CLINICAL STUDY PROTOCOL

Study Number	GBT2104-132
Study Title	A Randomized, Double-blind, Placebo-controlled, Multicenter Study of a Single Dose of Inclacumab to Reduce Re-admission in Participants with Sickle Cell Disease and Recurrent Vaso-occlusive Crises
Investigational Product	Inclacumab
IND Number	144073
EudraCT Number	2020-005287-60
Sponsor	Global Blood Therapeutics, Inc. 181 Oyster Point Blvd, South San Francisco, CA 94080 United States of America
Study Director	PPD, M.D. Global Blood Therapeutics, Inc. 181 Oyster Point Blvd. South San Francisco, CA 94080 United States of America Telephone: PPD Email: PPD
Original Protocol **Amendment 1**	17 Dec 2020, Version 1.0 08 Mar 2021, Version 2.0

CONFIDENTIALITY STATEMENT

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

STATEMENT OF APPROVAL AND COMPLIANCE

PROTOCOL NUMBER GBT2104-132: A Randomized, Double-blind, Placebo-controlled, Multicenter Study of a Single Dose of Inclacumab to Reduce Re-admission in Participants with Sickle Cell Disease and Recurrent Vaso-occlusive Crises

Amendment 1: 08 Mar 2021

Sponsor Approval

The signature of the Sponsor (Global Blood Therapeutics, Inc., "GBT") representative, below, signifies that the above-referenced clinical study is being conducted in accordance with applicable local regulatory requirements in all relevant jurisdictions where the study is being conducted. In addition, the study is being conducted in compliance with the procedures of International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) and associated regulatory guidance. Furthermore, GBT and the Institutional Review Board/Independent Ethics Committee will approve any changes to the protocol in writing before implementation. GBT will provide the Investigator with all information, including safety information, pertinent to the conduct of the study.

Sponsor Representative (Signature):	
Name:	
Date:	
Title:	Senior Medical Director, Clinical Science - Medical Affairs

Investigator Approval

The signature of the Investigator below constitutes approval of this protocol as written and reflects the Investigator's commitment to conduct the study in accordance with the protocol, the applicable laws and regulations, and in compliance with ICH GCP guidelines and the Declaration of Helsinki. All data obtained during the study will be provided to GBT. GBT requires that any presentation or publication of study data by an Investigator be reviewed by GBT before release.

Principal Investigator: (Print Name)	
Signature:	
Date:	

SYNOPSIS

Study Number:	**GBT2104-132**
Study Title:	**A Randomized, Double-blind, Placebo-controlled, Multicenter Study of a Single Dose of Inclacumab to Reduce Re-admission in Participants with Sickle Cell Disease and Recurrent Vaso-occlusive Crises**
Investigational Product:	Inclacumab
Sponsor:	Global Blood Therapeutics, Inc. 181 Oyster Point Blvd. South San Francisco, CA 94080 United States of America
Phase:	Phase 3
Number of Sites:	The study will be conducted at up to 60 clinical sites globally.
Number of Study Participants:	Up to approximately 280 participants will be enrolled.
Duration of Treatment:	The total duration of treatment for each participant will be 90 days with a single dose on Day 1.
Objective:	The primary objective of this study is to evaluate the safety and efficacy of a single dose of inclacumab compared to placebo to reduce the incidence of re-admission to a healthcare facility for a vaso-occlusive crisis (VOC) after an admission for an index VOC in participants with sickle cell disease (SCD). Additional objectives of the study are to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of inclacumab, the presence of anti-drug antibodies (ADAs), and changes in quality of life (QOL).
Endpoints:	**Primary Efficacy Endpoint:** The primary endpoint for this study is, following an index VOC, the proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days of randomization. An admission for a VOC includes: • A hospital admission, or • An admission to an emergency room, observation unit, or infusion center for ≥ 12 hours, or • 2 visits to an emergency room, observation unit, or infusion center over a 72-hour period. for an acute episode of pain with no other cause other than a vaso-occlusive event that includes the following: • Uncomplicated VOC, • Acute chest syndrome (ACS), • Acute hepatic sequestration, • Acute splenic sequestration, or • Priapism. The definition of the index VOC requiring admission is the same as the primary endpoint VOC requiring admission.

	To ensure consistency across study sites, all on-study VOCs reported by the study investigators will be adjudicated by an independent, blinded panel comprised of experts in SCD. The primary efficacy analysis will be performed on adjudicated data. **Secondary Efficacy Endpoints:** The secondary efficacy endpoints of the study are the following: • Time to first VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days of randomization. • Proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 30 days of randomization. • Rate of VOCs leading to a healthcare visit (hospital, emergency room, clinic visit, or remote contact with a healthcare provider) that requires parenteral pain medication (eg, parenteral narcotic agents or parenteral nonsteroidal anti-inflammatory drugs [NSAIDs]), or an increase in treatment with oral narcotics within 90 days following randomization. **Safety Endpoints:** The safety endpoints of the study are the following: • Incidence of treatment-emergent adverse events (TEAEs). • Change from Baseline in laboratory assessments (complete blood count, chemistry, and coagulation). **Exploratory Endpoints:** The exploratory endpoints of the study are the following: • Time to second VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days of randomization. • Rate of complicated VOCs (ie, acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism) during the 90 days following randomization. • Rate of inpatient hospital admissions for any reason during the 90 days following randomization • Number of days of inpatient hospitalization for any reason during the 90 days following randomization. • Proportion of participants rated as "very much improved" or "moderately improved" based on the Patient's Global Impression of Change (PGI-C) at Day 46 and Day 91. • Proportion of participants rated as "very much improved" or "moderately improved" based on the Clinician's Global Impression of Change (CGI-C) at Day 46 and Day 91. • Change from Baseline in the cumulative score for the Adult Sickle Cell Quality of Life Measurement (ASCQ-Me) Pain Impact – Short Form over time to Day 91.

	Exploratory Pharmacology Endpoints: The exploratory pharmacology endpoints of the study are the following: • Plasma PK of inclacumab as assessed by population PK analysis using nonlinear mixed-effects modeling. • Incidence of ADA to inclacumab. • Pharmacodynamics including CCI [redacted] • Biomarkers including CCI [redacted] Relationships between PK, PD, biomarkers, clinical labs, safety, and efficacy will be explored.
Study Design:	This study will be a randomized, placebo-controlled, double-blind, multicenter, parallel-group study to assess the safety and efficacy of a single dose of inclacumab in reducing the rate of re-admission to a healthcare facility for a VOC after an index VOC. The index VOC is any VOC that required admission to a healthcare facility and treatment with parenteral pain medication where the admission includes: • A hospital admission, or • An admission to an emergency room, observation unit, or infusion center for ≥ 12 hours, or • 2 visits to an emergency room, observation unit, or infusion center over a 72-hour period. for an acute episode of pain with no other cause other than a vaso-occlusive event that includes the following: • Uncomplicated VOC, • Acute chest syndrome (ACS), • Acute hepatic sequestration, • Acute splenic sequestration, or • Priapism. The study will include approximately 280 adult and adolescent participants (≥ 12 years of age) with SCD. Initial enrollment will include participants ≥ 16 years of age until the Data Monitoring Committee (DMC) recommends to the Sponsor that adequate safety and PK data support the enrollment of participants 12 to 15 years of age. Participants will be randomized with a 1:1 ratio into one of two treatment arms (140 participants per arm) as follows: • Inclacumab 30 mg/kg administered intravenously (IV); or • Placebo administered IV. Randomization may occur up to 5 days after the index VOC has resolved, as assessed by the Investigator (for example, hospital discharge, completion of

	parenteral analgesia, or transition to oral analgesics). On the day of randomization (Day 1), participants will receive a single dose of study drug. At the time of randomization, participants will be stratified by Baseline hydroxyurea (HU) use (yes; no), number of VOCs (2 to 4; 5 to 10) in the preceding 12 months, and geographic region (North America; rest of world). An independent DMC will regularly review the totality of accumulated safety data from all ongoing inclacumab studies on an ongoing, unblinded basis, with specific emphasis on adolescent participants. Details will be provided in the DMC Charter. Participants that complete the study through Day 90 will be provided the opportunity to enroll in an open-label extension (OLE) study.
Investigational Product, Dose & Mode of Administration:	Inclacumab drug product is a sterile, clear to opalescent liquid concentrate for infusion with an approximate pH of 5.5 provided in colorless, 10 mL single-use vials. Each vial contains 500 mg of inclacumab and the following excipients: CCI An inclacumab dose of 30 mg/kg will be administered IV. Participants will be monitored for 60 minutes after completion of study drug infusion for adverse reactions.
Comparator Product:	The comparator product is a placebo for inclacumab containing the same ingredients without the active drug. Placebo will be prepared and administered in the same manner as active study drug.
Eligibility Criteria	**Inclusion Criteria:** 1. Participant has an index VOC. The index VOC is any VOC that required admission to a healthcare facility and treatment with parenteral pain medication. An admission for the index VOC includes: a. A hospital admission, or b. An admission to an emergency room, observation unit, or infusion center for ≥ 12 hours, or c. 2 visits to an emergency room, observation unit, or infusion center over a 72-hour period. for an acute episode of pain with no other cause other than a vaso-occlusive event that includes the following: – Uncomplicated VOC, – Acute chest syndrome (ACS), – Acute hepatic sequestration, – Acute splenic sequestration, or – Priapism. 2. Participant has a confirmed diagnosis of SCD (any genotype). Documentation of SCD genotype is required and may be based on documented history of laboratory testing or confirmed by laboratory testing at Baseline. 3. Participant is male or female, ≥ 12 years of age at the time of informed consent.

	NOTE: Initial study enrollment will include participants ≥ 16 years of age until the DMC determines that adequate safety and PK data support the enrollment of participants 12 to 15 years of age. Sites will be informed by the Sponsor when participants 12 to 15 years of age may be enrolled. 4. Participant is able to complete screening and receive study drug within 5 days following investigator-assessed resolution of index VOC (for example, hospital discharge, discontinuation of parenteral pain medication, or transition to oral pain medication). 5. Participant has experienced between 2 and 10 VOCs within the 12 months prior to Screening as determined by documented medical history. The index VOC is not to be considered as one of the 2 to 10 events. A prior VOC is defined as an acute episode of pain that: a. Has no medically determined cause other than a vaso-occlusive event, and b. Results in a visit to a healthcare facility (hospital, emergency department, urgent care center, outpatient clinic, or infusion center) or results in a remote contact with a healthcare provider; and c. Requires parenteral narcotic agents, parenteral nonsteroidal anti-inflammatory drugs (NSAIDs), or an increase in treatment with oral narcotics. 6. Participants receiving erythropoiesis-stimulating agents (ESA, eg, erythropoietin [EPO]) must be on a stable dose for at least 90 days prior to Screening and expected to continue with the stabilized regimen throughout the course of the study. 7. Participants receiving HU, L-glutamine, or voxelotor must be on a stable dose for at least 30 days prior to Screening and expected to continue with the stabilized regimen throughout the course of the study. 8. Participant has adequate venous access, in the opinion of the Investigator, to comply with study procedures. 9. Participant understands the study procedures and agrees to participate in the study by giving written informed consent or parental permission/written assent. 10. Women of childbearing potential (WOCBP) are required to have a negative serum pregnancy test at the Screening Visit and negative urine pregnancy test on all subsequent clinic visits and must agree to use a highly effective method of contraception throughout the study period and for at least 165 days after dosing. Female participants will not be considered of childbearing potential if they are pre-menarchal, surgically sterile (hysterectomy, bilateral salpingectomy, tubal ligation, or bilateral oophorectomy) or postmenopausal (no menses for 12 months without an alternative medical cause, confirmed by follicle-stimulating hormone test results). **Exclusion Criteria:** 1. Participant is receiving regularly scheduled red blood cell (RBC) transfusion therapy (also termed chronic, prophylactic, or preventative transfusion). 2. Participant is taking or has received crizanlizumab (ADAKVEO®) within 90 days prior to Screening.

