who completed Multiple ascending-dose period
- Number and percent of subjects who completed the treatment
- Number and percent of subjects who discontinued the treatment and reason for early discontinuation of the treatment
- Number and percent of subjects who completed the study
- Number and percent of subjects who discontinued early and reason for early discontinuation
- Number and percent of participants in the PK full and PK evaluable population.

Percentage will be based on the number of safety population. Participant disposition will be presented in listing for all safety subjects.

7.10 Protocol Deviations

Major protocol deviations will be identified prior to database lock for any intentional or unintentional change, or noncompliance with the approved protocol procedures or requirements. All protocol deviations will be listed using safety population.

7.11 Participant Demographics and Baseline Characteristics

Participant demographics and baseline characteristics will be listed and summarized descriptively for all participants by overall. The summary will include the participants' age at informed consent (in years), gender, race, ethnicity, weight (in kg), height (in cm), and Body Mass Index (in kg/m^2) using safety population.

7.12 Baseline Sickle Cell Disease

Number of Vaso-Occlusive Crisis (VOC) including the number of VOCs requiring hospitalization and the number of blood transfusion during the previous 12 months will be summarized categorically.

Additional summaries including the number and percentage of subjects who currently use hydroxyurea, who have each genotype (HbSS or HbS β^0 Thalassemia) and who experienced a sickle cell complication prior to study enrolment will be presented. Baseline lab values including Hb and reticulocyte count will be summarized using descriptive statistics.

7.13 Hemoglobin Response

Hemoglobin response, defined as an increase in Hb > 1 g/dL, will be listed and summarized descriptively at each postdose visit. Subjects who discontinue early or do not have a postdose visit, are not included in the analysis for Hb response. No missing data imputation or adjustment for transfusion will be performed for this endpoint.

7.14 Medical and Surgical History

The medical and surgical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 24.0 or higher) and will be listed using safety population.

7.15 Measurements of Treatment Compliance

Individual participant listing will be provided for eCRF collected exposure data using safety population.

7.16 Pharmacokinetic Analysis

The PK population will be used for all concentration listings and individual figures. Plasma, RBC (if applicable) and whole blood GBT021601 concentrations will be listed and summarized for each visit/ time point for single dose including n, nBLQ, mean, SD, geometric mean, coefficient of variation (CV), median, minimum and maximum.

The drug concentrations will be presented in graphical formats (linear and semi-log scales) as mean and individual profiles. Overlay of individual RBC, plasma and whole blood GBT021601 concentration profiles over time will be provided.

All plasma, RBC (if applicable) and whole blood GBT021601 PK parameters for single dose will be listed for PK population. Summary statistics (n, mean, SD, geometric mean, median, minimum, maximum, and CV) will be calculated for the plasma, RBC and whole blood GBT021601 PK parameters. For t_{max}, only n, minimum, median and maximum will be reported.

7.17 Safety Analyses

All Safety analysis will be presented using the Safety population.

All safety data will be summarized by Part A (SAD), Part B (MAD) and Part C (extended treatment period) or overall (as applicable), and visit/ time point. No statistical tests will be performed.

7.17.1 Adverse Events

All AE summaries will include treatment emergent AEs and will be presented for SCD related and SCD non-related separately.

SCD related AEs include:

SCD-related AEs comprise the following PTs: sickle cell anemia with crisis, ACS, pneumonia grouped terms (includes all PTs of pneumonia reported in this study), priapism, and osteonecrosis.

All AEs will be coded by primary system organ class (SOC) and preferred term (PT) according to the MedDRA Version 24.0 or higher and presented by participant in data listings.

The overall incidence of TEAEs (number of events, number and percentage of participants) will be summarized parts and overall. It includes: AEs, TEAEs, TEAEs by severity, SAEs, causally related TEAEs and SAEs, TEAEs leading to study or treatment discontinuation, life-threatening SAEs, and SAEs resulting in death.

The TEAEs will be summarized and tabulated at both the participant (n [%] of participants) and event (number of events) level:

- TEAEs by SOC and PT
- TEAEs by SOC, PT and maximum reported severity
- TEAEs by SOC, PT and closest relationship to study drug
- TEAEs by SOC, PT

For the incidence at the participant level by SOC and PT, if a participant experiences more than 1 event within the same SOC and PT, only 1 occurrence will be included in the incidence.

