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CLINICAL STUDY PROTOCOL

Study Number	**GBT2104-133** (C5361003)
Study Title	**An Open-label Extension Study to Evaluate the Long-term Safety of Inclacumab Administered to Participants with Sickle Cell Disease Who Have Participated in an Inclacumab Clinical Trial**
Investigational Product	Inclacumab
IND Number	144073
EudraCT Number	2020-005289-32
Sponsor Legal Address	Global Blood Therapeutics, Inc., a wholly owned subsidiary of Pfizer, Inc. 181 Oyster Point Blvd, South San Francisco, CA 94080 United States of America
Original Protocol **Amendment 1.0** **Amendment 2.0** **Amendment 3.0**	30 March 2021, Version 1.0 11 April 2022, Version 2.0 30 January 2023, Version 3.0 13 July 2023, Version 4.0

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.

SUMMARY OF CHANGES

Amendment 3 (13 July 2023)

Overall Rationale for the Amendment:

To align the protocol with some sections of the Pfizer Protocol Template and Standard Operating Procedures

Protocol Amendment Summary of Changes Table

Section	Change	Brief Rationale	Substantial (Y/N)
Statement of Approval and Compliance	Removed	To align with Pfizer Protocol Template following the acquisition of GBT by Pfizer The information will be captured in a separate document.	N
Cover page Synopsis Sections: • 1.3 (Rationale for Inclacumab in SCD) • 3.1 (Study Design) • 7.2.3 (Abnormal Laboratory Values) • 7.3 (Adverse Events of Special Interest, Serious Adverse Events, Serious Adverse Drug Reactions, and Requirements for Immediate Reporting) • 7.4 (Reporting and Treatment of Overdose) - *new section* • 7.6 (Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure) - *new section* • 7.7 (Medication Errors) • 9.4 (Sponsor's Medically Qualified Individual) - *new section* • 9.5.1 (Regulatory and Ethical Considerations)	Added or revised language	To align with Pfizer Protocol Template following the acquisition of GBT by Pfizer	Y

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Section	Change	Brief Rationale	Substantial (Y/N)
• 9.5.2 (Reporting of Safety Issues and Serious Breach of the Protocol or ICH GCP) • 9.5.3(Informed Consent/Assent Process) • 9.5.4 (Data Protection) - *new section* • 9.5.7 (Dissemination of Clinical Study Data) - *new section* • 9.5.8 (Data Quality Assurance) - *new section* • 9.5.9 (Study and Site Start and Closure) - *new section* • 9.7 (Publication Policy)			
Synopsis Sections: • 3.1 (Study Design) • 3.3.1.2 (Exclusion Criteria) • 3.3.2.1.1 (Discontinuation of Individual Participants) • 3.4 (Study Duration) • 5.2 (Pregnancy Screen) • 5.3 (SARS-CoV-2 Infection) • 6.1.2 (Prohibited Medications and Therapies) • 7.2.1 (General – Adverse Events Reporting) Appendices (*new*): • 1 (Schedule of Assessments) • 4 (Liver Safety) • 5 (Country-Specific Amendments)	Integrated country-specific instructions and guidelines into the global protocol	To align with Pfizer Protocol Template following the acquisition of GBT by Pfizer	N

Amendment 2 (30 January 2023)

Overall Rationale for the Amendment:

To add a safety assessment (ECG) and an exploratory efficacy assessment (EQ-5D-5L) as well as a few corrections and clarifications

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Protocol Amendment Summary of Changes Table

Section	Change	Brief Rationale	Substantial (Y/N)
Synopsis Sections: • 3.2 (Study Outcome Measures) • 5.4.5 (Electrocardiograms) - *new section* • 7.2.4 (Electrocardiograms) - *new section* • 8.4.3 (Safety Analysis) Appendix 1 (Schedule of Assessments)	Added ECG assessment as an additional safety assessment	To enhance monitoring of subjects' safety	Y
Synopsis Sections 3.2 (Study Outcome Measures)	Revised data collection methodology for ASCQ-Me Pain Impact score assessment, as follows: ~~"Change from Baseline in the~~ cumulative score for the Adult Sickle Cell Quality of Life Measurement (ASCQ-Me) Pain Impact – Short Form over time through the first 48 weeks"	To correct an error and algin with the statistical analysis as the methodology was planned to be descriptive.	N
Synopsis Sections: • 3.2 (Study Outcome Measures) • 5.5.5 (Quality of Life Assessments) Appendix 1 (Schedule of Assessments)	Added EuroQol Health Questionnaire (EQ-5D-5L) as an additional tool for assessing HRQoL	EQ-5D-5L is the preferred tool for economic evaluation of patient-reported outcome by Health Technology Assessment authorities in many countries, such as the UK, where inclacumab is prescribed.	Y
Synopsis Sections: • 3.3.3 (Lost to Follow-up)	Specified that parent or legal guardian for participants ≤ 18 years of age should be the point of	Clarification	N

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Section	Change	Brief Rationale	Substantial (Y/N)
• 4.8 (Assessment of Treatment Compliance) • 5.5.1 (VOC Incidence) • 5.5.5 (Quality of Life Assessments) • 7 (Assessment of Safety) • 7.1.1 (Definition of Adverse Events) • 7.2.1 (General-Adverse Event Reporting) • 7.5 (Reporting Overdose) • 9.4.3 (Informed Consent/Assent) Appendix 1 (Schedule of Assessments)	contact for adolescent participants.		

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SYNOPSIS

Study Number:	GBT2104-133 (C5361003)
Study Title:	An Open-label Extension Study to Evaluate the Long-term Safety of Inclacumab Administered to Participants with Sickle Cell Disease Who Have Participated in an Inclacumab Clinical Trial
Investigational Product:	Inclacumab
Sponsor:	Global Blood Therapeutics, Inc., a wholly owned subsidiary of Pfizer, Inc. 181 Oyster Point Blvd. South San Francisco, CA 94080 United States of America
Number of Sites:	The study will be conducted at up to 80 clinical sites globally.
Number of Study Participants:	CCI [redacted] who have completed a prior inclacumab clinical trial will be enrolled.
Duration of Treatment:	Participants will be dosed every 12 weeks (Q12W) and may receive study drug if they continue to receive clinical benefit that outweighs risk, as determined by the Investigator, until the participant has access to inclacumab from an alternative source (eg, through commercialization or a managed-access program). Note: For Ghana-specific duration of treatment, refer to Appendix 5-2 in the body of the protocol.
Objective:	The primary objective of this study is to evaluate the long-term safety of Q12W dosing of inclacumab in participants with sickle cell disease (SCD) who have completed a prior inclacumab clinical trial. Additional objectives are to evaluate the incidence of vaso-occlusive crises (VOCs), hospitalizations, missed work/school days, red blood cell (RBC) transfusions, and quality of life (QOL) with long-term use of inclacumab.
Outcome Measures:	Safety will be evaluated through collection of the following: • Incidence of treatment-emergent adverse events (TEAEs), • Change from Baseline in laboratory (hemaotology, chemistry, and coagulation), vital signs, and physical examination assessments; • Change from Baseline in electrocardiogram (ECG) parameters (ie, QT/QTc interval). In addition to the safety assessments, the following outcome measures will be determined: • Annualized rate of VOCs. A VOC is defined as an acute episode of pain that: o Has no medically determined cause other than a vaso-occlusive event, and

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	○ 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. Complicated VOCs of acute chest syndrome (ACS), hepatic sequestration, splenic sequestration, and priapism, that meet the requirements listed above will be included. • Annualized rate of VOCs that require admission to a healthcare facility and treatment with parenteral pain medication where an 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. • Annualized number of days of inpatient hospitalization for a VOC. • Annualized rate of all SCD-related urgent care visits to the clinic, emergency room, and hospital. • Proportion of total days missed from school or work due to SCD pain symptoms for the first 48 weeks. • Annualized rate of complicated VOCs. • Annualized rate of RBC transfusions. • Annualized rate of inpatient hospital admissions for any reason. • Annualized number of days of inpatient hospitalization for any reason. • Proportion of participants rated as "very much improved" or "much improved" based on the Patient's Global Impression of Change (PGI-C) Q12W through Week 96. • Proportion of participants rated as "very much improved" or "much improved" based on the Clinician's Global Impression of Change (CGI-C) Q12W through Week 96. • Cumulative score for the Adult Sickle Cell Quality of Life Measurement (ASCQ-Me) Pain Impact – Short Form over time through the first 48 weeks. • Health-related quality of life (HRQoL) as assessed by the EuroQol Health Questionnaire (EQ-5D-5L) Q12W through Week 96. Pharmacology measures through Week 48 in a CCI [redacted] CCI [redacted] will include: • Plasma pharmacokinetic (PK) of inclacumab as assessed by population PK analysis using nonlinear mixed-effects modeling.