	3. Participant weighs > 133 kg (292 lbs.). 4. Participant has a significant active and poorly controlled (unstable) hepatic disorder clearly unrelated to SCD. 5. Participant has any of the following laboratory values at Screening: a. Absolute neutrophil count (ANC) < 1.0 × 109/L b. Platelet count < 80 × 109/L c. Hemoglobin < 4.0 g/dL for adults and < 5.0 g/dL for participants ages 12 to < 18 years of age d. Estimated glomerular filtration rate (eGFR) < 30 mL/min using Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula in adults, and Schwartz formula in adolescents. NOTE: Laboratory assessments conducted during Screening may be done by the local laboratory and must include at least a CBC with total and differential leukocyte count, platelet count, and hemoglobin, a chemistry panel with creatinine, and a serum pregnancy test to assess participant eligibility. Laboratory assessments conducted during the index VOC admission that are obtained within 7 days prior to screening may be used for Screening assessments if done as part of standard medical care. 6. Participant has known active (symptomatic) COVID infection or tests positive for COVID-19 at any time during their index admission. 7. Participant has a history of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to Screening including severe or unstable pulmonary hypertension. 8. Participant has had treatment for a malignancy within the 12 months prior to Screening (except non-melanoma skin cancer and in situ cervical cancers). 9. Participant has had a stroke within the 2 years prior to the Screening Visit. 10. Participant has a positive test indicative of active malaria infection at Screening. Testing to be conducted at local laboratories in malaria-endemic regions at the discretion of the Investigator. 11. Participant has any confirmed clinically significant drug allergy and/or known hypersensitivity to monoclonal antibody therapeutics or formulation components of the study drug or a related drug. 12. Participant has been treated with another investigational agent within 30 days or 5 half-lives of the investigational agent (whichever is greater) prior to Screening. 13. Participant has had a major surgery within 8 weeks prior to the Screening Visit. 14. Participant is pregnant, breastfeeding, or planning to become pregnant during the 90-day treatment period. 15. Participant, parent, or legal guardian are unlikely to comply with the study procedures. 16. Participant has other medical, or psychological, or behavioral conditions that, in the opinion of the Investigator, would: confound or interfere with evaluation of safety, efficacy, and/or PK of the investigational drug; prevent compliance with the study protocol; preclude informed consent; or,

	render the participant, parent, or legal guardian unable/unlikely to comply with the study procedures.
Outcomes Measures:	**Efficacy:** The outcome measures for efficacy are a VOCs that required admission to a healthcare facility and treatment with parenteral pain medication occurring within 90 days of randomization, VOCs that require healthcare visits but do not require admission, and QOL assessments. **Safety:** Participants will be monitored from the time the informed consent is signed through the end of study for TEAEs. Severity of TEAEs will be determined based on the Common Terminology Criteria for Adverse Events (CTCAE, v5.0). Safety assessments also include physical examinations, vital signs measurements (blood pressure, heart rate, and body temperature), clinical laboratory evaluations including a chemistry panel and complete blood count, additional laboratory evaluations including prothrombin time, activated partial thromboplastin time (aPTT), and reticulocyte count, pregnancy tests as appropriate, and concomitant medications. Additional assessments for safety will be collected when a participant presents with VOC, whether re-admitted or not, as feasible. **Pharmacokinetics:** In all participants, plasma samples will be collected for measurement of inclacumab concentrations before and after the dose on Day 1. PK samples will be collected on Day 46 and Day 91. Samples will also be collected at the Day 161 End of Study Visit in all participants not proceeding to the OLE study. Additional samples for PK will be collected when a participant presents with VOC, whether re-admitted or not, as feasible. Population PK analysis using nonlinear mixed-effects modeling will be performed to characterize inclacumab PK in plasma. **Anti-Drug Antibodies:** In all participants, plasma samples will be collected for characterization of ADA incidence at pre-dose (Day 1) and post-dose (Day 91). Samples will also be collected at the Day 161 End of Study Visit in all participants not proceeding to the OLE study. **Pharmacodynamics:** At selected study visits, whole blood samples will be collected for assessment of CCI [redacted]. Additional samples for PD will be collected when a participant presents with VOC, whether re-admitted or not, as feasible. Biomarkers including CCI [redacted] The relationships between PK, PD, biomarkers, clinical labs, safety, and efficacy will be explored.

Study Procedures:	The Schedule of Assessments is provided in Appendix 1. The schedule for collection of PK, ADA, and PD samples is provided in Appendix 2 and for collection of biomarkers in Appendix 3. Participants will be screened for eligibility at the onset of the index VOC through Day -1. Eligible participants will be randomized on Day 1 (Baseline) and receive study drug on the day of randomization. Participants will return to the clinical site on Day 46 and Day 91 for safety, pharmacology, and efficacy assessments. Given the long half-life of inclacumab at the dose to be evaluated in this study, the majority of participants receiving active study drug are expected to maintain target concentrations through Day 91. Each week, participants will record if they have had a VOC that required parenteral pain medication and complete the ASCQ-Me questionnaire, when available. Every 30 days (Day 31 ±7 days and Day 61 ±7 days), the participant will be contacted to assess for VOCs, adverse events, and changes in concomitant medications. Participants that complete the 90-day study will be provided the opportunity to enroll into the OLE study at Day 91. For participants enrolling in the OLE study, the Day 91 visit will be the end of study (EOS) visit. For participants not enrolling in the OLE study, an additional required Follow-up Visit at Day 161 will be the EOS visit.
Statistical Methods:	Detailed specifications of the methods for summary and analyses of the data collected in this study will be documented in the statistical analysis plan (SAP). **Sample Size:** Up to 280 participants will be enrolled in the study. Participants will be randomized in a 1:1 ratio to receive treatment with a single dose of inclacumab or placebo. The study uses a group sequential design to evaluate the primary efficacy endpoint based on 2 sequential analyses: (i) one interim analysis after a minimum of 75 participants per arm have completed the study through 90 days, and (ii) if required, a final study analysis based on approximately 140 participants per arm. For the primary endpoint, the planned sample size of up to 280 participants (140 participants per treatment group) provides approximately 90% power to detect a targeted 50% relative reduction in the proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days, from a rate of 35% for placebo to 17.5% for inclacumab, using a 2-sided test of the difference in 2 binomial proportions (Normal approximation). To maintain an overall Type I error rate of 0.05, calculations assumed an O'Brien-Fleming boundary of the Lan-DeMets alpha-spending function (East version 6.5). For the sample size calculation, a 5% drop-out rate during the 90-day study period was used. With this sample size, the smallest observed treatment difference expected to be statistically significant at the final analysis is approximately a 32% relative reduction (ie, reduction in the proportion of participants with at least 1 VOC that

required admission to a healthcare facility and treatment with parenteral pain medication within 90 days from 35% for placebo to 23.8% for inclacumab).

Efficacy Populations and Analysis:

Efficacy analyses will be based on an intent-to-treat (ITT) population consisting of all randomized participants, with participants grouped according to the treatment assigned at randomization.

Primary Efficacy Endpoint:

For the primary efficacy endpoint, the proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days, will be compared between treatment arms using the exact Cochran-Mantel-Haenszel general association test, stratified by the randomization stratification factors.

Every effort will be made to obtain the 90-day re-admission status for a VOC for each participant. For purposes of the primary analysis, participants with an unknown 90-day re-admission status will be classified as having experienced at least 1 protocol-defined VOC within 90 days (ie, treated as "failure"). Sensitivity analyses evaluating the robustness of results to assumptions regarding drop-outs will be performed, as appropriate.

Secondary Efficacy Endpoints:

For time to first VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days, treatment comparison will be performed based on a log-rank test stratified by the randomization factors and Kaplan-Meier plots generated.

For the proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 30 days, the same statistical methods used for the primary efficacy endpoint will be used.

For the rate of VOCs leading to a healthcare visit within 90 days, the total number of VOCs in the 90-day period will be compared between treatment arms using a negative binomial regression model stratified by the randomization factors.

Adjustment for Multiple Comparisons:

A fixed sequence hierarchical test procedure will be used to control Type I error when evaluating the treatment effect of inclacumab compared with placebo for the primary and secondary efficacy endpoints. The endpoints will be tested in a pre-specified order, with formal testing of endpoints continuing until the first non-significant result.

Interim Efficacy Analysis

One interim analysis for efficacy may be performed after a minimum of 75 participants per arm have completed the study through 90 days. At that time, the primary efficacy endpoint will be evaluated via the independent DMC. If statistical significance is achieved demonstrating a treatment benefit for the primary endpoint based on the pre-specified efficacy boundary, the trial will be considered positive.

If statistical significance is not achieved at the interim analysis, the trial will continue, and a final analysis will be performed after all randomized participants (approximately 140 per arm) have completed the 90-day study period or discontinued early, and all corresponding data have been entered into the database, reviewed, and verified.

	Safety Population and Analysis: Safety analysis will be based on all randomized participants receiving treatment with study drug. Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of TEAEs, defined as events that occur on or after Day 1 of study treatment or the worsening of a pre-existing condition on or after Day 1 of study treatment, will be tabulated by System Organ Class and preferred term. Additional summaries for TEAEs by severity, relationship to study drug, and leading to study drug discontinuation, as well as for adverse events of special interest (AESI), serious adverse events (SAEs), and deaths will be generated. VOC events will be collected and summarized separately (including ACS, hepatic sequestration, splenic sequestration, and priapism). Changes in laboratory parameters (hematology, serum chemistry, and coagulation) and vital signs (eg, blood pressure, heart rate, and body temperature) over time will be summarized descriptively.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACS	acute chest syndrome
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse events of special interest
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCQ-Me	adult sickle cell quality of life measurement
BP	blood pressure
CGI-C	Clinician's Global Impression of Change
CHO	Chinese hamster ovary
CKD-EPI	chronic kidney disease – epidemiology collaboration
COVID-19	corona virus disease-19
CRO	contract research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ESA	erythropoiesis-stimulating agent
ET	Early termination
EOS	End of Study
FDA	Food and Drug Administration
EPO	erythropoietin
FSH	follicle-stimulating hormone
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
Hb	hemoglobin
HR	heart rate
HSCT	human stem cell transplant
HU	hydroxyurea
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IRB	Institutional Review Board
IRR	infusion-related reaction

Abbreviation	Definition
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
MedDRA	Medical dictionary for regulatory activities
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
OLE	open-label extension
PAD	peripheral arterial disease
PD	pharmacodynamics
PE	physical examination
PGI-C	Patient's Global Impression of Change
PK	pharmacokinetics
PLA	platelet-leukocyte aggregate
PLT	platelet
PNH	paroxysmal nocturnal hemoglobinuria
PRO	patient-reported outcome
QOL	quality of life
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCD	sickle cell disease
SOC	standard of care
CCI [redacted]	
sRBC	sickled red blood cells
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TRAP	thrombin receptor activating peptide
ULN	upper limit of normal
US	United States
WOCBP	women of childbearing potential
VOC	vaso-occlusive crisis

NOTE: The first occurrence of some abbreviations is not spelled out in the document (eg units of measure).

1. INTRODUCTION

1.1. Sickle Cell Disease

Sickle cell disease (SCD) is an autosomal recessive red blood cell disorder characterized by chronic hemolysis and inflammation, vaso-occlusion presenting as recurrent pain episodes (variously termed sickle cell-related pain crises or vaso-occlusive crises [VOCs]), multiorgan dysfunction, and early death (Kato, 2018).

Vaso-occlusion in SCD is driven by a series of complex and often redundant receptor–ligand interactions involved in the adhesion of circulating cells to each other and to the damaged endothelium and exposed sub-endothelium.

Extensive research demonstrates that P-selectin mediated cellular interactions with sickled red blood cells (RBCs), leukocytes and platelets play a crucial role in the pathophysiology of vaso-occlusion in SCD. By contrast, blocking P-selectin-mediated cellular interactions or reducing the levels of P-selectin reduces or eliminates vaso-occlusion in animal models. Taken together, these data led to the hypothesis that blocking P-selectin could reduce the risk of VOCs in SCD patients.

Results from a randomized, placebo-controlled Phase 2b trial of crizanlizumab, a humanized monoclonal antibody against P-selectin, in patients with SCD bolstered the hypothesis that blocking the interaction of P-selectin with its receptors could prevent vaso-occlusion and VOCs (Ataga, 2017).

1.2. Current Therapy for Sickle Cell Anemia and the Unmet Need

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative therapy for SCD. HSCT in children with SCD is associated with overall and event-free survival rates of 95% and 92%, respectively. However, HSCT use is limited by the paucity of suitable donors, the risk of graft-versus-host-disease, infections, infertility, and other long-term transplant-related complications. Moreover, HSCT is generally available only in high-resource countries and not commonly used in older patients with significant morbidity (Kassim, 2017).

Three therapies, hydroxyurea (HU [DROXIA® US Prescribing Information]; also known as hydroxycarbamide), L-glutamine (ENDARI® US Prescribing Information) and crizanlizumab (ADAKVEO® US Prescribing Information), have been approved by the Food and Drug Administration (FDA) to reduce VOCs in patients with SCD (Charache, 1995; Niihara, 2018; (Ataga, 2017). However, the effectiveness of HU is impaired by low compliance rates and frequent treatment discontinuation (Shah, 2019).

Moreover, while L-glutamine is also approved to reduce the frequency of VOCs in patients with SCD, it provides only a modest 25% reduction in annual VOC rates (Niihara, 2018).

Crizanlizumab, a monoclonal antibody directed against human P-selectin approved in 2019, can be used alone and in combination with HU to reduce the frequency of VOCs in patients with SCD. However, patients are required to travel to an infusion center for drug administration once every 4 weeks, a potentially limiting factor in continued adherence to a life-long therapy. Treatment adherence is essential for quality care and non-adherence leads to poor health outcomes and increased healthcare costs, especially among patients with chronic conditions

(Osterberg, 2005; Simpson, 2006; Roebuck, 2011). Furthermore, medications with less frequent dosing result in better adherence (Saini, 2009; Richter, 2003). Patient preference for less frequent dosing has been established across many chronic conditions including inflammatory diseases such as rheumatoid arthritis and hematological diseases such as hemophilia and paroxysmal nocturnal hemoglobinuria (PNH) (Tkacz, 2015; Wells, 2019; Kaiser, 2020). Frequent intravenous (IV) infusions also extract a cost on patient and caregiver productivity because of the substantial time commitments and work absence required from both for such infusions. One recent study demonstrated that PNH patients receiving IV infusion eculizumab every 2 weeks had three times higher productivity losses compared to PNH patients treated every 8 weeks with ravulizumab solely due to more frequent dosing (Levy, 2019). Moreover, patients report that therapies with less frequent dosing regimens enable them to feel independent, better plan future activities, and lead more active lives, all important considerations in developing treatments for SCD, which is a debilitating disease characterized by idiosyncratic and unpredictable exacerbations (Wells, 2019; Kaiser, 2020).