For the incidence at the participant level by SOC, PT, and severity, if a participant experiences more than 1 event within the same SOC and PT, only the most severe occurrence will be included in the incidence.

For the incidence at the participant level by SOC, PT, and relationship, if a participant experiences more than 1 event within the same SOC and PT, only the closest relationship will be included in the incidence.

Any SAEs, AEs with outcome of death, or AEs resulting in discontinuation of study or study drug will be listed separately.

7.17.2 Clinical Laboratory Assessments

Observed values, change from baseline and percent change from baseline for each parameter of continuous clinical laboratory values (hematology, coagulation, chemistry and urinalysis) will be summarized by visit/time points using descriptive statistics.

A listing of all clinical laboratory data for each participant at each visit will be presented. Laboratory values that are abnormal clinically significant values will be presented.

If the character result is reported for quantitative laboratory parameter, then for summary and analysis it will be changed as follows into numerical value –

a) If less than '<' sign is used then the value will be reduced by 1 point from the last precision digit

b) If greater than '>' sign is used then 1 point will be added to the last precision digit.

Eg: if the lab parameter is reported to 2 decimal precision, <40.01 then for summary and analysis it will be treated as 40.00, if the parameter is reported with 1 decimal precision <40.1 then it will be considered as 40.0 and if lab parameter is reported as whole number >40 then it will be considered as 41.

7.17.3 Vital Signs

Observed and change from baseline vital signs values will be summarized at each time point using safety population. Vital signs data will be listed by participant at each visit/ time point.

7.17.4 Electrocardiograms

Observed values and change from baseline of 12-lead ECG parameters (heart rate, PR, QRS, QT, and QTcF intervals) will be summarized descriptively at each scheduled visit/ time point collected using safety population. For the timepoints where triplicate ECGs were collected, in listing all the three values and average will be presented and for summary statistics only average value will be used.

Individual ECG data including outlier will be listed. ECG interpretation will be summarized as counts and percentages and the same will be listed.

7.17.5 Prior and Concomitant Medications

Concomitant medication is defined as any medication with a start date prior to the date of the first dose of study drug and continuing after the first dose of study drug or with a start date on or after the date of the first dose of study drug.

Prior medication is defined as any medication with a stop date prior to the date of the first dose of study drug.

Prior and Concomitant medications will be coded using the WHO Drug Dictionary (WHO Global B3 format - March 2021 or higher) and classified according to anatomical therapeutic chemical code (ATC) levels 4 and Preferred Name. All prior and concomitant medications will be listed.

CCI [redacted]

7.18 Planned Interim Analysis

There is no planned interim analysis.

The site's Principal Investigator 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 Safety 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. Format of tables and listings for SMC meeting is provided in mocks document.

In the MAD 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 $t_{1/2}$, 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.

7.19 General Conventions for Tables, Listings and Figures

Tables and listings will be presented in landscape mode with minimum of 3/4" bound edge margin and 3/8" other margins on 8.5" x 11" paper.

Times new roman font size of no less than 8 point will be used for tables and listings.

A source line will be included on the bottom of each page of all tables and listings. It will contain the SAS code program name and the run date and time.

Each variable is recorded to a specific number of decimal places. If the raw data is presented with varying precision, then the least precise value will be considered as the data precision.

For all summary tables, unless otherwise specified, the number of decimal places provided in the tables and listings will be based on the accuracy of the least accurate value in the raw data as follows:

N	integer
Arithmetic mean	1 decimal place more than the least accurate number in the raw data
SD	2 decimal place more than the least accurate number in the raw data
CV(%)	2 decimal places
Geometric mean	1 decimal place more than the least accurate number in the raw data
Median	1 decimal place more than the least accurate number in the raw data
Minimum	same number of decimal places as raw data
Maximum	same number of decimal places as raw data
Confidence interval	same number of decimals as the associated statistic
Percentage	1 decimal place

Following is the mock presentation for tables and listings

1. Tables

Table 14.1.1 Summary of Participant Disposition (Safety Population)

Disposition	Overall (N=XX) n (%)
Subjects who were Dosed	
xxxxxx	
.....	

Safety tables will be presented by part and Overall.

CCI [redacted]

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[redacted]	[redacted]
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CCI [redacted]	[redacted]
[redacted]	[redacted]
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