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	• Incidence of anti-drug antibodies (ADA) to inclacumab. • Pharmacodynamics including changes in CCI [redacted] Note: The pharmacology substudy will not be performed at sites located in Egypt.
Study Design:	This study is a multicenter, global, open-label extension, study to assess the safety of long-term use of inclacumab in participants with SCD. The incidence of VOCs, hospitalizations, days missed from school/work, RBC transfusions, and QOL assessments will also be collected. The study will include participants with SCD who have completed a prior GBT sponsored inclacumab clinical study (originating study) and meet eligibility criteria. CCI [redacted] All participants will receive inclacumab CCI [redacted] Q12W. Note: For Germany- and Ghana-specific study design, refer to Appendix 5-1 and Appendix 5-2, respectively, in the body of the protocol.
Investigational Product, Dose & Mode of Administration:	Inclacumab drug product is a sterile, CCI [redacted] for infusion with an approximate CCI [redacted] provided in colorless, CCI [redacted] Each vial contains CCI [redacted] mg of inclacumab and the following CCI [redacted] An inclacumab dose of [redacted] Participants will be monitored throughout the infusion and for at least 60 minutes after completion of study drug infusion for adverse reactions.
Eligibility Criteria	Eligibility will be based on assessments performed prior to receiving study drug on Day 1 in this study. A participant will be considered enrolled after signing of the informed consent form and/or assent form for this study. Informed consent/assent must be properly executed prior to the performance of any protocol-required assessment or procedure. <u>Inclusion Criteria</u> Participants who meet all the following criteria will be eligible for study enrollment: 1. Male or female participant with SCD who participated and received study drug in a GBT-Sponsored inclacumab clinical study. 2. Participant has completed the originating inclacumab study within 30 days prior to the Day 1 Visit. Participants who discontinued study drug in the originating study due to a non-study drug-related adverse event (AE), but who remained on study, may be eligible for treatment in this study provided the AE does not pose a risk for treatment with inclacumab. 3. Female participants of childbearing potential are required to have a negative urine pregnancy test (UPT) prior to dosing on Day 1.

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	Note: Female participants who become childbearing during the study must be willing to have a negative UPT to remain in the study. 4. If sexually active, female participants of childbearing potential must use highly effective methods of contraception until 165 days after the last dose of study drug. If sexually active, male participants must use barrier methods of contraception until 165 days after the last dose of study drug. 5. Participant has provided written informed consent/assent. For underage participants (ie, ≤ 18 years of age), both the consent of the participant's legal representative or legal guardian and the participant's assent (where applicable) must be obtained based on local requirement. <u>Exclusion Criteria</u> Participants meeting any of the following exclusion criteria will not be eligible for study enrollment: 1. Female participant who is breastfeeding or pregnant. 2. Participant had an infusion-related reaction (IRR) in the originating inclacumab clinical study. Note: For UK-specific criterion, refer to Appendix 5-3 in the body of the protocol. 3. Participant withdrew consent from the originating inclacumab clinical study. 4. Participant was lost to follow-up from the originating inclacumab clinical study. 5. Participant has any other medical, psychological, safety, or behavioral conditions that, in the opinion of the Investigator, may confound safety interpretation, interfere with compliance, or preclude informed consent.
Study Procedures:	The Schedule of Assessments is provided in Appendix 1. Eligible participants will receive open-label inclacumab on Day 1. It is intended that Day 1 coincides with the final visit from the originating inclacumab study. End of Study assessments from the originating study will serve as Baseline assessments for this study. If Day 1 does not occur on the same day, the Day 1 Visit must occur within 30 calendar days of completion of the originating study. If Day 1 for this study is greater than 7 days from the completion of the originating study, new Baseline assessments will be obtained. Participants will return to the clinical site 6 weeks after administration of the first inclacumab dose for safety assessments. They will then return Q12W after the Day 1 dose administration for inclacumab administration, safety assessments, and collection of VOC events. Collection of QOL assessments and days missed from school/work will be collected at these visits. The study will continue with Q12W visits for dosing if participants continue to receive clinical benefit that outweighs risk, as determined by the Investigator, until the participant has access to inclacumab from an alternative source (eg, through commercialization or a managed-access program).

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	Note: For Ghana- and UK-specific procedures, refer to Appendix 5-2 and Appendix 5-3, respectively, in the body of the protocol.
Statistical Methods:	Analyses will be based on all enrolled participants receiving treatment with study drug (inclacumab) in this open-label extension study. Analyses may be presented with participants grouped according to originating study enrollment and/or treatment received in originating study, as appropriate. 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 (AESIs), serious adverse events (SAEs), and deaths will be generated. Changes from Baseline in laboratory parameters (hematology, serum chemistry, and coagulation), ECG parameters, and vital signs (blood pressure, heart rate, and body temperature) over time will be summarized descriptively. Changes from the originating study Baseline may also be considered, as appropriate. The additional study outcome measures (as specified in the Study Outcome Measures section) will be summarized descriptively. Differences in outcome measures between participants randomized to inclacumab versus placebo in the originating GBT-Sponsored inclacumab study may be evaluated.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACS	acute chest syndrome
ADA	anti-drug antibodies
ADCC	antibody-dependent cellular cytotoxicity
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ASCQ-Me	Adult Sickle-cell Quality of Life Measurement
ALT	alanine transaminase
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
BP	blood pressure
CFR	Code of Federal Regulations
CGI-C	Clinician's Global Impression of Change
CCI	[redacted]
CBC	complete blood count
CIOMS	Council for International Organizations of Medical Sciences
COVID-19	coronavirus disease 2019
CRO	clinical contract research organization
CSR	clinical study report
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trials Information System
DCT	data collection tool
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
EC	Ethics Committee
ECC	emergency contact card
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDC	electronic data capture

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Abbreviation	Definition
EDP	exposure during pregnancy
EOS	end of study
EPO	erythropoietin
ESA	erythropoiesis-stimulating agent
EU	European Union
Eudra	European Union Drug Regulating Authorities Clinical Trials Database
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GBT	Global Blood Therapeutics Inc
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HC	hydrocarbamide
HR	heart rate
HRQoL	Health-related quality of life
HSCT	hematopoietic stem cell transplantation
HU	hydroxyurea
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identifier
IgG	immunoglobulin G
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MQI	Medically Qualified Individual
NCI	National Cancer Institute
NSAID	non-steroidal anti-inflammatory drug
PD	pharmacodynamics

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Abbreviation	Definition
PGI-C	Patient's Global Impression of Change
PK	pharmacokinetics
CCI [redacted]	
PNH	paroxysmal nocturnal hemoglobinuria
PSGL-1	P-selectin glycoprotein ligand-1
PT	prothrombin time
Q12W	every 12 weeks
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
SRSD	Single Reference Safety Document
CCI [redacted]	
sRBC	sickled red blood cells
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TIBC	total iron binding capacity
CCI [redacted]	
ULN	upper limit of normal
UPT	urine pregnancy test
UK	United Kingdom
US	United States
WHO	World Health Organization
WOCBP	women of child-bearing potential
VOC	vaso-occlusive crisis

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1. INTRODUCTION

1.1. Sickle Cell Disease

Sickle cell disease (SCD) is an autosomal recessive disease 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 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 (PLTs) 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 patients with SCD.

Results from a randomized, placebo-controlled Phase 2b trial of crizanlizumab, a humanized monoclonal antibody, in SCD supports 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 VOCs in Sickle Cell Anemia

Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative therapy for SCD. Hematopoietic stem cell transplantation 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-income 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 (Niihara, 2018; Ataga, 2017; Charache, 1995). However, the effectiveness of HU is impaired by low compliance rates and frequent treatment discontinuation (Shah, 2019).

L-glutamine provides a modest 25% reduction in annual VOC rates (Niihara, 2018).

Crizanlizumab 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. Medication adherence is essential for quality care and medication non-adherence leads to poor health outcomes and increased healthcare costs, especially among patients with chronic conditions (Roebuck, 2011; Simpson, 2006; Osterberg, 2005). 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

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hematological diseases such as hemophilia and paroxysmal nocturnal hemoglobinuria (PNH) (Kaiser, 2020; Wells, 2019; Tkacz, 2015). Frequent intravenous (IV) infusions also extract a cost on patient and caregiver productivity because of the substantial time commitments required from both patients and their caregivers for the IV administration of treatment at infusion clinics. One recent study demonstrated that PNH patients on every 2-week IV infusion eculizumab had three times higher productivity losses compared to PNH patients on every 8-week IV infusion of 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 unpredictable exacerbations (Kaiser, 2020; Wells, 2019).