Re-admission to the hospital for a VOC within 30 days is one of the highest single causes of all re-admission in the United States (Brousseau, 2010). Several studies have shown that approximately one third of all SCD patients hospitalized for a VOC will be re-admitted within 30 days with the vast majority due to a VOC. Over the course of 90 days, approximately 50% of patients hospitalized for an index VOC will be re-admitted (GBT Claims Data ON FILE). As such, patients are at high risk of re-admission following a VOC leading to an enormous burden on patients, caregivers, and the healthcare system. Re-admissions are particularly problematic during the COVID-19 pandemic and patients with SCD may try to avoid admissions (McFarling, 2020; Powell, 2020) and the risk of nosocomial infections (eg, SARS-CoV-2). Thus, a therapy that significantly reduces the rate of re-admission following admission for a VOC would reduce the burden and provide substantial clinical benefit.

Not all patients with SCD are appropriate candidates for chronic therapy to prevent VOCs. Some patients have infrequent VOCs such that they may not need chronic preventative therapy but could still reduce their risk of re-admission following admission for a VOC. Others may not want to be on chronic therapy or may not be adherent to long-term treatment. Yet, for others, poor peripheral venous access may make a monthly intravenous treatment regimen difficult. None of the currently approved medications meet this unmet need.

In summary, despite the recent availability of new options to treat VOCs, an unmet medical need exists to further reduce the frequency of VOCs while reducing patient burden and enhancing patient adherence to therapy. In addition, there is a need for an "on demand" therapy to prevent re-admissions for patients that do not require or are unable to adhere to chronic therapy.

1.3. Rationale for Inclacumab in SCD

Inclacumab is a recombinant, fully human, monoclonal antibody based on a human immunoglobulin 4 (IgG4)-type framework containing heavy chain V_H gamma 4 and light chain V_L kappa subgroup sequences. Inclacumab is directed against the human P-selectin (CD62P).

The monoclonal antibody consists of two heavy chains (451 amino acid residues each) and two light chains (214 amino acid residues each) with inter- and intra-chain disulfide bonds that are typical of IgG4 antibodies. Two single-point mutations were introduced into the hinge (S228P)

and Fc (L235E) region of inclacumab to prevent Fab arm exchange, an inherent feature of IgG4 antibodies, and to mitigate antibody-dependent cellular cytotoxicity (ADCC), respectively.

Inclacumab binds to P-selectin, which is a cell adhesion molecule produced by endothelial cells and platelets. Upon activation of these cells (eg, by thrombin, cytokines, complement components, hypoxia, and heme), P-selectin is translocated to the cell surface where it binds to its primary ligand P-selectin glycoprotein ligand-1 (PSGL-1) in leukocytes and mediates leukocytes recruitment by platelets or endothelial cells. The same mechanism is also responsible for abnormal adhesion of sickled red blood cells (sRBC) to the endothelium, initiating acute vascular occlusion and chronically impairing microvascular blood flow in patients with SCD. Inclacumab binding of P-selectin and prevention of P-selectin binding to its ligands is the putative mechanism by which inclacumab effectively blocks interactions between endothelial cells, platelets, sickled RBCs and leukocytes, thereby preventing VOCs. P-selectin inhibition has demonstrated safety and efficacy in the SCD population with the recently approved monoclonal antibody therapeutic crizanlizumab.

Nonclinical studies have been conducted to characterize inclacumab including primary and secondary pharmacodynamics (PD), safety pharmacology, pharmacokinetics (PK), and toxicology of inclacumab. The nonclinical studies are described in detail in the inclacumab Investigator's Brochure (IB).

1.3.1. Study Design Rationale

This study is a randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of a single dose of inclacumab compared to placebo when administered to patients with a diagnosis of SCD who have experienced between 2 and 10 VOCs in the 12 months preceding enrollment and have been hospitalized for an index VOC. Given the long half-life of inclacumab (terminal half-life of 21 to 28 days) at the dose to be evaluated in this study, the majority of participants receiving active study drug are expected to maintain target concentrations through Day 91.

The primary endpoint for this study is, following an index VOC, the proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days following randomization.

This study is designed to determine if a single dose of inclacumab can significantly reduce the rate of 90-day re-admissions for patients admitted for an index VOC and provide another treatment option of the management of patients with SCD. This is analogous to "on demand" factor therapy (vs chronic prophylactic therapy) for patients with hemophilia.

1.3.2. Rationale for Dose Regimen

In this study, a single IV dose of 30 mg/kg will be administered on Day 1 to reduce the frequency of re-admissions due to a VOC in patients with SCD. More than 700 participants in prior studies (healthy or cardiovascular disease patients) have been exposed to inclacumab; a maximum tolerated dose was not identified.

Chronic IV dosing of inclacumab (20 mg/kg every 4 weeks for 32 weeks) in a cohort of 188 patients with severe cardiovascular disease was shown to be safe and well tolerated with the majority of adverse events (AEs) considered unrelated to study drug. Moreover, P-selectin

inhibition with a monoclonal antibody has demonstrated safety and efficacy in the SCD population with the use of crizanlizumab.

In a recent Phase 1 study in healthy participants, the safety and tolerability of a single IV dose of up to 40 mg/kg of inclacumab within 72 hours post-infusion is consistent with the safety profile of previous studies with inclacumab up to 20 mg/kg IV (refer to Investigator's Brochure, Section 5.6 for details).

Inclacumab plasma concentrations above 10 µg/mL have been associated with maximal inhibition of ex vivo thrombin receptor activating peptide (TRAP)-induced platelet-leukocyte aggregate (PLA) formation in healthy volunteers and patients with peripheral arterial disease (PAD) from prior clinical studies. Population PK simulations project that a single dose of 30 mg/kg inclacumab will maintain concentrations above 10 µg/mL throughout the 90-day study period in the majority of participants, thereby attaining levels required for an effective and sustained reduction of re-admissions due to a VOC in the SCD population.

1.3.3. Use of a Placebo Control

This study uses placebo as a comparator on the background of standard of care (SOC) treatment for a VOC. Placebo was chosen as the control because it is necessary to determine the safety and efficacy of inclacumab by allowing efficacy to be estimated controlling for background VOCs with SOC and safety signals to be distinguished from AEs occurring due to SCD.

Treatments with stable SOC are allowed including stable doses of HU, erythropoietin-stimulating agents (ESAs), voxelotor, and L-glutamine. However, initiation of these agents during screening or after randomization and use of crizanlizumab within 90 days prior and during the study is prohibited. Crizanlizumab has a similar mechanism of action that would confound interpretation of this study. All other standard therapeutic interventions for SCD (eg, hydration, analgesia, acute transfusions) are allowed under this protocol.

Randomization to placebo treatment in this study does not place study participants at increased risk, as the SOC (other than the use of crizanlizumab) will be allowed during the study.

2. OBJECTIVES

The primary objective of this study is to evaluate the safety and efficacy of a single dose of inclacumab to reduce the incidence of re-admission to a healthcare facility for a VOC after an admission for an index VOC in participants with SCD.

Additional objectives of the study are to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of inclacumab, the presence of anti-drug antibodies (ADAs), and changes in quality of life (QOL).

3. INVESTIGATIONAL PLAN

This is a Phase 3, randomized, double-blind, placebo-controlled, 2-arm, multicenter, parallel-group study.

3.1. Study Design

This study will assess the safety and efficacy of inclacumab in reducing the frequency of re-admissions due to VOCs after an index VOC in approximately 280 adult and adolescent participants (≥ 12 years of age) with SCD. Initial enrollment will include participants ≥ 16 years of age until the independent Data Monitoring Committee (DMC) determines that adequate safety and PK data support the enrollment of participants 12 to 15 years of age.

Eligible participants will be randomized to a single dose of study drug with a 1:1 ratio into one of two treatment arms as follows:

- Inclacumab 30 mg/kg administered IV; or
- Placebo administered IV.

At the time of randomization, participants will be stratified by Baseline HU use (yes; no), number of VOCs (2 to 4; 5 to 10) in the preceding 12 months, and geographic region (North America; rest of world).

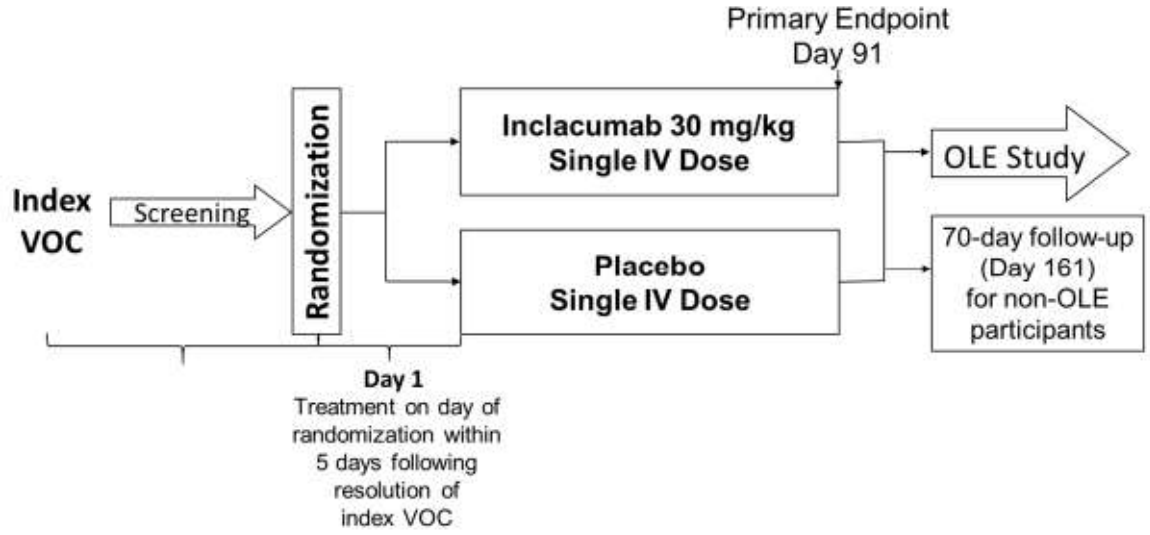
All participants will undergo safety, efficacy, and PK/PD assessments at Baseline and Day 91. An additional visit at Day 46 will occur for safety, PK, and PD monitoring. The incidence of VOC events will be collected every 4 weeks, with participants contacted by phone at Day 31 and Day 61.

Following completion of the Day 91 visit, eligible participants will be given the option to enroll in an open-label extension (OLE) study (under a separate protocol) to receive inclacumab. Participants will receive their first dose in the OLE study at the same Day 91 visit. Participants enrolling in the OLE study will not be required to return to clinic for the Day 161 visit. Safety, efficacy, and PK/PD assessments will occur at Day 161 for participants not enrolling into the OLE study.

The DMC will regularly review the totality of accumulated safety data from all ongoing inclacumab studies on an unblinded basis with additional emphasis on adolescent participants. Details will be provided in the DMC Charter.

A diagram of the study design is provided in Figure 1.

Figure 1: GBT2104-132 Study Design



Abbreviations: IV, intravenous; OLE, open-label extension.

3.2. Study Endpoints

3.2.1. Primary Efficacy Endpoint

The primary endpoint for this study is, following an index VOC, the proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days of randomization.

An admission for a VOC includes:

- A hospital admission, or
- An admission to an emergency room, observation unit, or infusion center for $\geq$ 12 hours, or
- 2 visits to an emergency room, observation unit, or infusion center over a 72-hour period.

for an acute episode of pain with no other cause other than a vaso-occlusive event that includes the following:

- Uncomplicated VOC, or
- Acute chest syndrome, or
- Acute hepatic sequestration, or
- Acute splenic sequestration, or
- Priapism

The definition of the index VOC requiring admission is the same as the primary endpoint VOC requiring admission.

To ensure consistency across all sites, on-study VOCs to be used for the primary endpoint will be confirmed by adjudication by an independent, blinded panel comprised of experts in SCD. The primary efficacy analysis will be performed on adjudicated data.

3.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints of the study are the following:

- Time to first VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days of randomization.
- Proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 30 days of randomization.
- Rate of VOCs leading to a healthcare visit (hospital, emergency room, clinic visit, or remote contact with a healthcare provider) that requires parenteral pain medication (eg, parenteral narcotic agents or parenteral nonsteroidal anti-inflammatory drugs [NSAIDs]), or an increase in treatment with oral narcotics within 90 days following randomization.

3.2.3. Safety Endpoints

The safety endpoints of the study are the following:

- Incidence of treatment-emergent adverse events (TEAEs).
- Change from Baseline in laboratory assessments (complete blood count, chemistry, and coagulation).

3.2.4. Exploratory Endpoints

The exploratory endpoints for the study are the following:

- Time to second VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days of randomization.
- Rate of complicated VOCs (ie, acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism) during the 90 days following randomization.
- Rate of inpatient hospital admissions for any reason during the 90 days following randomization.
- Number of days of inpatient hospitalization for any reason during the 90 days following randomization.
- Proportion of participants rated as "very much improved" or "moderately improved" based on the Patient's Global Impression of Change (PGI-C) at Day 46 and Day 91.

- Proportion of participants rated as "very much improved" or "moderately improved" based on the Clinician's Global Impression of Change (CGI-C) at Day 46 and Day 91.
- Change from Baseline in the cumulative score for the Adult Sickle Cell Quality of Life Measurement (ASCQ-Me) Pain Impact – Short Form over time to Day 91.

3.2.5. Exploratory Pharmacology Endpoints

The following exploratory pharmacology endpoints will be assessed:

- Plasma PK of inclacumab as assessed by population PK analysis using nonlinear mixed-effects modeling.
- Incidence of ADA to inclacumab.
- Pharmacodynamics including CCI [redacted].
- Biomarkers including CCI [redacted]

Relationships between PK, PD, biomarkers, clinical labs, safety, and efficacy will be explored.

3.3. Selection of Study Population

A total of up to 280 participants (140 per treatment group) at approximately 60 global clinical sites will be enrolled in this study.

3.3.1. Eligibility

Eligibility assessment will be conducted during Screening (start of index VOC admission through Day -1) and prior to receiving study drug on Day 1.

Participants who meet all the following inclusion criteria and none of the exclusion criteria will be eligible for enrollment in this study.

For Investigator questions regarding participant eligibility or clinical significance of abnormalities, discussion with the study Medical Monitor is strongly encouraged.

3.3.1.1. Inclusion Criteria

1. Participant has an index VOC. The index VOC is any VOC that required admission to a healthcare facility and treatment with parenteral pain medication. An admission for the index VOC includes:
   a. A hospital admission, or
   b. An admission to an emergency room, observation unit, or infusion center for $\geq$ 12 hours, or
   c. 2 visits to an emergency room, observation unit, or infusion center over a 72-hour period.

for an acute episode of pain with no other cause other than a vaso-occlusive event that includes the following:

- Uncomplicated VOC,
- Acute chest syndrome (ACS),
- Acute hepatic sequestration,
- Acute splenic sequestration, or
- Priapism.

2. Participant has a confirmed diagnosis of SCD (any genotype).

   Documentation of SCD genotype is required and may be based on documented history of laboratory testing or confirmed by laboratory testing at Baseline.

3. Participant is male or female, ≥ 12 years of age at the time of informed consent.

   NOTE: Initial study enrollment will include only participants ≥ 16 years of age until the DMC recommends to the Sponsor that adequate safety and PK data support the enrollment of participants 12 to 15 years of age. Sites will be informed by the Sponsor when participants 12 to 15 years of age may be enrolled.

4. Participant is able to complete screening and receive study drug within 5 days following investigator-assessed resolution of index VOC (for example, hospital discharge, discontinuation of parenteral pain medication, or transition to oral pain medication).

5. Participant has experienced between 2 and 10 VOCs (inclusive) within the 12 months prior to Screening as determined by documented medical history. The index VOC is not to be considered as one of the 2 to 10 events. A prior VOC is defined as an acute episode of pain that:

   - Has no medically determined cause other than a vaso-occlusive event, and
   - Results in a visit to a medical facility (hospital, emergency department, urgent care center, outpatient clinic, or infusion center) or results in a remote contact with a healthcare provider; and
   - Requires parenteral narcotic agents, parenteral nonsteroidal anti-inflammatory drugs (NSAIDs), or an increase in treatment with oral narcotics.

6. Participants receiving erythropoiesis-stimulating agents (ESA, eg, erythropoietin [EPO]) must be on a stable dose for at least 90 days prior to Screening and expected to continue with the stabilized regimen throughout the course of the study.

7. Participants receiving HU, L-glutamine, or voxelotor must be on a stable dose for at least 30 days prior to Screening and expected to continue with the stabilized regimen throughout the course of the study.

8. Participant has adequate venous access, in the opinion of the Investigator, to comply with study procedures.

9. Participant understands the study procedures and agrees to participate in the study by giving written informed consent or parental permission/written assent.

10. Women of childbearing potential (WOCBP) are required to have a negative serum pregnancy test at the Screening Visit and negative urine pregnancy tests on all subsequent clinic visits and must agree to use a highly effective method of contraception throughout the study period and for at least 165 days after dosing. (Section 6.2).

    Female participants will not be considered of childbearing potential if they are pre-menarchal, surgically sterile (hysterectomy, bilateral salpingectomy, tubal ligation, or bilateral oophorectomy) or postmenopausal (no menses for 12 months without an alternative medical cause, confirmed by follicle-stimulating hormone test results).

3.3.1.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening or Baseline visits or at the timepoint specified in the individual criterion listed.

1. Participant is receiving regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventative transfusion).
2. Participant is taking or has received crizanlizumab (ADAKVEO®) within 90 days prior to Screening.
3. Participant weighs > 133 kg (292 lbs.).
4. Participant has a significant active and poorly controlled (unstable) hepatic disorder clearly unrelated to SCD.
5. Participant has any of the following laboratory values at Screening:
   a. Absolute neutrophil count (ANC) < 1.0×10^9/L
   b. Platelet count < 80×10^9/L
   c. Hemoglobin < 4.0 g/dL for adults and < 5.0 g/dL for participants ages 12 to < 18 years of age
   d. Estimated glomerular filtration rate (eGFR) < 30 mL/min using Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula in adults, and Schwartz formula in adolescents.

   NOTE: Laboratory assessments conducted during Screening may be done by the local laboratory and must include at least a CBC with total and differential leukocyte count, platelet count, and hemoglobin, a chemistry panel with creatinine, and a serum pregnancy test to assess participant eligibility. Laboratory assessments conducted during the index VOC admission that are obtained within 7 days prior to screening may be used for Screening assessments if done as part of standard medical care.
6. Participant has known active (symptomatic) COVID infection or tests positive for COVID-19 at any time during their index admission.
7. Participant has a history of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to Screening including severe or unstable pulmonary hypertension.
8. Participant has had treatment for a malignancy within the 12 months prior to Screening (except non-melanoma skin cancer and in situ cervical cancers).
9. Participant has had a stroke within the 2 years prior to the Screening Visit.

10. Participant has a positive test indicative of active malaria infection at Screening. Testing to be conducted at local laboratories in malaria-endemic regions at the discretion of the Investigator.
11. Participant has any confirmed clinically significant drug allergy and/or known hypersensitivity to monoclonal antibody therapeutics or formulation components of the study drug or a related drug.
12. Participant has been treated with another investigational agent within 30 days or 5 half-lives of the investigational agent (whichever is greater) prior to Screening.
13. Participant has had a major surgery within 8 weeks prior to the Screening Visit.
14. Participant is pregnant, breastfeeding, or planning to become pregnant during the 90-day treatment period.
15. Participant, parent, or legal guardian are unlikely to comply with the study procedures.
16. Participant has other medical, or psychological, or behavioral conditions that, in the opinion of the Investigator, would: confound or interfere with evaluation of safety, efficacy, and/or PK of the investigational drug; prevent compliance with the study protocol; preclude informed consent; or render the participant, parent, or caretaker unable/unlikely to comply with the study procedures.

3.3.2. Participant Completion

Participants not enrolling in the OLE study will complete the study at the time of the last scheduled study procedures at the Day 161 visit. For participants who enroll in the OLE study, the Day 91 visit will be the final study visit. Participants may receive their first dose in the OLE study on the same day as the completion of the study assessments for the Day 91 visit. Participants who terminate the study prior to the Day 91 visit will be requested to complete the assessments as outlined for the Early Termination (Day 91) Visit. Participants not enrolling in the OLE study that complete the Day 91 visit but terminate prior to the Day 161 visit will be requested to complete the assessments as outlined for the End of Study (EOS; Day 161) Visit. Participants who require further follow-up for an AE/serious adverse event (SAE) will be followed according to Section 7.9.

3.3.3. Study Discontinuation

The Sponsor has the right to terminate this study at any time. In any instance of early termination of the study, the Sponsor will notify, in writing, the Investigators, regulatory authorities and ethics committees (Institutional Review Board [IRB]/Ethics Committee [EC]) and will specify the reason(s) for termination.

3.3.3.1. Early Discontinuation of Individual Participants

Participants will be informed that they are free to withdraw from the study at any time and for any reason. The Investigator must withdraw from the study any participant who requests to be withdrawn. Participants who ask to leave the study early (withdraw consent) should be encouraged to undergo the tests and evaluations listed for the Early Termination (ET) Visit (ie, early termination is intended for participants who withdraw consent). If a participant

withdraws before completing the study, the date and reason for withdrawal is to be documented on the electronic case report form (eCRF).

Participants may discontinue the study for any of the following reasons:

- Adverse event
- Withdrawal of consent
- Discretion of the Investigator
- Participant is lost to follow-up
- Participant is noncompliant
- Pregnancy. Report the pregnancy according to the instructions in Section 7.4.

A participant that withdraws from the study or is lost to follow-up will not be replaced.

3.3.4. Lost to Follow-up

Participants who do not return for a scheduled visit, as defined by the visit schedule, and cannot be reached to determine the reason for the missed visit, may be considered lost to follow-up. The site will attempt to contact the participant through a minimum of 2 telephone calls. If the participant still cannot be contacted, the site will send a certified letter to the last known address of the participant. If no contact is made by the participant, the site will consider the participant lost to follow-up. All follow-up attempts will be documented and kept with the participant's source documentation, and the applicable eCRFs will be completed.

3.4. Study Duration

The total study duration for each participant will be variable based on the time from the start of the index VOC admission to Day 1. For example, if a participant begins screening at the start of a 10-day index VOC admission and is randomized the day of their index VOC resolution, the study duration would be 170 days, including a 10-day Screening period, a 90-day treatment period, and a 70-day (10 week) follow-up period.

Participants who enroll in the OLE study after Day 91 will have a total study duration of 91 days plus the length of their Screening period.

3.5. Treatments

Study drug will be provided to the study sites in a blinded fashion as a solution for IV infusion. All study drug will be administered at the clinical study site. Participants will be randomized into one of 2 treatment groups: inclacumab or placebo. The active inclacumab and placebo solutions will look identical to maintain the blind. The Investigator, site staff, participant, and Sponsor study personnel (or their designees) will be blinded to the study group to which the participant is randomized. Participants will be dosed as follows:

- Inclacumab: 30 mg/kg inclacumab administered IV on Day 1
- Placebo: placebo administered IV on Day 1

4. STUDY DRUG INFORMATION

4.1. Description of Active Study Drug – Inclacumab

The inclacumab drug substance is manufactured by fermentation cell culture using Chinese hamster ovary (CHO) cells followed by purification. The drug substance and drug product are manufactured in accordance with Good Manufacturing Practice (GMP).

Inclacumab drug product is a sterile, clear to opalescent liquid concentrate for infusion with an approximate pH of 5.5 provided in colorless, 10 mL single-use vials. Each vial contains 500 mg of inclacumab and the following excipients: CCI [redacted]

4.2. Description of Placebo for Inclacumab

The placebo for inclacumab to be used in this study will be a matched placebo for IV infusion with the same excipients found in inclacumab without the active product.

4.3. Packaging and Labeling

The study drug will be packaged and labeled in a manner consistent with the study design.

Vials of study drug will be labeled according to applicable regulations for an investigational drug.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the vials or study drug, do not use the study drug. The vial in question should be saved at the study site and the problem immediately reported to the Sponsor, or designee per the Pharmacy Manual (provided separately).

4.4. Storage and Handling

The inclacumab and placebo vials are to be stored at 2° to 8°C (36 to 46°F) prior to dilution in a monitored, locked refrigerator with limited access. Detailed instructions for storage and handling of study drug after dilution are provided in the Pharmacy Manual.

Study drug must be stored in a secure location and should not be used after the expiration, expiry, or use-by date.

The study drug will be provided by the Sponsor in 10-mL single-use vials that should be protected from light.

4.5. Instructions for Use and Administration

Detailed instructions for preparation and administration of study drug can be found in the Pharmacy Manual.

4.6. Management of Infusion-Related Reactions (IRR)

Participants will be monitored throughout the infusion and for 60 minutes after completion of study drug infusion for adverse reactions. If an infusion-related reaction (IRR) or hypersensitivity reaction of Grade 3 or higher (Appendix 4) occurs during study drug administration, the infusion should be paused, and the participant should be treated for the

reaction per site standard operating procedures as indicated. The participant will be monitored for resolution of the infusion or hypersensitivity reaction. If the reaction resolves to Grade 1 or less, study drug infusion may be reinitiated. Specific instructions for re-initiation of infusion are provided in the Pharmacy Manual. If the reaction recurs at a level of Grade 3 or higher, study drug administration should be permanently discontinued. Exact times of infusion stop and start must be recorded.

All IRRs will be recorded as an adverse event of special interest (AESI, Section 7.3) or SAE (if serious criterion is met; Section 7.1.2). If the study drug infusion is permanently discontinued, the participant should continue in the study to complete all safety, PK, and PD assessments through Day 161. However, the participant will be ineligible for the OLE study.

4.7. Accountability

A Drug Accountability Record will be used for the study drug. The record must be kept current and should contain the dates and quantities of study drug received, study number, lot or batch number(s), participants receiving study drug, the date and quantity of study drug dispensed and remaining, and the initials of the dispenser.

All study drug inventory forms must be made available for inspection by an authorized representative of the Sponsor or designee. The Investigator is responsible for the accountability and security of all used and unused study supplies at the site.

The Investigator must return all used and unused vials of study drug as instructed by the Sponsor, or designee, unless approved for onsite destruction. If any study drug supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from the Sponsor, or designee, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, The Sponsor, or designee, must be notified, in writing, of the details of the study drug destruction (eg, lot or kit numbers, quantities).

4.8. Methods of Assigning Participants to Treatment Groups

4.8.1. Participant Screening

A signed and dated informed consent or parental/guardian consent and participant assent must be obtained before any protocol specified Screening procedures or study specific tests may be performed.