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.

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 PLTs. 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 leukocyte recruitment by PLTs or endothelial cells. The same mechanism is also responsible for abnormal adhesion of sRBCs 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, PLTs, sickled RBCs, and leukocytes, thereby preventing VOCs.

Nonclinical studies that have been conducted to characterize inclacumab include primary and secondary pharmacodynamics (PD), safety pharmacology, pharmacokinetics (PK), and toxicology. The nonclinical studies are described in detail in the inclacumab Investigator's Brochure (IB), which is the Single Reference Safety Document (SRSD) for this study.

1.3.1. Study Design Rationale

This study is an open-label study to evaluate the safety of long-term administration of inclacumab. Participants in this study will have completed a study of inclacumab (originating

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study) in which they will have received inclacumab or placebo in a double-blind fashion. This study will evaluate the first exposure to inclacumab in some participants. As such, the safety of initial exposure to inclacumab will also be evaluated in this study. All participants will receive CCI mg/kg open-label inclacumab every 12 weeks (Q12W). Given the long half-life of inclacumab at the dose to be evaluated in this study, the majority of participants are expected to maintain target concentrations throughout the study.

This study includes, as part of the definition of a VOC, allowance for telemedicine in addition to the requirement for a visit to a healthcare facility. Based on the changes in treatment practices that have occurred as a result of the coronavirus disease 2019 (COVID-19) pandemic, patients with SCD are less likely to visit a healthcare facility and are more frequently reaching out to their healthcare provider for pain medication changes/prescriptions (McFarling, 2020; Powell, 2020). Even though patients are not making as many visits to a healthcare facility for a VOC, the telemedicine visit nonetheless represents a VOC on the part of the patient that requires intervention by a healthcare practitioner. Use of a telemedicine-based health care interaction for evaluation and potential treatment of a VOC is therefore justified.

1.3.2. Rationale for Dose Regimen

In this study, an CCI dose of CCI mg/kg will be administered Q12W. More than 700 participants in prior studies (healthy volunteers or cardiovascular disease patients) have been exposed to inclacumab; a maximum tolerated dose was not identified in these studies. The CCI mg/kg, did not demonstrate any drug-related safety or tolerability signals in a Phase 1 study in healthy participants. Chronic IV dosing of CCI in a cohort of 142 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. Finally, P-selectin inhibition 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 CCI mg/kg of inclacumab was consistent with the safety profile of previous studies with CCI IV performed in healthy participants and individuals with cardiovascular disease (refer to the current version of the IB for details).

Inclacumab plasma concentrations above CCI µg/mL have been associated with maximal inhibition of ex vivo thrombin receptor activating peptide CCI CCI formation in healthy volunteers and patients with peripheral arterial disease from prior clinical studies. Chronic dosing to maintain inclacumab plasma concentrations above CCI µg/mL is expected to be required for maximal sustained benefit. Population PK simulations project that the inclacumab dose regimen of CCI mg/kg Q12W will maintain concentrations above CCI µg/mL throughout the study period in the majority of participants, thereby maximizing the pharmacology required for effective reduction of VOCs in the SCD population.

2. OBJECTIVES

The primary objective of this study is to evaluate the long-term safety of Q12W dosing of inclacumab in participants with SCD that have completed a prior inclacumab clinical trial.

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Additional objectives are to evaluate the incidence of VOCs, hospitalizations, missed work/school days, RBC transfusions, and quality of life (QOL) with long-term use of inclacumab.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This multicenter, global, open-label extension study is designed to assess the safety of long-term treatment with inclacumab in participants with SCD. The study will be conducted globally and will be available to eligible participants enrolled in a prior GBT-Sponsored inclacumab clinical study (originating study). Participants must have completed participation in their originating clinical study and must meet the entry criteria for this study to be eligible for enrollment (see Section 3.3). The study will be conducted at up to 80 global clinical sites, and CCI [redacted]

Eligible participants will receive inclacumab CCI [redacted] Q12W if they continue to receive clinical benefit that outweighs risk, as determined by the Investigator, until the participant has access to inclacumab from an alternative source (eg, through commercialization or a managed-access program).

All participants will undergo safety and outcome assessments at Baseline (Day 1), CCI [redacted] and Q12W thereafter. Visits to the clinical site for infusion of study drug will occur at Baseline (Day 1) and Q12W CCI [redacted]

A Data Monitoring Committee (DMC) will regularly review the totality of accumulated safety data from all ongoing inclacumab studies on an ongoing, unblinded basis with additional emphasis on adolescent participants. DMC review will continue until the originating studies have been completed and the randomization assignments are unblinded. Details are provided in the DMC Charter.

Note: For Germany-, Ghana-, and UK- specific study design, refer to Appendix 5-1, Appendix 5-2, and Appendix 5-3, respectively.

3.2. Study Outcome Measures

Safety will be evaluated through collection of the following:

- Incidence of treatment-emergent adverse events (TEAEs)
- Change from Baseline in laboratory assessments (hematology, chemistry, and coagulation)
- Physical examinations
- Electrocardiograms (ECG)
- Vital signs.

In addition to the safety assessments, the following outcome measures will be determined:

- Annualized rate of VOCs. A VOC is defined as an acute episode of pain that:
  - Has no medically determined cause other than a vaso-occlusive event, and

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  - 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.

  Complicated VOCs of acute chest syndrome (ACS), hepatic sequestration, splenic sequestration, and priapism (requiring a visit to a medical facility), that meet the requirements listed above will be included.

- Annualized rate of VOCs that require admission to a healthcare facility and treatment with parenteral pain medication where an 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.
- Annualized number of days of inpatient hospitalization for a VOC.
- Annualized rate of all SCD-related urgent care visits to the clinic, emergency room, and hospital.
- Proportion of total days missed from school/work due to SCD pain symptoms for the first 48 weeks.
- Annualized rate of complicated VOCs.
- Annualized rate of RBC transfusions.
- Annualized rate of inpatient hospital admissions for any reason.
- Annualized number of days of inpatient hospitalization for any reason.
- Proportion of participants rated as “very much improved” or “much improved” based on the Patient’s Global Impression of Change (PGI-C) Q12W through Week 96.
- Proportion of participants rated as “very much improved” or “much improved” based on the Clinician’s Global Impression of Change (CGI-C) Q12W through Week 96.
- Cumulative score for the Adult Sickle Cell Quality of Life Measurement (ASCQ-Me) Pain Impact – Short Form over time through the first 48 weeks.
- Health-related quality of life (HRQoL) as assessed by the EuroQol Health Questionnaire (EQ-5D-5L) Q12W through Week 96.

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Pharmacology measures through Week 48 in a CCI [redacted] that consent to these collections will include:

- Plasma PK of inclacumab as assessed by population PK analysis using nonlinear mixed-effects modeling.
- Incidence of anti-drug antibodies (ADA) to inclacumab.
- Pharmacodynamics including changes in CCI [redacted]

Note: The pharmacology substudy will not be performed at sites located in Egypt.

3.3. Selection of Study Population

A total of CCI [redacted] at approximately 80 global clinical sites will be enrolled in this study.

3.3.1. Eligibility

Eligibility will be based on assessments performed prior to receiving study drug on Day 1 in this study.

A participant will be considered enrolled after signing of the informed consent document (ICD) and/or the assent form for this study. Informed consent/assent must be properly executed prior to the performance of any protocol-required assessment or procedure.

3.3.1.1. Inclusion Criteria

Participants who meet all the following criteria will be eligible for study enrollment:

1. Male or female participant with SCD who participated and received study drug in a GBT-Sponsored inclacumab clinical study.
2. Participant has completed the originating inclacumab study within 30 calendar days of the Day 1 Visit. Participants who discontinued study drug in the originating study due to a non-study drug-related AE, but who remained on study, may be eligible for treatment in this study provided the AE does not pose a risk for treatment with inclacumab.
3. Female participants of childbearing potential are required to have a negative urine pregnancy test prior to dosing on Day 1.

   Note: Female participants who become of childbearing potential during the study must be willing to have a negative urine pregnancy test to remain in the study.
4. If sexually active, female participants of childbearing potential must consistently use highly effective methods of contraception consistently throughout the study and for at least 165 days after the last dose of study drug. If sexually active, male participants must use barrier methods of contraception until 165 days after the last dose of study drug.
5. Participant has provided written informed consent/assent. For underage participants (ie, ≤ 18 years of age), both the consent of the participant's legal representative or

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legal guardian and the participant's assent (where applicable) must be obtained based on local requirement.