All participants will be given a participant ID number upon signing the informed consent. This number will be used to identify the participant throughout the clinical study and must be used on all study documentation related to that participant. Re-screening may be considered at the discretion of the Investigator and in consultation with the Sponsor. Participants who re-screen will have all assessments redone and a new participant ID number assigned.

The Screening Period for a particular participant will commence when the participant undergoes the first study specific Screening assessment and must be completed prior to randomization on Day 1.

All study visits are to be scheduled relative to the Day 1 visit date.

4.8.2. Randomization Method

After all Screening assessments have been completed and the participant is deemed eligible per criteria in Section 3.3.1, participants will be randomized on Day 1 through a central interactive response technology (IRT) system.

Participants will be randomized with a 1:1 ratio to receive treatment with inclacumab or placebo. A stratified permuted block design will be used, with randomization stratified by Baseline HU use (yes; no), number of VOCs (2 to 4; 5 to 10) in the preceding 12 months, and geographic region (North America; rest of world).

The first dose of study drug is to be administered on the same day as randomization (Day 1). No participant may begin treatment with study drug prior to randomization. Any participant identification numbers that are assigned will not be reused even if the participant does not receive treatment.

4.8.3. Blinding Procedures

This is a randomized, double-blinded, placebo-controlled study. Investigators, study site staff, the Sponsor's study staff, the Sponsor's clinical contract research organization (CRO), and study participants, as well as members of the VOC Adjudication Committee, will remain blinded to the randomized treatment assignments. During the study, access to participant treatment assignment will be limited to DMC members and service providers supporting DMC reviews, including the independent Data Coordinating Center and the independent PK/PD bioanalytical laboratory and analysis personnel.

The Investigator must contact the Medical Monitor prior to unblinding of study drug for any participant. In an emergency, however, where knowledge of the study drug is critical to participant safety, the blind may be broken. In cases where the Investigator is unable to contact the Medical Monitor prior to unblinding, the Investigator must notify the Sponsor, or designee, as soon as possible (ie, within 24 hours) after unblinding. In addition, the Investigator must record the date, time, and reason for unblinding the study drug treatment in the source documentation.

5. STUDY ASSESSMENTS

The Schedule of Assessments (Appendix 1) summarizes the clinical procedures to be performed. Appendix 2 provides the schedule for collection of PK, ADA, and PD samples, and Appendix 3 provides the schedule for collection of samples for biomarkers. Assessments and procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the Investigator or designee and/or the Sponsor for reasons related to participant safety.

5.1. Primary Efficacy Assessment

The primary endpoint for this study is the proportion of participants, following an index VOC, that have at least one VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days of randomization, as described in Section 3.2.1.

Participants will be instructed to contact the investigational site for VOCs requiring a visit to a healthcare facility. However, in cases where visits to other healthcare facilities are required for treatment of their VOCs, (eg, emergency room, hospital, urgent care center, or infusion center), participants will be instructed to notify the investigational site within 48 hours when one of these visits occurs.

VOCs are categorized as:

Uncomplicated VOC: a VOC that is NOT classified as an acute chest syndrome, hepatic sequestration, splenic sequestration, or priapism.

Complicated VOCs:

- Acute Chest Syndrome (ACS), defined as a finding of a new pulmonary infiltrate, but excluding atelectasis (as indicated by chest X-ray). Must also present with at least one of the following signs or symptoms: patient-reported chest pain, body temperature of more than 38.5°C, tachypnea, wheezing, or cough.
- Hepatic sequestration, defined as findings of right upper quadrant pain, an enlarged liver, and an acute decrease in hemoglobin concentration.
- Splenic sequestration, defined as findings of left upper quadrant pain, an enlarged spleen, and an acute decrease in hemoglobin concentration.
- Priapism, defined as having a sustained penile erection requiring a visit to a medical facility.

To ensure consistency across all sites, all on-study VOCs will be adjudicated by an independent, blinded VOC Adjudication Committee comprised of experts in SCD (See Section 7.6.2). The primary efficacy analysis will be performed on adjudicated data.

5.2. Secondary and Exploratory Efficacy Assessments

The secondary efficacy endpoints are based on collection of the incidence and timing of VOCs requiring a re-admission (per the definition in the primary endpoint) after randomization and study drug administration, and for all VOCs requiring parenteral pain medication.

For the exploratory efficacy endpoints, in addition to incidence and timing of VOCs and medications to treat VOCs, hospitalization and hospitalization duration for any reason, quality of

life (QOL) assessments will be collected as patient-reported outcomes (PROs) or clinician reported outcomes (ClinRO), including:

- Patient's Global Impression of Change (PGI-C).
- Clinician's Global Impression of Change (CGI-C).
- ASCQ-Me Pain Impact – Short Form, when available.

5.3. Safety Assessments

5.3.1. Adverse Events

Safety will be monitored throughout the study as outlined in the Schedule of Assessments (Appendix 1). Adverse events will be collected throughout the study and graded for severity and relationship to study drug. Reported TEAEs will be analyzed. See Section 7 for details on definitions and requirements for adverse event collection.

5.3.2. Physical Examination

A full physical examination will be performed at each visit (excluding Day 46). A 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.

5.3.3. Vital Signs

Measurements of heart rate (HR), blood pressure (BP), and body temperature will be obtained. Additional vital signs may be taken at any other time, if deemed necessary.

HR and BP measurements will be performed with participants in a supine position for at least 5 minutes, except when they are seated or semi-reclined because of study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the Investigator or designee.

At the Baseline Visit (Day 1) vital signs will be collected prior to the Baseline blood collection and prior to study drug administration. Vital signs will also be collected at the completion of infusion and at one hour after completion of infusion. Participants should be clinically well with stable vital signs and without signs or symptoms of an infusion-related reaction prior to release from observation.

5.3.4. Clinical Laboratory Tests

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

For the purpose of this study, a clinically significant laboratory value will be any abnormal result that, in the judgment of the Investigator, is an unexpected or unexplained laboratory value or if medical intervention or corrective action (transfusion, hydration, initiation of antibiotics or other concomitant medication) is required. Any abnormal values that persist should be followed at the discretion of the Investigator.

Additional and repeat laboratory safety testing for the evaluation of abnormal results and/or AEs during the study may be performed at the discretion of the Investigator or upon request of the Sponsor. Repeat laboratory testing of abnormal potentially clinically significant or clinically significant results for the Screening evaluation of the participant may be repeated once at the discretion of the Investigator.

Laboratory assessments conducted during Screening may be done by the local laboratory and must include at least a CBC with total and differential leukocyte count, platelet count, and hemoglobin, a chemistry panel with creatinine, and a serum pregnancy test to assess participant eligibility.

Laboratory assessments conducted during the index VOC admission that are obtained within 7 days prior to screening may be used for Screening assessments if done as part of standard medical care.

Laboratory safety testing is intended to be performed by a central laboratory for Day 1 (Baseline) assessments and all subsequent visits. Exceptions may be made as necessary for local laboratory testing.

Tests listed in Table 1 will be performed as outlined in the Schedule of Assessments (Appendix 1). Details on collection, preparation, and shipping of blood samples are provided in the Laboratory Manual.

Table 1: Clinical Laboratory Tests

Hematology • Hemoglobin • Hematocrit • Total and differential leukocyte count • Red blood cell count • Percent and absolute reticulocyte count • Iron panel (iron, total iron binding capacity [TIBC], ferritin) • Platelet count **Coagulation** • Prothrombin time • Activated partial thromboplastin time • D-dimer • Von Willebrand factor • Fibrinogen • Thrombin-antithrombin complex	**Serum Chemistry** • Blood Urea Nitrogen • Bilirubin (total, direct and indirect) • Alkaline phosphatase • Aspartate aminotransferase • Alanine aminotransferase • Albumin • Sodium • Potassium • Magnesium • Calcium • Chloride • Bicarbonate • Glucose • Creatine kinase • Creatinine • Lactate dehydrogenase • C-reactive protein (CRP) • High sensitivity C-Reactive protein (hs-CRP) • Total globulin • Total protein • IgG • Cystatin C • Lipid Panel – Total cholesterol – HDL – LDL – Triglycerides
Additional Tests • Hemoglobin genotype at Baseline Visit (Day 1; if not previously determined) • Fetal hemoglobin at Baseline (Day 1) Visit • Serum pregnancy test at Screening (WOCBP only) • Urine pregnancy test at Baseline and subsequent visits (WOCBP only) • Follicle-stimulating hormone (FSH) for postmenopausal women at Baseline (Day 1) Visit * WOCBP, women of child-bearing potential.	

5.4. Clinical Assessments

5.4.1. Demographic/Medical History

Demographic information (sex, date of birth, race/ethnicity, height, weight) will be recorded. Participants will be asked to provide a thorough medical history, including VOC history. Weight will also be measured on Day 1 for study drug dosing.

5.4.2. Pregnancy Screen

Pregnancy tests will be performed on female participants of childbearing potential as indicated in the Schedule of Assessments (Appendix 1). A serum pregnancy test will be conducted at

Screening with urine pregnancy tests conducted thereafter. If the Day 1 urine test is positive, a pre-dose serum pregnancy test should be performed and dosing should be postponed until a negative result is confirmed; if positive, the participant will be considered a screen failure.

Female participants will not be considered of childbearing potential if they are pre-menarchal, surgically sterile (hysterectomy, bilateral salpingectomy, tubal ligation or bilateral oophorectomy) or postmenopausal (no menses for 12 months without an alternative medical cause, confirmed by follicle-stimulating hormone test results).

5.4.3. SARS-CoV-2 (COVID-19) Infection

During the study, participants who are exposed to, are suspected of having, or have documented COVID-19 should be tested, evaluated, and treated per institutional requirements. Participants that acquire COVID-19 during the study are not required to be withdrawn from study.

5.4.4. Quality of Life Assessments

Participants will be asked to provide responses to 2 QOL surveys (PGI-C and ASCQ-Me). Participants will complete the ASCQ-Me questionnaire weekly, when available. Administration of some of these surveys may occur over the phone with the clinic staff.

Clinicians will also complete a QOL assessment (CGI-C) on their global impression of participant improvement.

5.4.5. VOC Incidence and Monthly Follow-up

The incidence of VOCs requiring parenteral pain medication will be recorded by the participant each week. Each month (Day 31 and Day 61), participants will be contacted by phone to determine if a VOC requiring parenteral pain medication was not reported to the site within 48 hours. The site will then follow-up to obtain the necessary information on the VOC event. In addition, the site will collect AEs and record changes to concomitant medications, including dosing changes in pain medications, during this call.

5.5. Pharmacology Assessments (PK, ADA, PD, and Biomarkers)

The schedule for collection of plasma, serum, and/or whole blood samples for inclacumab PK, ADA, and PD samples is provided in Appendix 2. The schedule for collection of inclacumab biomarkers is provided in Appendix 3. The analyses will be performed at central laboratories. Details on collection, processing, and shipping of samples is provided in the Laboratory Manual. Samples collected for analysis of inclacumab PK, immunogenicity, or PD may additionally be used for further development and validation of the respective assay.

5.5.1. Pharmacokinetics

In all participants, plasma samples will be collected for measurement of inclacumab concentrations at a central laboratory using a validated ligand-binding assay under the supervision of the Sponsor. Plasma concentrations of inclacumab will be measured before and after study drug administration on Day 1, at the Day 46 visit, at the end of the treatment period (Day 91), and – in all participants not enrolling in the OLE – at the Day 161 End of Study Visit.

Population PK analysis using nonlinear mixed-effects modeling will be performed to characterize inclacumab PK in plasma.

5.5.2. Anti-drug Antibodies

In all participants, plasma samples will be collected for characterization of ADA on Day 1 (pre-dose), and at the Day 91 Study Visit, and – in all participants not enrolling in the OLE – at the Day 161 End of Study Visit. The detection and characterization of anti-inclacumab antibodies will be performed at a central laboratory using validated bridging ADA assays under the supervision of the Sponsor. Other analyses may be performed to further characterize the immunogenicity of inclacumab, including assessment of neutralizing antibodies.

5.5.3. Pharmacodynamics

Blood-based PD will be evaluated in all participants and will be assessed pretreatment and post-treatment with inclacumab. Assessments for PD include:

CCI

Additional samples for PK and PD will be collected when a participant presents with VOC on a non-study visit day, as feasible.

5.5.4. Biomarkers

Biomarkers to be evaluated include:

CCI

The relationships between PK, PD, biomarkers, clinical labs, safety, and efficacy will be explored.

Biological samples will be retained for up to 10 years, unless local regulatory requirements are for longer storage. These stored samples may be used by GBT or their research partners to help answer questions about the study drug, SCD and its associated conditions, or clinical laboratory testing to provide additional safety data. No human genetic testing will be performed without express consent of the study participant. The samples will be handled such that neither the participants name nor other identifying information will be recorded in the data belonging to the sample.

5.6. Unscheduled Visits for a VOC

Participants that visit a medical facility for treatment of a VOC will have blood samples obtained for complete blood counts (CBC), chemistry, coagulation, PK/PD, and biomarkers as outlined in Appendix 1, Appendix 2, and Appendix 3. Instructions for collection, preparation, and shipping of samples are provided in the Laboratory Manual.

5.7. Additional Unscheduled Visits

Additional visits may be scheduled, as necessary, to ensure the safety and well-being of participants. All additional exams should be fully documented in the source documents and on Unscheduled Visit eCRFs, as appropriate. Visits intended to fulfill scheduled visit requirements that fall outside the designated scheduled visit range are not Unscheduled Visits. In these cases, the visit data will be collected and transcribed to the appropriate scheduled visit eCRF.

If a participant is seen for multiple visits during a given visit window, the data from the visit that is intended to meet the protocol requirements for the scheduled visit should be captured on the visit eCRF. Where such a determination cannot be made, the first visit within the scheduled visit interval will be used for completion of the protocol-required scheduled visit eCRF. Data from any additional visits within a scheduled visit interval will be captured on an Unscheduled Visit eCRF.

5.8. Missed Visits

Missed visits should be rescheduled and performed as close to the original scheduled date as possible. If a participant misses any scheduled visit outside of the window for that visit, the visit is considered missed and will be recorded as a protocol deviation.

5.9. Post-study Follow-up

If a participant requires further follow-up of AEs/SAEs upon discontinuation or completion of the study, the Investigator must schedule post-study follow-up visits, as necessary. Refer to Section 7.8 for follow-up of AEs following study exit. If a post-study follow-up occurs, document the visit on the Unscheduled Visit eCRF.

5.10. Study Completion

The Sponsor, or designee, will notify the Investigator when to contact the IRB/EC to inform them that the study is complete.

5.10.1. Early Study Termination

If during the study it becomes evident to the Sponsor that the study should be stopped prematurely, the study will be terminated and appropriate notification will be given to the Investigator(s), IRB/EC, FDA, and local health authority, as applicable. The Sponsor, or designee, will instruct the Investigators to stop dispensing study materials/treatment and to arrange for study closeout at each site.

6. CONCOMITANT MEDICATIONS AND PROCEDURES

6.1.1. Concomitant Medications

A concomitant medication is any drug or substance administered between the signing of the informed consent and the EOS/ET Visit.

Enrollment in any other drug, biologic, or device clinical study or treatment with an approved therapy for investigational development or unapproved investigational drug under development is not allowed.

Adverse events related to administration of concomitant medication must be documented in the appropriate eCRF.

Other than the medications listed in Section 6.1.2, medications that are used as the standard of care for patient with SCD will be allowed during the study.

Participants receiving HU, ESA, (eg, EPO), L-glutamine, or voxelotor should maintain a stable dose throughout the study.

6.1.2. Prohibited Medications and Therapies

Treatment with the following is not allowed during the study:

- Initiation of treatment with HU, ESA (eg, EPO), voxelotor, crizanlizumab, or L-glutamine.
- Stem cell transplant.
- Active treatment on another investigational trial, including gene therapy for SCD.
- Initiation of a chronic transfusion program (pre-planned series of transfusions for prophylactic purposes).

6.1.3. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (eg, surgery/biopsy, physical therapy) or diagnostic assessment (eg, blood gas measurement, bacterial cultures) performed between the time the participant is enrolled in the study and the EOS/ET Visit.

The use of concomitant therapies or procedures must be recorded on the participant's eCRF, according to instructions for eCRF completion. Adverse events related to administration of these therapies or procedures must be documented in the appropriate eCRF.

6.2. Contraception Requirements

All female participants of childbearing potential (post-menarchal) should avoid pregnancy during the study, and all sexually active male participants should avoid fathering a child during the study.

Female participants will not be considered of childbearing potential if they are pre-menarchal, surgically sterile (hysterectomy, bilateral salpingectomy, tubal ligation, or bilateral oophorectomy) or postmenopausal (no menses for 12 months without an alternative medical cause, confirmed by follicle-stimulating hormone test results).

6.2.1. Instructions for Female Participants of Childbearing Potential

For female participants of childbearing potential (post-menarchal) who are sexually active, pregnancy should be avoided by the use of a highly effective method of contraception (as outlined in Section 6.2.3) consistently throughout the study and for at least 165 days after dosing.

Female participants who become pregnant during the study will be withdrawn from the study. Pregnancy reporting requirements are outlined in Section 7.4.

6.2.2. Instructions for Male Participants Capable of Fathering a Child

No information is available about the effects inclacumab may have on the development of the fetus in humans. Therefore, it is important that the partners of male participants do not become pregnant during the study and for a total period of 165 days after the male participant has received his last dose of inclacumab. Sperm donation should be avoided for this same period.

Male participants who are not surgically sterilized must agree to practice true abstinence, or agree to use acceptable contraception (see Section 6.2.3) if sexually active with a female partner of childbearing potential, throughout the study, and for at least 165 days after dosing.

6.2.3. Acceptable Forms of Contraception for Sexually Active Participants

For Female Participants:

Highly effective methods of birth control are defined as those that result in a low failure rate (ie, < 1% per year) when used consistently and correctly. Highly effective methods of birth control are as follows:

- Hormonal contraceptives:
  - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral; intravaginal; injected; implanted; or transdermal.
  - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral; injectable; or implantable.
  - Hormonal contraception must be supplemented with a barrier method (preferably male condom).
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion.
- Sexual abstinence:
  - Sexual abstinence is a highly effective method only if the participant is refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.
- Male partner who has been vasectomized with confirmation of azoospermia (verbal confirmation is acceptable).

For Male Participants with Female Partners Capable of Reproduction:

- For male participants who are not surgically sterile with confirmed absence of sperm, condom plus effective contraception for their female partners (ie, established use of oral, injected, or implanted hormonal contraception, or an IUD or IUS).
- Vasectomy at least 3 months prior to Day 1 with confirmation of azoospermia (verbal confirmation is acceptable).

Pregnancy reporting is described in Section 7.4.

6.3. Continuation of Treatment

Participants who complete the treatment and study through Day 91 will not receive any further treatment with the study drug on this study. Participants who complete the study, and meet eligibility requirements, will be provided with the opportunity to receive open-label inclacumab in the OLE study. The first dose administered in the OLE study will occur after completion of the end-of-study evaluations at the Day 91 visit.

7. ASSESSMENT OF SAFETY

Safety assessments will consist of AE and SAE monitoring, protocol-specified hematology, serum chemistry, and coagulation tests, physical examinations, protocol-specified vital sign measurements, and the results from other protocol-specified tests that are deemed critical to the safety evaluation of inclacumab.

The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in this section. At each visit/phone contact, the study participant or participant caregiver will be asked about any new or ongoing AE since the previous visit. Assessments of AEs will occur at each study visit and during monthly phone calls. See Section 7.2 for details regarding the required time periods for AE reporting.

Clinically significant changes from study Baseline in physical examination findings, weight, vital signs, and clinical laboratory test results will be recorded as AEs or SAEs, as appropriate.

7.1. Adverse Events

7.1.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product during the course of a clinical investigation. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not thought to be related to the investigational product. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the participant signs the ICF for participation is considered 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.

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 (RSI) section of the current IB or is not listed at the specificity or severity that has been observed.

7.1.2. Definition of Serious Adverse Events

An SAE or serious suspected adverse reaction is an AE or suspected adverse reaction that, at any dose, in the view of the 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
- 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. Any complications arising from a planned hospitalization may be considered an adverse event and should be reported as applicable. Hospitalizations that occur for pre-existing conditions that are scheduled after study enrollment are considered SAEs.

The Investigator will assess each AE for seriousness, severity, and relationship to investigational product.

7.1.3. Severity of Adverse Events

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.

The CTCAE quick reference guide can be found at the Cancer Therapy Evaluation Program CTCAE website (CTCAE Website).

For AEs not adequately addressed in the NCI-CTCAE, Version 5.0, the criteria presented in Table 2 should be used.

Table 2: Grading for Adverse Events not Covered in the NCI-CTCAE

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

Abbreviations: ADL, activities of daily living; NCI-CTCAE, National Cancer Institute - Common Terminology Criteria for Adverse Events.

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.

7.1.4. Relationship to Investigational Product

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 investigational product 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.

7.2. Adverse Event Reporting

7.2.1. General

All AEs will be recorded from the time the study participant signs the ICF/assent form until the Day 91/Day 161 EOS Visit or Early Termination visit, whichever comes first. All AEs must be reported on the AE eCRF via the electronic data capture (EDC) 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 (both serious and nonserious) AEs must be followed until they are resolved or stabilized, or until reasonable attempts to determine resolution of the event are exhausted.

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

7.2.2. Diagnosis Versus Signs and Symptoms

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

7.2.3. 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 × upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (eg, cholecystitis) needs to 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, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the AE eCRF, unless their severity, seriousness, or etiology changes.

7.3. Adverse Events of Special Interest, Serious Adverse Events, Serious Adverse Drug Reactions, and Requirements for Immediate Reporting

Any biologic agent administered IV may have the potential to cause infusion-related reactions (IRR; see Investigator's Brochure). In this study, IRRs should be reported as adverse events of special interest (AESI). Signs or symptoms of IRRs may include chills/rigors, myalgias, headache, rash, fatigue, nausea, vomiting, dyspnea, and/or hypotension. Shock may occur during or shortly after infusion and usually occurs during and/or up to 24 hours after the first infusion.

All AESIs or SAEs, regardless of causal attribution, must be reported by the Investigator or designee or site personnel within 24 hours of AESI or SAE awareness. The AESI or SAE will be reported by completing the SAE eCRF. AESIs will be recorded on the SAE eCRF within 24 hours of the site's awareness of them, even if they do not meet criteria for an SAE.

The Sponsor or designee may request additional source documentation pertaining to the AESI or 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 AESI or SAE information must be submitted within 24 hours of awareness as additional information becomes available. All AESI or SAEs regardless of causal attribution must be followed to resolution or stabilization, or until reasonable attempts to determine resolution of the AESI or SAE are performed.

7.3.1. 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, IRBs/ECs, 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 IRBs or ECs of all SAEs that occur at his or her site as required by local regulations or IRB/EC 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/ECs, and investigators, as applicable, of any events (eg, change to the safety profile of inclacumab, major safety findings that may place study participants at risk) that may occur during the clinical trial that do not fall within the definition of a SUSAR but may adversely affect the safety of study participants.

7.4. Reporting Pregnancy

If a participant becomes pregnant during the 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 counselling is provided).

Reported pregnancy of a participant or a participant's partner, 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).

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 7.3. 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 7.3.

Information regarding pregnancy testing (including definition of females of childbearing potential) is provided in Section 6.2. Highly effective means of contraception are also listed in Section 6.2.

7.5. Reporting Overdose

If a participant receives more than the protocol-defined dose of study drug and experiences a drug-related AE, this will be reported as an overdose (AEs must be recorded on the AE eCRF) and a protocol deviation. However, if the participant did not experience any AEs, this will only be reported as a protocol deviation.

The Investigator will discuss the risks and concerns of investigational agent exposure with the participant. An overdose with associated AEs must be reported within 24 hours of the Investigator, designee, or site personnel learning of the overdose and reported to the Study Director/Medical Monitor. An overdose must be followed until any adverse effects are resolved or stabilized, or until reasonable attempts to determine resolution of the event are exhausted.

7.6. Adverse Events That Are VOC Endpoint Events

VOC events that are listed in Table 3 are being captured as endpoints and **SHOULD NOT** be reported as an AE or SAE for purposes of this study. These events will not be considered as SAEs for reporting requirements.

Table 3: VOC Events Not Requiring AE/SAE Reporting

Uncomplicated VOC*
Acute chest syndrome
Hepatic sequestration
Splenic sequestration
Priapism requiring a visit to a medical facility

* Defined as an acute episode of pain with no medically determined cause other than a vaso-occlusive event, results in a visit to a medical facility (hospitalization, emergency department, urgent care center, outpatient clinic, or infusion center), or results in a remote contact with a healthcare provider, and requires parenteral narcotic agents, parenteral nonsteroidal anti-inflammatory drugs (NSAIDs), or an increase in treatment with oral narcotics, but is NOT classified as an acute chest syndrome, hepatic sequestration, splenic sequestration, or priapism.

7.6.1. Procedures for Reporting and Documenting VOC Event Data

All VOCs, as defined in Section 5.1, are to be documented within the eCRF within **5 days** of a site becoming aware of such event. Each VOC is to be recorded only once on the "Vaso-occlusive Event" eCRF page. All VOCs are to be recorded throughout the entire treatment period, up to Day 91, and should continue until the Follow-Up Visit at Day 161 for participants who do not enroll in the OLE study (or earlier if participant discontinues from the study). The Investigator will classify and provide all the following information for each VOC as follows:

- Diagnosis, which will be limited to one of the five pre-defined VOC events as described in Section 5.1:
  - Uncomplicated VOCs
  - ACS
  - Hepatic sequestration
  - Splenic sequestration
  - Priapism (requiring a visit to a medical facility)

- Onset date,
- Stop date,
- Action taken (None, Required concomitant medication, Temporarily withheld study drug, Permanent discontinuation of study drug, or Other [explain]),
- Whether or not hospitalization or a visit to emergency department, urgent care center, outpatient clinic, or infusion center was required and the duration of the visit,
- Concomitant medications given, and
- Outcome (Recovered without sequelae, Resolved with sequelae, Ongoing, Unknown, Death).

If a participant is hospitalized due to a VOC and during hospitalization develops a non-VOC event that meets the criteria for an SAE, then that event should be reported as a SAE. Any prolongation of a hospitalization due to a non-VOC event (even though they may have initially been hospitalized due to a VOC) is reportable as a SAE in the eCRF.