3.3.1.2. Exclusion Criteria

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

1. Female participant who is breastfeeding or pregnant.
2. Participant had an infusion-related reaction (IRR) in the originating inclacumab clinical study.
   Note: For UK-specific exclusion criteria, refer to Appendix 5-3.
3. Participant withdrew consent from the originating inclacumab clinical study.
4. Participant was lost to follow-up from the originating inclacumab clinical study.
5. Participant has any other medical, psychological, safety, or behavioral conditions that, in the opinion of the Investigator, may confound safety interpretation, interfere with compliance, or preclude informed consent.

3.3.2. Study Discontinuation

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

In any instance of discontinuation of the study, the Sponsor will notify, in writing, the Investigators, regulatory authorities, and Institutional Review Boards (IRBs)/Ethics Committees (ECs) and will specify the reason(s) for termination.

3.3.2.1. Discontinuation of Individual Participants

3.3.2.1.1. Discontinuation of Study Treatment

Participants may be discontinued from study treatment 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. Study drug must be discontinued immediately. Report the pregnancy according to the instructions in Section 7.6.1.

The participant should return to the study site for an End of Study (EOS) Visit within 12 weeks (84 days + 7 days) of the last dose of study drug, as indicated in Appendix 1.

Note: For UK-specific guidelines, refer to Appendix 5-3.

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3.3.2.1.2. Withdrawal of Consent

Participants and/or their caregivers/legal representatives will be informed that they are free to discontinue treatment or 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 or whose caregiver/legal guardian requests withdrawal.

3.3.3. 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 (and/or their parent or legal guardian for participants ≤ 18 years of age) through a minimum of two telephone calls. If the participant (and/or their parent or legal guardian for participants ≤ 18 years of age) still cannot be contacted, the site will send a certified letter to the last known address of the participant (and/or their parent or legal guardian for participants ≤ 18 years of age). If no contact is made by the participant, the site will consider the participant (and/or their parent or legal guardian for participants ≤ 18 years of age) lost to follow-up. All follow-up attempts will be documented and kept with the participant's source documentation, and the applicable electronic case report forms (eCRFs) will be completed.

3.4. Study Duration

The study will continue until all participants are no longer participating in the study or until the Sponsor determines that the study should be discontinued due to safety or other reasons (Section 5.4.1). Participants may receive study drug if they continue to receive clinical benefit that outweighs risk, as determined by the Investigator, until the participant has access to inclacumab from an alternative source (eg, through commercialization or a managed-access program).

Note: For Ghana-specific study duration, refer to Appendix 5-2.

3.5. Treatments

All participants will receive inclacumab CCI [redacted] Q12W. All infusions of inclacumab will be administered at the study site.

4. STUDY DRUG INFORMATION

4.1. Description of Active Study Drug – Inclacumab

The inclacumab drug substance is CCI [redacted]

Inclacumab drug product is a sterile, CCI [redacted] for infusion with an approximate CCI [redacted] provided in colorless, CCI [redacted] Each vial contains CCI [redacted] mg of inclacumab and the following CCI [redacted] CCI [redacted]

The drug substance and drug product are manufactured in accordance with Good Manufacturing Practice (GMP).

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4.2. 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).

4.3. Storage and Handling

The inclacumab vials are to be stored at CCI [redacted] 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 CCI [redacted] that should be protected from light.

4.4. Instructions for Use and Administration

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

4.5. 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 IRR (see Section 7.3) or hypersensitivity reaction of Grade 3 or higher (Section 7.2.1 and Appendix 3) occurs during study drug administration, the infusion will be discontinued, and the participant should be treated for the reaction using best clinical practices as indicated. The participant will not receive further treatment with study drug but will continue on study until the EOS Visit. The exact time when the infusion was stopped must be recorded.

If a Grade 1 or Grade 2 (mild or moderate) IRR occurs, the study drug infusion should be temporarily interrupted at the discretion of the Investigator. Upon re-initiation of infusion, the infusion rate should be reduced, and the new infusion rate, as well as the stop and restart times for the infusion will be recorded. Specific instructions for re-initiation of infusion are provided in the Pharmacy Manual.

All IRRs will be recorded as adverse events of special interest (AESIs, Section 7.3) or SAEs (if serious criterion is met; Section 7.1.2). If study drug is permanently discontinued, the participant should continue on study to complete all safety, PK, and PD assessments through Week 96.

4.6. 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

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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).

4.7. Methods of Assigning Participants to Treatment Groups

4.7.1. Assignment of Participant Identification

A signed and dated informed consent or parental/guardian consent and participant assent, as appropriate, must be obtained before any study-specific tests may be performed.

Participants will be assigned a new, unique participant identifier (ID) for this study. 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. If a participant is ineligible per Section 3.3, they will not be re-screened.

All study visits are to be scheduled relative to the Day 1 Visit date on this study.

4.7.2. Blinding Procedures

This is an open-label, non-randomized study. Investigators, study site staff, the Sponsor's study staff, the Sponsor's clinical contract research organization (CRO), and study participants will know that participants are receiving inclacumab. However, Investigators, study site staff, the Sponsor's study staff, the Sponsor's clinical CRO, and study participants will remain blinded to the randomized treatment assignments, as applicable, from the originating GBT-Sponsored inclacumab study. During the study, access to participant treatment assignment from the originating study will be limited to DMC members and service providers supporting DMC reviews, including the independent Data Coordinating Center, until the database from the originating study is locked and primary endpoint analysis is complete.

If a need arises for unblinding of the originating GBT-Sponsored inclacumab study, the instruction for unblinding as outlined in the originating study protocol will be followed.

4.8. Assessment of Treatment Compliance

Drug disposition records will be maintained, specifying the amount of study drug dispensed to each participant (and/or their parent or legal guardian for participants ≤ 18 years of age) and the date of dispensation. This record will be available for Sponsor review at any time. Compliance will be determined by used/unused vial count.

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5. STUDY ASSESSMENTS

The Schedule of Assessments (Appendix 1) summarizes the clinical procedures to be performed. Collection of samples for PK, ADA, and PD assessments is summarized in Appendix 2. Additional evaluations/testing may be conducted as deemed necessary by the Investigator or designee and/or the Sponsor for reasons related to participant safety.

It is intended that Day 1 coincides with the final visit from the originating inclacumab study. End of Study assessments from the originating study will serve as Baseline assessments for this study. Baseline (Day 1) assessments will be performed prior to dosing. If any of the Day 1 assessments were performed on the same date or within 7 days following the last study visit in the originating GBT-Sponsored clinical study, they do not need to be repeated. If Day 1 for this study is greater than 7 days from the completion of the originating study, new Baseline assessments will be obtained. Enrollment must occur within 30 calendar days of the last study visit in the originating study.

Note: The pharmacology substudy will not be performed at sites located in Egypt.

5.1. Demographics and Baseline Characteristics

Demographic information and Baseline characteristics (including but not limited to sex, date of birth, race/ethnicity, height, weight, creatinine level, geographic location) will be recorded. Weight will be measured at each study drug administration visits and height will be collected every 6 months. Weight will be used for determination of study drug dosing.

5.2. Pregnancy Screen

Pregnancy tests will be performed on female participants of child-bearing potential as indicated in the Schedule of Assessments (Appendix 1). A urine pregnancy test will be conducted on Day 1. If the Day 1 urine test is positive, it should be confirmed per local standard of care (eg, ultrasound or serum pregnancy test) and dosing should be postponed until a negative result is confirmed; if positive, the participant will not be enrolled in this 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).

Note: For UK-specific guidelines, refer to Appendix 5-3.

5.3. 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 have their study drug discontinued or to be withdrawn from study.

Note: For UK-specific guidelines, refer to Appendix 5-3.

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5.4. Safety Assessments

5.4.1. 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. See Section 7 for details on definitions and requirements for AE collection and reporting.

5.4.2. Physical Examination

An abbreviated physical examination will be performed at each visit. An abbreviated physical examination includes general appearance; examination of eyes, skin, cardiovascular system, and respiratory system; abdominal examination; and a symptom-directed examination.

5.4.3. 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 times, if deemed necessary.

Heart rate and BP measurements will be performed after participants have been 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 visits where participants receive study drug, vital signs, and weight will be measured 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 IRR prior to release from observation.

When scheduled at the same time as a blood draw, vital signs will be performed prior to the blood collection.

5.4.4. 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.

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 may be repeated once at the discretion of the Investigator.

Laboratory safety testing is intended to be performed by a central laboratory. Exceptions may be made as necessary for local laboratory testing.

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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.

Note: For Egypt-specific guidelines, refer to Appendix 5-5.

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** • PT • Activated partial thromboplastin time	**Serum Chemistry** • Blood urea nitrogen • Bilirubin (total, direct, and indirect) • Alkaline phosphatase • Aspartate aminotransferase • Alanine aminotransferase • Albumin • Sodium • Potassium • Calcium • Chloride • Bicarbonate • Glucose • Creatine kinase • Creatinine • Lactate dehydrogenase • Total globulin • Total protein • Immunoglobulin G (IgG) • Cystatin C
Additional Tests • Urine pregnancy test (WOCBP only)	

PT, prothrombin time; WOCBP, women of child-bearing potential.

5.4.5. Electrocardiograms

At baseline and scheduled timepoints (Appendix 1), single ECG assessments will be performed with standard 12-lead ECG equipment according to standard procedures to determine the absolute and corrected QT interval. All ECGs will be performed after the subject has rested in a supine position for at least 5 minutes. Electrocardiogram must be collected prior to any blood sampling that falls at the same timepoint.

Electrocardiograms will be performed prior to (5 – 10 minutes) inclacumab infusion and approximately 1 hour (± 15 minutes) following the end of infusion at scheduled visits (ie, Baseline and Week 24 visits). If the participant discontinues the study prior to Week 24, the ECG will be collected at the EOS visit (Appendix 1).

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5.5. Additional Outcome Assessments

5.5.1. VOC Incidence

At each visit, participants (and/or their parent or legal guardian for participants ≤ 18 years of age) will be asked if a VOC event leading to contact with a healthcare provider over the prior 12 weeks has occurred. Information regarding treatments received and the location/duration of the contact will be collected to determine if the event met the protocol definition of a VOC as well as the protocol definition of a VOC that required admission to a healthcare facility or remote contact with a healthcare provider and treatment with parenteral pain medication or an increase in oral narcotics. Complicated VOCs of ACS, hepatic sequestration, splenic sequestration, and priapism, that meet the requirements listed above will be collected (see Section 3.2).

Participants (and/or their parent or legal guardian for participants ≤ 18 years of age) will be instructed to visit the clinical site for VOCs requiring a visit to a healthcare facility. However, in cases where visits to other healthcare facilities are required for treatment of participant's VOCs, (eg, emergency room, hospital, urgent care center, outpatient clinic or infusion center), participants (and/or their parent or legal guardian for participants ≤ 18 years of age) will be instructed to notify the clinical site within 48 hours when one of these visits occurs.

VOCs are categorized as:

Uncomplicated VOC: a VOC that is NOT classified as ACS, hepatic sequestration, splenic sequestration, or priapism.

Complicated VOCs:

- Acute chest syndrome, 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.

5.5.2. Hospitalizations and Visits to the Clinic and Emergency Room

Admission and discharge dates for all hospitalizations will be recorded. The reason for the hospitalization will also be recorded (VOC or other SCD-related urgent care visit).

In addition, all visits to the clinic or emergency room for a SCD-related urgent care visit will be recorded, including the admission and discharge date and time of each visit, as applicable.

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5.5.3. Days Missed From School or Work

Each week the participant will record the days and the reason for missed school/work over the past week for the first 48 weeks of the study. The clinical site will collect the participant recorded information at each visit and record it in the eCRF.

5.5.4. Red Blood Cell Transfusion

All RBC transfusions will be recorded in the eCRF.

5.5.5. Quality of Life Assessments

Participants (and/or their parent or legal guardian for participants ≤ 18 years of age) will be asked to provide responses to 3 QOL surveys (PGI-C, ASCQ-Me, and EQ-5D-5L). The PGI-C and EQ-5D-5L will be administered Q12W through Week 96. Participants (and/or their parent or legal guardian for participants ≤ 18 years of age) will complete the ASCQ-Me questionnaire weekly, when available, through the first 48 weeks of the study. Administration of the ASCQ-Me survey may occur over the phone with the clinic staff and will only be administered when available in local language.

Clinicians will also complete a QOL assessment (CGI-C) of their global impression of participant change in HRQoL Q12W through Week 96.

5.6. Pharmacology Substudy (PK, ADA, PD)

Samples collected for analysis of inclacumab PK, immunogenicity, or PD may additionally be used for further development and validation of the respective assay.

Note: In Egypt, samples for the determination of PK, PD, ADA, and biomarker endpoints will not be collected.

5.6.1. Pharmacokinetics

In the CCI [redacted] that consent to these collections, plasma samples will be collected CCI [redacted] Population PK analysis using nonlinear mixed effects modeling will be performed to characterize inclacumab PK in plasma. If the Day 1 predose collection was performed on the same day as the last study visit in the originating GBT-Sponsored clinical study, the predose sample does not need to be collected. If Day 1 for this study is on a different day than the completion of the originating study, CCI [redacted] per Appendix 2.

Note: For Germany-specific instructions, refer to Appendix 5-1.

5.6.2. Antidrug Antibodies

In the CCI [redacted] that consent to these collections, CCI [redacted]

Note: For Germany-specific instructions, refer to Appendix 5-1.

5.6.3. Pharmacodynamics

In the CCI [redacted] that consent to these collections, CCI [redacted]

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CCI [redacted]

Note: For Germany-specific instructions, refer to Appendix 5-1.

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/serious adverse events (SAEs) upon discontinuation or completion of the study, the Investigator must schedule post-study follow-up visits, as necessary. Refer to Section 7.9 for follow-up of AEs following study exit.

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. 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. Concomitant Medications

A concomitant medication is any drug or substance administered between the signing of the informed consent and the EOS Visit. All concomitant medications will be recorded in the appropriate eCRF.

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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 SCD will be allowed during the study.

Participants receiving HU, erythropoiesis-stimulating agents (ESAs; eg, erythropoietin [EPO]), L-glutamine, or voxelotor should maintain a stable dose throughout the study.

6.1.1. Prohibited Medications and Therapies

Treatment with the following is not allowed during the study:

- Treatment with crizanlizumab.
- A stem cell transplant.
- Active treatment on another investigational trial, including gene therapy for SCD.

Note: For UK-specific guidelines, refer to Appendix 5-3.

6.2. 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 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.

6.3. Contraception Requirements

All female participants of childbearing potential (post-menarche and pre-menopausal) 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).

6.3.1. Instructions for Female Participants of Childbearing Potential

For female participants of childbearing potential who are sexually active, pregnancy should be avoided using a highly effective method of contraception (as outlined in Section 6.3.3) consistently throughout the study and for at least 165 days after last dose of study drug.

Female participants who become pregnant during the study will be withdrawn from the study. Pregnancy reporting requirements are outlined in Section 7.6.1.

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6.3.2. 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 6.3.3) if sexually active with a female partner of childbearing potential, throughout the study, and for at least 165 days after dosing.

6.3.3. 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 must be supplemented with a barrier method (preferably male condom):
  - 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.
- 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 of Childbearing Potential:

- 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).

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- Vasectomy at least 3 months prior to Day 1 with confirmation of azoospermia (verbal confirmation is acceptable).

Pregnancy reporting is described in Section 7.6.1.

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 and ECG 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, the study participant, participant's caregiver, (or their parent or legal guardian for participants ≤ 18 years of age) will be asked about any new or ongoing AE since the previous visit. Assessments of AEs will occur at each study visit. 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 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 (and/or their parent or legal guardian for participants ≤ 18 years of age) signs the ICD 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 section of the current IB or is not listed at the specificity or severity that has been observed.

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7.1.2. Definition of Serious Adverse Events

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

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or disability (substantial disruption of the ability to conduct normal life functions)
- A congenital anomaly/birth defect
- 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 AE 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:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

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

Table 2. Severity 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)

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

Severity	Description
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 (see seriousness criteria presented in Section 7.1.1).

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/SAEs will be recorded from the time the study participant (and/or their parent or legal guardian for participants ≤ 18 years of age) signs the ICD/assent form 6 months after last dose until the EOS Visit. All AEs/SAEs must be reported on the AE eCRF via the electronic data capture (EDC) system and reported to Pfizer Safety. The Investigator is responsible for evaluating all AEs/SAEs, obtaining supporting documents, and ensuring that documentation of the event is complete. Details of each reported AE/SAE must include at a minimum severity, relationship to study treatment, duration, and outcome. All (both serious

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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/SAE may be discontinued from study treatment at any time at the discretion of the Investigator. The Sponsor and the Study Medical Monitor must be notified of the study participant discontinuation.

Follow-up by the Investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the Investigator.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the Investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the Investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the eCRF and the SAE reported to Pfizer Safety. Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has completed the study, and they consider the event to be reasonably related to study intervention, the Investigator must promptly report the SAE to the Sponsor.

7.2.2. Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the AE 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”.

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

Note: Potential drug-induced liver injury (DILI; Hy's law) cases are to be reported as SAEs (Section 7.3). For suggested actions and follow-up assessments in the event of potential DILI, refer to Appendix 4.