7.6.2. Source Document Collection for VOC Event Adjudication

For each reported on-study VOC, blinded source documentation to support the reported diagnosis will be submitted by the site to Sponsor, or designee, for review during the VOC adjudication process. Adjudication of VOC events will be performed by a study Adjudication Committee – an independent, blinded panel comprised of experts in SCD. Responsibilities of the Adjudication Committee and definition of VOCs for adjudication will be provided in the Adjudication Committee Charter.

Source documents may include (but are not limited to) the following:

- Clinical notes (including history and PE findings),
- Emergency Department notes (including history and PE findings),
- Hospital discharge summary,
- Clinical laboratory values (eg, hemoglobin concentration values for diagnoses of hepatic or splenic sequestration),
- Physical examination findings,
- Concomitant medications, and
- Chest X-ray (required for reporting an ACS).

7.7. Data Monitoring Committee

In addition to the Sponsor's pharmacovigilance oversight, an independent, unblinded Data Monitoring Committee (DMC) will oversee the safety of participants and overall study conduct for the Phase 3 program, with the support of an independent data coordinating center.

Initial enrollment of study participants will be limited to adults and adolescents 16 years of age or older. The DMC will review all available safety data and PK/PD data (as applicable) from the first 20 participants who have completed a minimum of 90 days of study participation in the

Phase 3 program to make a recommendation about enrollment of participants 12 to 15 years of age. Should the DMC recommend enrollment of participants 12 to 15 years of age, sites will be informed by the Sponsor. The DMC will continue close monitoring by meeting to review data of each 20 participants enrolled 12 to 15 years of age, or every 6 months, whichever occurs first. The DMC may also schedule ad hoc meetings at their discretion or at the Sponsor's request (eg, for a safety signal).

The full description of the DMC structure and responsibilities, as well as details of data to be reviewed and the frequency of the meetings, will be described in the DMC Charter.

7.8. Follow-up of AEs and SAEs

All AEs and SAEs must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the participant is lost to follow-up. This includes AEs/SAEs ongoing at completion of the study. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, relevant hospital records (ie, discharge summary), or consultation with other health care professionals. The site must ensure that all participant identifiers are redacted from supportive documentation prior to submission.

The Sponsor, or designee, may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a participant dies during participation in the study or during a recognized follow-up period, the Sponsor, or designee, should be provided with a copy of any postmortem findings, including histopathology.

New or updated information obtained during SAE follow-up should be recorded on the originally completed SAE form with all changes signed and dated by the Investigator or designee. By signing the SAE form, the Investigator or designee attests to the accuracy and completeness of the data and that he/she has reviewed the report being submitted and approved.

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.

7.9. Safety Responsibilities

7.9.1. Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, regardless of the severity or relationship to study drug.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.

- Monitor and record all pregnancies and follow up on the outcome of the pregnancy in female participants or the partners of male participants.
- Complete the SAE eCRF within 24 hours of the study site staff becoming aware of the event.
- Complete the AE/SAE and/or AESI eCRF within 24 hours of the study site staff becoming aware of the event.
- Pursue AESI or SAE follow-up information actively and persistently. Follow-up information must be reported to Sponsor, or designee, within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the participants' medical records and submit documentation (with participant identifiers redacted) with SAE reports as required.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable.
- Report SAEs to IRB/IEC, as required by local law.

7.9.2. Sponsor

The Sponsor's responsibilities include the following:

- Safety monitoring/surveillance of AEs and SAEs.
- Before study site activation and participant enrollment, the Medical Monitor, or designee, is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- The Sponsor, or designee, is to notify all appropriate regulatory authorities, central IRBs/ECs, and Investigators of SUSARs, as required by local law, within required time frames.

8. STATISTICAL METHODS

Detailed specifications of the methods for summary and analysis of the data collected in this study will be documented in the statistical analysis plan (SAP).

8.1. Study Endpoints

Study endpoints are provided in Section 3.2.

8.2. Determination of Sample Size

Up to 280 participants will be enrolled in the study. Participants will be randomized in a 1:1 ratio to receive treatment with a single dose of inclacumab or placebo.

The study uses a group sequential design to evaluate the primary efficacy endpoint based on 2 sequential analyses: (i) one interim analysis after a minimum of 75 participants per arm have completed the study through 90 days, and (ii) if required, a final study analysis based on approximately 140 participants per arm.

For the primary endpoint, the planned sample size of up to 280 participants (140 participants per treatment group) provides approximately 90% power to detect a targeted 50% relative reduction in the proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days from a rate of 35% for placebo to 17.5% for inclacumab, using a 2-sided test of the difference in 2 binomial proportions (Normal approximation). To maintain an overall Type I error rate of 0.05, calculations assumed an O'Brien-Fleming boundary of the Lan-DeMets alpha-spending function (East version 6.5). For the sample size calculation, a 5% drop-out rate during the 90-day study period was used.

With this sample size, the smallest observed treatment difference expected to be statistically significant at the final analysis is approximately a 32% relative reduction (ie, reduction in the proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days of randomization from 35% for placebo to 23.8% for inclacumab).

8.3. Analysis Populations

Two main analysis populations are defined for this study: the intent-to-treat (ITT) population and the safety population.

- The ITT population includes all randomized participants. For analyses based on this population, participants will be grouped according to treatment assigned at randomization. The ITT population will be the main analysis population for efficacy analyses and summaries of demographic and Baseline characteristics.
- The safety population includes randomized participants who received treatment with study drug. For analyses based on this population, participants will be grouped according to the actual treatment received. The safety population will be the main analysis population for safety analyses and summaries of study drug exposure.

Additional analysis populations, such as a per protocol population, will be defined in the SAP, as appropriate.

8.4. Statistical Analysis

8.4.1. Summaries of Study Conduct

The number of participants randomized will be tabulated by region, country, study site, and treatment group. Participant disposition (the number of participants randomized, treated, and completing the study) will be tabulated by treatment group. Reasons for study drug interruption and discontinuation, as well as study discontinuation will be summarized. Any eligibility criteria deviations, dosing errors, and other major protocol deviations will also be tabulated and evaluated for potential impact on the interpretation of study results.

8.4.2. Summaries of Demographics, Baseline Characteristics, and Concomitant Medications

Demographic and Baseline characteristics, such as age, sex, race, body weight in kg, sickle cell genotype, number of VOCs in the prior 12 months, concomitant HU/hydrocarbamide (HC) use, prior crizanlizumab use, and geographic region, will be summarized for the ITT population by treatment group. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized. Exposure to study drug (amount of study drug administered and infusion time) and time on study will also be summarized.

8.4.3. Efficacy Analyses

8.4.3.1. Primary Endpoint

For the primary efficacy endpoint, the proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days, will be compared between treatment arms using the exact Cochran-Mantel-Haenszel general association test, stratified by the randomization stratification factors.

Every effort will be made to obtain the 90-day re-admission status for a VOC for each participant. For purposes of the primary analysis, participants with an unknown 90-day re-admission status will be classified as having experienced at least 1 protocol-defined VOC within 90 days (ie, treated as "failure"). Sensitivity analyses evaluating the robustness of results to assumptions regarding drop-outs will be performed, as appropriate.

8.4.3.2. Secondary Endpoints

For time to first VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days, treatment comparison will be performed based on a log-rank test stratified by the randomization factors and Kaplan-Meier plots generated. For participants who do not experience a VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days of randomization, time to first VOC will be censored at the end of their time at risk (date of last study assessment or Study Day 91, whichever is earlier).

For the proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 30 days, the same statistical methods used for the primary efficacy endpoint will be used.

For the rate of VOCs leading to a healthcare visit within 90 days, the total number of VOCs in the 90-day period will be compared between treatment arms using a negative binomial regression model stratified by the randomization factors.

8.4.3.3. Exploratory Endpoints

Exploratory endpoints will be summarized by descriptive statistics. Details will be provided in the SAP.

8.4.3.4. Interim Efficacy Analysis

One interim analysis for efficacy may be performed after a minimum of 75 participants per arm have completed the study through 90 days. At that time, the primary efficacy endpoint will be evaluated via the independent DMC. The O'Brien-Fleming boundary of the Lan-DeMets alpha-spending function will be used to determine significance levels for the primary endpoint at the interim and final analyses, while maintaining the overall Type I error rate of 0.05. If statistical significance is achieved demonstrating a treatment benefit for the primary endpoint based on the pre-specified efficacy boundary, the trial will be considered positive. If statistical significance is achieved for the primary endpoint at the interim analysis, secondary endpoints will be analyzed according to the fixed sequence test procedure outlined in Section 8.4.3.5. Exploratory endpoints will also be analyzed.

If statistical significance is not achieved at the interim analysis, the trial will continue, and a final efficacy analysis based on the pre-specified efficacy boundary will be performed after all randomized participants (approximately 140 per arm) have completed the 90-day study period or discontinued early, and all corresponding data have been entered into the database, reviewed, and verified.

If the interim efficacy analysis is not conducted, then all statistical tests will be conducted based on a 2-sided $\alpha = 0.05$ level.

The details for interim analysis will be provided in the SAP.

8.4.3.5. Adjustment for Multiple Comparisons

A fixed sequence hierarchical test procedure will be used to control Type I error when evaluating the treatment effect of inclacumab compared with placebo for the primary and secondary efficacy endpoints. The endpoints will be tested sequentially based on the following pre-specified order:

1. Proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days of randomization (primary endpoint).
2. Time to first VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days of randomization.
3. Proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 30 days.
4. Rate of VOCs leading to a healthcare visit (hospital, emergency room, clinic visit, or remote contact with a healthcare provider) within 90 days.

If statistical significance is achieved for the primary endpoint at the interim analysis, secondary endpoints will also be tested at that time according to the sequence above. Otherwise, secondary endpoints will not be tested until following analysis of the primary endpoint at the final analysis. Significance levels used for testing secondary endpoints, controlling for the overall Type 1 error at 0.05, will be provided in the SAP.

Formal testing of secondary endpoints will continue until the first non-significant result. Testing of endpoints subsequent to a non-significant result will be considered exploratory in nature.

8.4.3.6. Safety Analyses

Safety will be assessed through descriptive summaries of adverse events, laboratory test results, and vital signs.

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of TEAEs, defined as events that occur on or after Day 1 of study treatment or the worsening of a pre-existing condition on or after Day 1 of study treatment, will be tabulated by System Organ Class and preferred term. Additional summaries for TEAEs by severity, relationship to study drug, and leading to study drug discontinuation, as well as for AESIs, SAEs, and deaths will be generated.

VOC events will be collected and summarized separately (including ACS, hepatic sequestration, splenic sequestration, and priapism).

Changes in laboratory parameters (hematology, serum chemistry, and coagulation) and vital signs (eg, blood pressure, heart rate, and body temperature) over time will be summarized descriptively.

8.5. PK, ADA, and PD Analyses

8.5.1. Pharmacokinetic Analyses

CCI [redacted]

8.5.2. Anti-drug Antibody Analyses

CCI [redacted]

CCI [redacted]

8.5.3. Pharmacodynamic Analyses

CCI [redacted]

9. STUDY ADMINISTRATION

9.1. Direct Access to Source Data/Documents

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

The Sponsor, or designee, will determine a risk evaluation plan and implement an action plan considering the need to reduce unnecessary contacts in a period of COVID-19 or another epidemiological emergency. Site visits may be replaced by an enhanced centralized monitoring or local visits may be postponed. These methods will be described in the monitoring plan by the Sponsor, or designee.

9.1.1. 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 patient into the study, a representative of the Sponsor and/or designee will visit the investigational study site 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 investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRF with the patient'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 patient (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/EC.

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

9.2. 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, a 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 Form FDA 1572, or similar document, 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.

9.3. Quality Control and Quality Assurance

9.3.1. 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, onsite monitoring visits may be conducted pre-study, 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 requirements. Additionally, individual participants may be excluded if a medical record review indicates protocol violations 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.

9.3.2. 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.

9.3.3. Laboratory Accreditation

The laboratory facilities 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.

9.4. Regulatory, Ethical, and Legal Obligations

9.4.1. 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/EC 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/EC prior to implementation (refer to Section 9.4.4).

9.4.2. 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.

9.4.3. Informed Consent/Assent

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. Under age participants (and their parent or legal guardian) will review the ICF and sign a Child Assent Form, according to local institution/IRB/EC 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.

It is the Investigator's responsibility to obtain written informed consent from the parent(s) of the participant and assent from the participant after adequate explanation of the objectives, methods,

anticipated benefits, and potential risks of the study and before any study procedures are commenced. The parent or legal guardian should be given a copy of the ICF and the participant should be given a copy of the assent in their native language. The informed consent and assents processes should be recorded in the source documentation. The original copies of the signed and dated informed consent and assent must be retained in the institution's records and are subject to inspection by representatives of the Sponsor, or representatives from regulatory agencies.

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.

9.4.4. IRB/EC and Regulatory Approval

The Investigator must inform and obtain approval from the IRB/EC 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 investigational product.

Proposed amendments to the protocol and documents must be discussed with the Sponsor and CRO, and then submitted to the IRB/EC 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/EC 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/EC 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/EC to facilitate their continuing review of the study (if needed) and that the IRB/EC 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/EC of any reportable AEs.

9.4.5. 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 investigational product shipment to the site.

9.4.6. 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/ECs 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.

9.4.7. 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 patient information sheet/informed consent for the study will inform patients of their rights.

9.4.8. 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 9.5.2. 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.

9.5. Data Handling and Recordkeeping

9.5.1. Inspection of Records

The Sponsor, or designee, 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/EC.