7.2.4. Electrocardiograms

If at any time on study the QTc absolute value is > 500 ms per the site's ECG read, two additional ECGs must be performed within 30 minutes after the initial ECG.

If at any time, in the absence of confounding clinical factors, a single ECG shows a QTc with an absolute value > 500 ms or an increase in the QTc of at least 60 ms from Baseline, two additional ECGs must be performed within 30 minutes after the initial ECG, and the average of the three consecutive results for QTc will be used as the value assessed. If the average of the three QTc values is > 500 ms or increased > 60 ms from Baseline, the Study Medical Monitor should be contacted.

If the QTc prolongation is deemed possibly related to treatment with inclacumab, then the average QTc value will be included in the final QT analysis.

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

Any biologic agent given IV may have the potential to cause IRRs (refer to the current version of the IB for details). In this study, IRRs should be reported as AESIs. 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 SAEs, regardless of causal attribution, must be reported by the Investigator or designee or site personnel within 24 hours of SAE awareness. AESIs also must be reported within 24 hours of the site's awareness of the AESI, even if they do not meet criteria for an SAE. The AESI or SAE will be reported by completing the designated eCRF in EDC. In addition, an AESI that is also an SAE must be reported to Pfizer Safety.

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 ID 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.

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 per local laws and regulations. Fatal and life-threatening SUSARs will be

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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 and Treatment of 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 (and/or their parent or legal guardian for participants ≤ 18 years of age). 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.

In the event of an overdose, the Investigator or treating physician should:

- Contact the study Medical Monitor within 24 hours.
- Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.
- Obtain a blood sample for PK analysis if requested by the study medical monitor (determined on a case-by-case basis). Document both the date of the last dose of study intervention and the time of sample collection.
- Report to Sponsor Safety **only when associated with an SAE**.

7.5. Adverse Events That are VOC Events

VOC events that are listed in Table 3 **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.

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Table 3. VOC Events Not Requiring AE/SAE Reporting

Uncomplicated VOC*
ACS
Hepatic sequestration
Splenic sequestration
Priapism requiring a visit to a medical facility

Abbreviations: ACS, acute chest syndrome; AE, adverse event; NSAID, nonsteroidal anti-inflammatory drug; SAE, serious adverse event; VOC, vaso-occlusive crisis.
* 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 NSAIDs, or an increase in treatment with oral narcotics, but is NOT classified as an ACS, hepatic sequestration, splenic sequestration, or priapism.

7.5.1. Procedures for Reporting and Documenting VOC Event Data

All VOCs, as defined in Section 3.2, are to be documented within the eCRF. 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 and should continue until the EOS Visit. 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 5.5.1:
  - Uncomplicated VOCs
  - ACS
  - Hepatic sequestration
  - Splenic sequestration
  - Priapism (requiring a visit to a medical facility)
- Onset date,
- Resolution 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, infusion center, or telemedicine visit was required,
- 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 a SAE, then that event should be reported as a SAE. Any prolongation of a hospitalization due to a non-VOC event (even though the participant may

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have initially been hospitalized due to a VOC) is a reportable as a SAE in the eCRF and to Pfizer Safety within 24 hours.

7.6. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy (EDP), exposure during breastfeeding (EDB), and occupational exposure.

Any such exposures to study intervention under study are reportable to the Pfizer Safety within 24 hours of Investigator awareness.

7.6.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below is an example of environmental EDP:
    - A female family member of healthcare provider reports that she is pregnant after having been exposed to study intervention by all possible routes of exposure, eg, ingestion, inhalation, or skin contact.
    - A male family member or healthcare provider who has been exposed to study intervention by all possible routes of exposure, eg, ingestion, inhalation, or skin contact, then inseminates his female partner prior to or around the time of conception.

The Investigator must report EDP to the Pfizer Safety within 24 hours of the Investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below of information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner, the Investigator must report this information to the Pfizer Safety regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until at least 165 days after the last dose.
- If EDP occurs in the setting of environmental exposure, the Investigator must report information to the Pfizer Safety. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on

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the eCRF; however, a copy of the completed report is maintained in the Investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The Investigator will follow the pregnancy until completion (or until pregnancy termination) and notify the Sponsor or designee of the outcome as a follow-up to the initial report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criterial for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the Investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the Investigator assesses the infant death as related or possibly related to exposure to study intervention.

Additional information regarding the EDP may be requested by the Sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the Investigator will provide the participant with the Parental Partner: Information Sheet and Informed Consent Form to deliver to his partner. The Investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

7.6.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female nonparticipant is found to be breastfeeding while exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to study intervention by all possible routes of exposure, eg, ingestion, inhalation, or skin contact.

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The Investigator must report EDB to Pfizer Safety within 24 hours of the Investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the report form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on the eCRF. However, a copy of the completed report is maintained in the Investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

7.6.3. Occupational Exposure

The Investigator must report any instance of occupational exposure to the Sponsor or designee within 24 hours of the Investigator's awareness using the report form regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on the eCRF; however, a copy of the completed report is maintained in the Investigator site file.

7.6.4. Lack of Efficacy

The Investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

7.7. Medication Errors

Medication errors may result from the administration or consumption of study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors are recorded and reported as follows:

Table 4. Reporting of Medication Errors

Recorded on the Medication Page of the eCRF	Recorded on the Adverse Event Page of the eCRF	Reported to the Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Abbreviations: AE, adverse event; eCRF, electronic case report form; SAE, serious adverse event.

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of an incorrect dosage;
- The administration of expired study intervention;

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- The administration of an incorrect study intervention;
- The administration of study intervention that has undergone temperature excursion from the specified storage range unless it is determined by the Sponsor that the study drug under question is acceptable to use.

Whether or not the medication error is accompanied by an AE, as determined by the Investigator, such medication errors occurring to a study participant are recorded on the medication page of the eCRF, which is a specific version of the AE page, and, if applicable, any associated serious and nonserious AE(s) are recorded on the AE page of the eCRF.

In the event of a medication dosing error, the Sponsor should be notified within 24 hours.

Medication errors resulting in SAE should be reported to the Pfizer Safety within 24 hours via the eCRF.

7.8. Data Monitoring Committee

In addition to the Sponsor's pharmacovigilance oversight, an independent, unblinded DMC will oversee the safety of participants and overall study conduct for this study, with the support of an independent Data Coordinating Center. The DMC will review data from this study along with data from participants' originating studies until the originating studies are completed and unblinded for the primary endpoint analysis.

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

7.9. 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 IDs 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, if available.

New or updated information obtained during SAE follow-up should be recorded on the SAE eCRF.

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.

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7.10. Safety Responsibilities

7.10.1. 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.
- Report all SAEs to Pfizer Safety within 24 hours.
- 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 IDs 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/EC, as required by local law.

7.10.2. 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.

7.10.3. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool (DCT)

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT.
- If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours.

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- The site will enter the SAE data into the electronic DCT as soon as the data become available.

- After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the back-up method to transmit this information to Pfizer Safety in case the electronic DCT is unavailable for more than 24 hours.

- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the Investigator to complete and sign the CT SAE Report Form/ pages within the designated reporting time frames.

8. STATISTICAL METHODS

All statistical analyses conducted will be descriptive in nature; no formal statistical tests are planned.

8.1. Outcome Measures

Study outcome measures are provided in Section 3.2.

8.2. Determination of Sample Size

The sample size of CCI [redacted] is based on the combined sample sizes from the originating studies.

8.3. Analysis Populations

The primary analysis population for this study is the safety population, defined as all enrolled participants who received treatment with study drug in this study (inclacumab).

Analysis of other outcome measures will be based on the population of participants with at least one measurement for the analysis parameter.

Analyses may be presented with participants grouped based on originating study enrollment and/or treatment received in prior study, as appropriate.

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8.4. Statistical Analysis

8.4.1. Summaries of Study Conduct

The number of participants enrolled will be tabulated by originating study enrollment, geographic region, country, and study site. Participant disposition (the number of participants enrolled, treated, and completing the study) will be tabulated. Reasons for early study drug discontinuation and 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, sickle cell genotype, randomized treatment in prior study (inclacumab or placebo), concomitant HU/hydrocarbamide (HC) use, and geographic region will be summarized. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized. Exposure to study drug (number of study drug treatments) and time on study will also be summarized.

8.4.3. Safety Analyses

Safety will be assessed through descriptive summaries of AEs, laboratory test results, physical examinations, ECG parameters, 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 preexisting 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 from Baseline in laboratory parameters (hematology, serum chemistry, and coagulation) and vital signs (eg, BP, HR, and body temperature) over time will be summarized descriptively. Changes from the originating study Baseline may also be considered, as appropriate.

Changes from Baseline in ECG parameters will be summarized descriptively.

8.4.4. Analysis of Other Outcome Measures

The additional study outcome measures (as specified in Section 3.2) will be summarized descriptively.

CCI [redacted]

Differences in outcome measures between participants randomized to inclacumab versus placebo in the originating inclacumab study may be evaluated.

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Note: In Egypt, samples for the determination of PK, PD, ADA, and biomarker endpoints will not be collected.

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 direct 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 the context of the COVID-19 pandemic 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 a 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.

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- 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 FDA Form 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, on-site 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

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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. Sponsor's Medically Qualified Individual

The contact information for the sponsor's Medically Qualified Individual (MQI; ie, Medical Monitor) for the study is documented in the study contact list located in the Medical Monitor Card.

To facilitate access to their Investigator and the Sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an emergency contact card (ECC) at the time of informed consent. The ECC contains, at a minimum (a) protocol and study intervention identifiers, (b) participant's study identification number, and (c) site emergency phone number active 24 hours/day, 7 days per week.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their Investigator and site staff, and between the Investigator and Sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the Investigator or site staff related to the care of a participant.

9.5. Regulatory, Ethical, and Study Oversight Considerations

9.5.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the Investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

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Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

9.5.2. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the Investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, the Sponsor should be informed immediately.

In addition, the Investigator will inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the Investigator becomes aware of.

9.5.3. Informed Consent/Assent Process

9.5.3.1. Adult Participants

The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the participant (and/or their parent or legal guardian for participants ≤ 18 years of age) and answer all questions regarding the study. The participant (or their legally authorized representative) should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants (and/or their parent or legal guardian for participants ≤ 18 years of age [if allowed by local regulation]) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The Investigator must ensure that each participant (and/or their parent or legal guardian for participants ≤ 18 years of age) is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant (and/or their parent or legal guardian for participants ≤ 18 years of age) must be informed that their personal study-related data will be used by the Sponsor in accordance

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with local data protection law. The level of disclosure must also be explained to the participant (and/or their parent or legal guardian for participants ≤ 18 years of age).

The participant (and/or their parent or legal guardian for participants ≤ 18 years of age) must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The Investigator further must ensure that each study participant (and/or their parent or legal guardian for participants ≤ 18 years of age) is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participant (and/or their parent or legal guardian for participants ≤ 18 years of age) must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant (and/or their parent or legal guardian for participants ≤ 18 years of age). Participants who are rescreened are required to sign a new ICD.

Participants who are rescreened are required to sign a new ICD.

9.5.3.2. Pediatric Participants

The Investigator or their representative will explain the nature of the study to the participant and their parent(s)/legal guardian and answer all questions regarding the study. The participant and their parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the Investigator determines that a participant's decisional capacity is so limited they cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide his or her own assent, the source documents must record why the participant did not provide assent (for example, child is not of assenting age per local regulations or policies), how the Investigator determined that the person signing the consent was the participant's parent(s)/legal guardian, the consent signer's relationship to the study participant, and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If study participants are minors who reach the age of majority or if a child reaches the age of assent (per local IRB/IEC requirements) during the study, as recognized under local law, the child or adolescent must then provide the appropriate assent or consent to document their willingness to continue in the study. For an adolescent, who reaches the age of consent,

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parental consent would no longer be valid. If the enrollment of emancipated minors is permitted by the IRB/EC and local law, the participant must provide documentation of legal status to give consent without the permission of a legally authorized representative.

Participants and their parent(s)/legal guardian must be informed that their participation is voluntary. Participant's parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The Investigator must ensure that each study participant's parent(s)/legal guardian and the study participant as applicable are fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant's parent(s)/legal guardian must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant's parent(s)/legal guardian.

The participant's parent(s)/legal guardian must be informed that the participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The Investigator further must ensure that each study participant's parent(s)/legal guardian is fully informed about his or her right to access and correct his or her child's personal data and to withdraw consent for the processing of his or her child's personal data, keeping in mind the privacy rights that may restrict access of older adolescents' medical records by their parent(s)/legal guardian in certain regions.

The source documentation must include a statement that written informed consent and as applicable, assent, was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Parent(s)/legal guardian and the participant must be reconsented to the most current version of the ICD(s)/assent during their participation in the study.

A copy of the ICD(s) and assent, if written, must be provided to the parent(s)/legal guardian and the participant.

Participants who are rescreened are required to sign a new ICD.

9.5.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

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Participant's personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the Sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the Sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the Sponsor will protect the confidentiality of participant' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The Sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of Sponsor information or systems.

9.5.5. 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 ICD, 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.

9.5.6. 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.

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9.5.7. Dissemination of Clinical Study Data

The Sponsor fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulation. In addition, the Sponsor reports study results outside of the requirement of local laws/regulations pursuant to its standard operating procedures.

In all cases, study results are reported by the Sponsor in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

The Sponsor posts clinical trial results on www.clinicaltrials.gov for GBT/Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

The Sponsor posts clinical trial results on EudraCT/CTIS for GBT/Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

The Sponsor posts clinical study report (CSR) synopses and plain-language study results summaries on www.pfizer.com for GBT/Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

The Sponsor complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

The Sponsor provides researchers secure access to participant-level data or full CSRs for the purposes of “bona-fide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. The Sponsor will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not

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be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

9.5.8. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The Investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

Quality tolerance limits (QTLs) are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

The Investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and documents. This verification may also occur after study completion. It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time in devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan maintained and utilized by the Sponsor or designee.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the Sponsor. The Investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the Investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The Investigator(s) will notify the Sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the Investigator will cooperate with the Sponsor or its agents to prepare the Investigator site for the inspection and will allow the Sponsor or its agent, whenever feasible, to be present during the inspection. The

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Investigator site and Investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The Investigator will promptly provide copies of the inspection findings to the Sponsor or its agent. Before response submission to the regulatory authorities, the Investigator will provide the Sponsor or its agents with an opportunity to review and comment on responses to any such findings.

9.5.9. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time upon notification to the Sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the Sponsor may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the Investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

9.5.10. 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 ICD) 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.

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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

For multicenter trials, the primary publication will be a joint publication developed by the Investigator and the Sponsor reporting the primary endpoint(s) of the study covering all study sites. The Investigator agrees to refer to the primary publication in any subsequent publications. The Sponsor will not provide any financial compensation for the Investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The Investigator will provide the Sponsor an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to the Sponsor 30 days before submission. If any patent action is required to protect intellectual property rights, the Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from the Sponsor. This allows the Sponsor to protect proprietary information and to provide comments, and the Investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Sponsor-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the Investigator and the Sponsor will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The Investigator will disclose any relationship with the Sponsor and any relevant potential conflicts of interest, including any financial or personal relationship with the Sponsor, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

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Appendix 1. Schedule of Assessments

Note: For UK- and Egypt-specific instructions, refer to Appendix 5-3 and Appendix 5-5, respectively.

Study Day/Week	**Treatment Period**				**EOS + 7 Days** [b]
Procedure	**Baseline Day 1** [a]	**Week 6 ± 5 Days**	**Week 12 ± 5 Days**	**Q12W After Week 12 ± 10 Days**	
Informed consent/assent	X				
Review eligibility criteria	X				
Medication and medical history	X				
Weight and height [c]	X		X	X	
Abbreviated physical examination [d]	X	X	X	X	X
Vital signs [e]	X	X	X	X	X
Hematology	X	X	X	X	X
Serum chemistry	X	X	X	X	X
Coagulation	X	X	X	X	X
Urine pregnancy test [g]	X	X	X	X	X
Chest X-ray [h]	◄----------	----------	----------	----------►	
12-lead ECG (prior [5 – 10 min] to and 1 hour [± 15 min] after the end of inclacumab administration) [f]	X	~~X~~		X (Week 24 only)	
Inclacumab administration	X		X	X	
PGI-C [i]			X	X	
CGI-C [i]			X	X	
ASCQ-Me weekly at home by participant (and/or their parent or legal guardian for participants ≤ 18 years of age) [j]	X	X	X	X	
ASCQ-Me and missed school/work [j]	X	X	X	X	
HRQoL EQ-5D-5L [j]	X	X	X	X	
Assessments of VOCs [k]	◄----------	----------	----------	----------►	
Schedule for assessments for substudy of PK, ADA, and PD is provided in Appendix 2					
Adverse events	X	X	X	X	X
Concomitant medications	X	X	X	X	X

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Study Day/Week	Treatment Period				EOS + 7 Days [b]
Procedure	Baseline Day 1 [a]	Week 6 ± 5 Days	Week 12 ± 5 Days	Q12W After Week 12 ± 10 Days	