9.5.2. 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 United States (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 investigational product 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/EC 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.

9.5.3. 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 (as appropriate) 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/EC; and other authorized parties. All information concerning the study medication 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 inclacumab 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.

9.6. Insurance and Financial Disclosure

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

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

9.7. Publication Policy

The results of the study may be published once all participants have completed the study and the study data have been analyzed.

The Investigator or the Sponsor may not submit for publication or present the results of this study without allowing each of the other parties to review and comment on the prepublication manuscript, as defined in the site's clinical trial agreement.

The Investigator may not submit any of the results of the study for publication without the prior consent of the Sponsor.

10. REFERENCES

ADAKVEO® (crizanlizumab) US Prescribing Information. Novartis Pharmaceuticals Corporation. November 2019.

Ataga K, et al. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. N Engl J Med. 2017; 376(5): 429–439.

Brousseau D, Owens, P Mosso A, et al. Acute Care Utilization and Rehospitalizations in Adults with Sickle Cell Disease. The Journal of the American Medical Association. 2010;303(13):1288-1294

Charache S, Terrin M, Moore R, et al. Effect of Hydroxyurea on the Frequency of Painful Crisis in Sickle Cell Anemia. N Engl J Med. 1995;332(20):1317-1322.

CTEP CTCAE website for grading severity of adverse events – (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf)

DROXIA® (hydroxyurea capsules, USP) US Prescribing Information. Bristol-Myers Squibb. December 2017.

ENDARI (L-glutamine Oral Powder) US Prescribing Information. Emmaus Medical, Inc. July 2017.

Kaiser K, Yount SE, Martens CE, Webster KA, Shaunfield S, Sparling A, et al. Assessing Preferences for Rare Disease Treatment: Qualitative Development of the Paroxysmal Nocturnal Hemoglobinuria Patient Preference Questionnaire (PNH-PPQ©). Patient Prefer Adherence. 2020 Apr 5;14:705-715.

Kassim A, Sharma D. Hematopoietic Stem Cell Transplantation for Sickle Cell Disease: The Changing Landscape. Hematol Oncol Stem Cell Ther. 2017;10:259-266.

Kato G, Piel F, Reid C, et al. Sickle Cell Disease. Nature Reviews – Disease Primers. 2018;4(18010):1-22.

Levy AR, Dysart L, Patel Y, Briggs A, Schneider J, et al. Comparison of Lost Productivity Due to Eculizumab and Ravulizumab Treatments for Paroxysmal Nocturnal Hemoglobinuria in France, Germany, Italy, Russia, Spain, the United Kingdom, and the United States. Blood. 2019;134:4803.

McFarling UL. 'They are really afraid': Fears about Covid-19 are complicating care for patients with sickle cell. STATNews September 17, 2020. (https://www.statnews.com/2020/09/17/sickle-cell-treatment-covid19-pandemic/)

Niihara Y, Miller ST, Kanter J, et al. A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. N Engl J Med. 2018;379(3):226-235.

Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005 Aug 4;353(5):487-97.

Powell L. Sickle Cell Disease Brings Higher Risk of Coronavirus Death, but Inconsistent Treatment. The City. 2020 Jul 14. https://www.thecity.nyc/coronavirus/2020/7/14/21324875/sickle-cell-disease-coronavirus-death-new-york-city

Richter A, Anton SF, Koch P, Dennett SL. The impact of reducing dose frequency on health outcomes [published correction appears in Clin Ther. 2015 Aug;37(8):1870. Anton, Susan E [corrected to Anton, Susan F]. Clin Ther. 2003;25(8):2307-2306.

Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. Health Aff (Millwood). 2011;30(1):91-99.

Saini SD, Schoenfeld P, Kaulback K, Dubinsky MC. Effect of medication dosing frequency on adherence in chronic diseases. Am J Manag Care. 2009;15(6):e22-e33. (Published 2009 Jun 1)

Shah N, Bhor M, Xie L, et al. Treatment Patterns and Economic Burden of Sickle-Cell Disease Patients Prescribed Hydroxyurea: A Retrospective Claims-Based Study. Healthy and Quality of Life Outcomes. 2019;17(155):1-11

Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, Johnson JA. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ. 2006 Jul 1;333(7557):15.

Tkacz J, Ingham MP, Brady BL, Meyer R, Ruetsch C. Novel Adherence Measures for Infusible Therapeutic Agents Indicated for Rheumatoid Arthritis. Am Health Drug Benefits. 2015;8(9):494-505.

Wells JR, Gater A, Marshall C, Tritton T, Vashi P, Kessabi S. Exploring the Impact of Infusion Frequency in Hemophilia A: Exit Interviews with Patients Participating in BAY 94-9027 Extension Studies (PROTECT VIII). Patient. 2019;12(6):611-619.

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Study Period	Screening	Treatment Period					Follow-up	
Procedure	Start of Index VOC to Day -1 [a]	Baseline Visit Day 1 [b]	Day 31 Phone Call ±7 days	Day 46 Visit ±7 days	Day 61 Phone Call ±7 days	Day 91 Visit (EOS [c]/ET) ±7 days	Day 161 Visit (EOS) [d] ±14 days	Upon Presentation for a VOC [n]
Informed consent/assent	X							
Review of eligibility criteria	X	X						
Demographics	X							
Medical history	X							
VOC history	X							
Height (cm) and weight (kg)	X	X						
Vital signs [e]	X	X		X		X	X	
Physical examination	X	X				X	X	
Chest X-ray [f]		←	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	→
CBC/diff [g] & chemistry [h] (w FSH [i])	X	X		X		X		X
Hemoglobin genotype [j]		X						
Fetal hemoglobin		X						
Coagulation assessments [k]		X		X		X	X	X
Pregnancy test for WOCBP [i]	X	X		X		X	X	
Assessment of VOCs requiring admission [l]		X	X	X	X	X	X	
Randomization		X						
Study drug infusion		X						
CGI-C				X		X		
PGI-C				X		X		
ASCQ-Me [m]		←	- - - X - - -	- - - - -	- - - X - - -	→		
PK, ADA, PD, and biomarker sampling – Refer to the Schedule of Assessments in Appendix 2 and Appendix 3								
Adverse events	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X

Abbreviations: ADA, anti-drug antibody; aPTT, activated partial thromboplastin time; ASCQ-Me, Adult Sickle Cell Quality of Life Measurement; CBC, complete blood count; CGI-C, clinician's global impression of change; EOS, end of study; ET, early termination; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein, HIV, human immunodeficiency virus; LDL, low-density lipoprotein; OLE, open-label extension; PD, pharmacodynamics; PGI-C, patient's global impression of change; PK, pharmacokinetics; PT, prothrombin time; VOC, vaso-occlusive crisis.
Note: At the Baseline (Day 1) Visit, study assessments are to be collected pre-dose unless otherwise specified.

Footnotes to Appendix 1: Schedule of Assessments

[a] Screening may be performed during the participant's index VOC admission. Laboratory assessments completed within 7 days prior to screening the participant for the study may be used as the screening assessment. Laboratory assessments done > 7 days prior to screening, must be repeated during screening.

[b] Vital signs and physical exam will be conducted prior to study drug infusion regardless of time from last assessment.

[c] For participants electing to enroll in the OLE study, the Day 91 visit will be the EOS Visit. For participants not enrolling in the OLE study, an additional required visit will occur on Day 161 for safety and PK/ADA/PD follow-up.

[d] The Day 161 visit will be for participants who do not enroll in the open-label extension study. At this visit, safety and efficacy assessments and samples for PK, ADA, PD, and biomarkers will be collected.

[e] Vital signs (blood pressure, heart rate, body temperature) will be measured after a participant has rested for at least 5 minutes in the supine or recumbent position, as age appropriate and feasible. At the Baseline Visit (Day 1) vital signs will be collected prior to the Baseline blood collection and prior to study drug administration. Vital signs will also be collected at the completion of infusion and at one hour after completion of infusion. Participants should be clinically well with stable vital signs and without signs or symptoms of an infusion-related reaction prior to release from observation. A repeated measurement of any of the vital sign parameters will be taken within 5 minutes if the first reading is outside the normal range and deemed clinically significant.

[f] Chest X-ray is required for all suspected cases of acute chest syndrome (ACS).

[g] Hematology assessments conducted during Screening may be done by the local laboratory and must include at least a CBC with total and differential leukocyte count, platelet count, and hemoglobin, a chemistry panel with creatinine, and a serum pregnancy test to assess participant eligibility. Laboratory assessments conducted during the index VOC admission that are obtained within 7 days prior to screening may be used for Screening assessments if done as part of standard medical care. Hematology assessments for the Baseline (Day 1) and subsequent visits include the following: hemoglobin, hematocrit, white blood cells with differential, red blood cells, % and absolute reticulocytes, and platelets. An iron panel will also be performed (iron, ferritin, total iron binding capacity [TIBC]).

[h] Chemistry assessments conducted during Screening may be done by the local laboratory and must include at least a chemistry panel with creatinine to assess participant eligibility. Laboratory assessments conducted during the index VOC admission that are obtained within 7 days prior to screening may be used for Screening assessments if done as part of standard medical care. Chemistry assessments for the Baseline (Day 1) and subsequent visits include the following: blood urea nitrogen, bilirubin (total, direct and indirect), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, serum albumin, sodium, potassium, magnesium, calcium, chloride, glucose, bicarbonate, creatinine kinase, serum creatinine, total protein, total globulin, IgG, lactate dehydrogenase, cystatin C, C-reactive protein (CRP), high sensitivity-reactive protein (hs-CRP), and lipid panel (total cholesterol, HDL, LDL, triglycerides).

[i] Pregnancy tests will be performed on women of childbearing potential (WOCBP). A serum test will be conducted at screening and a urine test at subsequent visits. A positive urine pregnancy test at any time during the study requires confirmation via a serum pregnancy test. Female participants will not be considered of childbearing potential if they are pre-menarchal, surgically sterile (hysterectomy, bilateral salpingectomy, tubal ligation, or bilateral oophorectomy) or postmenopausal (no menses for 12 months without an alternative medical cause, confirmed by follicle-stimulating hormone test results at the Baseline, [Day 1] Visit).

[j] Hemoglobin genotyping will be performed if the genotype is unknown.

[k] Coagulation parameters are PT, aPTT, D-dimer, von Willebrand factor (vWF), fibrinogen, thrombin-antithrombin complex (TAT), and tissue factor (TF), as feasible.

[l] The incidence of VOC events requiring parenteral pain medication will be recorded by the participant weekly. On non-visit days (Day 31 ±7 days and Day 61 ±7 days) participants will be contacted by phone to determine if a VOC event requiring parenteral pain medication was recorded by the participant, but not reported within 48 hours to the site. In addition, adverse events (AEs) and changes to concomitant medications will be collected.

[m] Participants will complete the ASCQ-Me questionnaire weekly, when available in local language. Clinical sites will contact the participant on Day 31 ±7 days and Day 61 ±7 days to collect the ASCQ-Me results recorded by the participant. The ASCQ-Me will be collected during the participant's visits to the clinical site at Day 46 and Day 91.

[n] When a participant is treated with parenteral pain medication for a VOC, per the primary endpoint definition, samples will be obtained, if feasible.

APPENDIX 2. SCHEDULE OF ASSESSMENTS FOR INCLACUMAB PK, ADA, AND PD SAMPLING

Timepoint	Time Window	Inclacumab PK	Inclacumab ADA	CCI		
		Plasma	Plasma	Serum	Whole Blood	Plasma
Day 1 Pre-dose	-30 min	X	X	X	X	X
Day 1 EOI	+5 min	X		X	X	X
Day 1 EOI + 45 min	± 15 min	X		X	X	X
Day 46	± 15 days	X		X	X	X
Day 91	± 7 days	X	X	X	X	X
Day 161[a]	± 7 days	X	X	X	X	X
Upon Presentation for a VOC [b]		X			X	X

Abbreviations: ADA, anti-drug antibody; EOI, end of infusion; PD, pharmacodynamic; PK, pharmacokinetic; CCI [redacted]; VOC, vaso-occlusive crisis.

[a] The Day 161 visit will be for participants who choose not to enroll, or are ineligible for, the open-label extension study.

[b] Sample will be obtained from participant during VOC requiring parenteral pain medication, if feasible.

APPENDIX 3. SCHEDULE OF ASSESSMENTS FOR BIOMARKERS

Timepoint	Time Window	CCI			
		Whole blood	Whole blood	Serum	Plasma and Whole Blood
Day 1 pre-dose	-30 min	X	X	X	X
Day 1 EOI + 45 min	±15 min	X			
Day 46	±15 days	X			
Day 91	±7 days	X	X	X	X
Day 161 [d]	±7 days			X	
Upon presentation for VOC [e]				X	

Abbreviations: EOI, end of infusion; CCI ; VOC, vaso-occlusive crisis.

CCI

[d] Day 161 visit will be for participants that choose not to enroll, or are ineligible for, the open-label extension study.
[e] As feasible.

APPENDIX 4. INFUSION-RELATED REACTION GRADING

The severity of infusion-related reactions (IRRs) will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0 per Table 4, below. The CTCAE quick reference guide can be found at the Cancer Therapy Evaluation Program CTCAE website (CTCAE Website).

Table 4: Infusion-related Reactions

Grade 1	Mild transient reaction; infusion interruption not indicated; intervention not indicated
Grade 2	Therapy of infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours
Grade 3	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement hospitalization indicated for clinical sequelae
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death