Abbreviations: ACS, acute chest syndrome; ADA, anti-drug antibodies; AE, adverse event; ASCQ-Me, Adult Sickle Cell Quality of Life Measurement; BP, blood pressure; CGI-C, Clinician's Global Impression of Change; ECG, electrocardiogram; EOS, end of study; HR, heart rate; HRQoL, health-related quality of life; IRR, infusion-related reaction; PD, pharmacodynamics; PGI-C, Patient's Global Impression of Change; PK, pharmacokinetics; Q12W, every 12 weeks; VOC, vaso-occlusive crisis.

a Day 1 assessments will be performed prior to dosing. If any of the Day 1 assessments were performed on the same date or within 7 days following the last study visit in the originating GBT-Sponsored clinical study, the tests do not need to be repeated. If Day 1 for this study is greater than 7 days from the completion of the originating study, new Baseline assessments will be obtained. Enrollment must occur within 30 calendar days of the last study visit in the originating study.

b The participant should return to the study site for an EOS visit within 12 weeks (84 days) of the last dose of study drug (+ 7-day window).

c Weight will be collected at each study drug administration visit and used for determination of dosing. Height will be collected every 6 months (Week 24 for first post-Baseline measurement).

d Abbreviated physical examination will include general appearance; examination of eyes, skin, cardiovascular system, and respiratory system; abdominal examination; and a symptom-directed examination.

e Vital signs (BP, HR, 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. On inclacumab administration days, vital signs will be collected prior to inclacumab administration, at the completion of infusion, and at 1 hour after completion of infusion. Participants should be clinically well with stable vital signs and without signs or symptoms of an IRR prior to release from observation. A repeat 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. When scheduled at the same time as a blood draw, vital signs will be performed prior to the blood collection.

f All 12-lead ECGs will be obtained after the participant has rested in a supine position for at least 5 minutes and prior to any blood sample collection that falls at the same timepoint. Additional ECG should be performed per guidelines in Section 7.2.4. If the participant discontinues the study prior to Week 24, the ECG will be collected at the EOS visit.

g Female participants of childbearing potential are required to have a negative urine pregnancy test within 7 days prior to dosing on Day 1. A urine pregnancy test will be performed for female participants of childbearing potential. If the urine pregnancy test is positive, the result must be confirmed per local standard of care (eg, ultrasound or serum pregnancy test). Participants with a confirmed positive test will be discontinued from 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).

h Chest X-ray required for all suspected cases of ACS.

i The PGI-C and CGI-C will be collected Q12W through Week 96.

j The participant (and/or their parent or legal guardian for participants ≤ 18 years of age) will complete the ASCQ-Me and HRQoL questionnaires, when available, and record days of missed school/work weekly. Questionnaires and days of missed school/work will be collected during the participant's visits to the clinical site through Week 48. Administration of questionnaires may occur over the phone with the clinic staff and will only be administered when available in local language.

k The incidence of VOC events will be collected at each visit. Participants (and/or their parent or legal guardian for participants ≤ 18 years of age) will be queried to determine if a VOC event leading to contact with a healthcare provider without a visit to a medical facility has occurred, to collect AEs, and record changes to concomitant medications.

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Appendix 2. Pharmacology Substudy Schedule of Assessments

Note: This Appendix is not applicable to sites in Egypt. For Germany-specific schedule, refer to Appendix 5-1.

Timepoint	Time Window	PK	ADA	CCI [redacted][a]	
		Plasma	Plasma	Serum	Whole Blood
Day 1 pre-dose	-30 min	X	X	X	X
Week CCI [redacted]	± 5 days	X			
Week [redacted] pre-dose	-30 min	X	X	X	X
Week CCI [redacted] pre-dose	-30 min	X		X	X
Week CCI [redacted] pre-dose	-30 min	X		X	X
Week CCI [redacted] pre-dose	-30 min	X	X	X	X

Abbreviations: ADA, anti-drug antibody; PK, pharmacokinetic; CCI [redacted]
CCI [redacted]
Note: Substudy will be conducted in the CCI [redacted] that consent to these collections.
a CCI [redacted]; also includes measurement of CCI [redacted]

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Appendix 3. 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 the table below. The CTCAE quick reference guide can be found at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

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

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Appendix 4. Liver Safety: Suggested Actions and Follow-Up Assessments and Study Drug Rechallenge Guidelines

This appendix is included to support Study transition to Pfizer Pharmacovigilance processes and systems.

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × the upper limit of normal (ULN) should be monitored more frequently to determine if they are "adaptors" or are "susceptible."

*For studies in which liver function tests (LFTs) are not required as a routine procedure, the following paragraph should be added as an introduction to the text below (delete this paragraph if LFTs are being monitored in this study):*Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an Investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

The following text MUST be included in ALL protocols, regardless of whether LFTs are monitored as part of scheduled safety assessments. Studies that include more detailed hepatic safety assessments (eg, an external hepatic expert panel or an E-DMC that has separate definitions and charter) will still need to follow the reporting guidelines described below for applicable cases.

In the majority of DILI cases, elevations in AST (aspartate transaminase) and/or ALT (alanine transaminase) precede total bilirubin elevations (> 2 × ULN) by several days or weeks. The increase in total bilirubin typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and total bilirubin values will be elevated within the same laboratory sample). In rare instances, by the time total bilirubin elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST or ALT in addition to total bilirubin that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and total bilirubin values within the normal range who subsequently present with AST/ALT values ≥ 3 × ULN AND a total bilirubin value ≥ 2 × ULN with no evidence of hemolysis and an alkaline phosphatase value < 2 × ULN or not available.

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- For participants with baseline AST **OR** ALT **OR** total bilirubin values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
  - Preexisting AST/ALT baseline values above the normal range: AST/ALT values ≥ 2 times the baseline values AND ≥ 3 × ULN; or ≥ 8 × ULN (whichever is smaller).
  - Preexisting values of total bilirubin above the normal range: total bilirubin level increased from baseline value by an amount of ≥ 1 × ULN **or** if the value reaches ≥ 3 × ULN (whichever is smaller).

Rises in AST/ALT and total bilirubin separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the Investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and total bilirubin for suspected Hy's law cases, additional laboratory tests should include albumin, creatine kinase, direct and indirect bilirubin, gamma-glutamyl transferase, PT/international normalized ratio (INR), eosinophils (%), and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, total bile acids, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and total bilirubin elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

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Appendix 5. Country-specific amendments

Appendix 5-1. Germany-Specific Amendment

3.1. Study Design

This multicenter, global, open-label extension study is designed to assess the safety of long-term treatment with inclacumab in participants with SCD. The study will be conducted globally and will be available to eligible participants enrolled in a prior GBT-Sponsored inclacumab clinical study (originating study). Participants must have completed participation in their originating clinical study and must meet the entry criteria for this study to be eligible for enrollment (see Section 3.3). The study will be conducted at up to 80 global clinical sites, and CCI [redacted] In Germany, only participants ≥ 18 years of age will be enrolled.

Eligible participants will receive inclacumab CCI [redacted] Q12W if they continue to receive clinical benefit that outweighs risk, as determined by the Investigator, until the participant has access to inclacumab from an alternative source (eg, through commercialization or a managed-access program).

All participants will undergo safety and outcome assessments at Baseline (Day 1), CCI [redacted] and Q12W thereafter. Visits to the clinical site for infusion of study drug will occur at Baseline (Day 1) and Q12W CCI [redacted]

A Data Monitoring Committee (DMC) will regularly review the totality of accumulated safety data from all ongoing inclacumab studies on an ongoing, unblinded basis with additional emphasis on adolescent participants. DMC review will continue until the originating studies have been completed and the randomization assignments are unblinded. Details are provided in the DMC Charter.

5.6.1. Pharmacokinetics

In the CCI [redacted] that consent to these collections, plasma samples will be collected CCI [redacted] Population PK analysis using nonlinear mixed effects modeling will be performed to characterize inclacumab PK in plasma. If the Day 1 predose collection was performed on the same day as the last study visit in the originating GBT-Sponsored clinical study, the predose sample does not need to be collected. If Day 1 for this study is on a different day than the completion of the originating study, CCI [redacted], per Appendix 2.

5.6.2. Anti-drug Antibodies

In the CCI [redacted] that consent to these collections, CCI [redacted]

5.6.3. Pharmacodynamics

In the CCI [redacted] that consent to these collections, CCI [redacted]

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CCI [redacted]

Appendix 2. Pharmacology Substudy Schedule of Assessments

Timepoint	Time Window	PK	ADA	CCI [redacted]	
		Plasma	Plasma	Serum	Whole Blood
Day 1 pre-dose	-30 min	X	X	X	X
Week CCI [redacted]	±5 days	X			
Week [redacted] pre-dose	-30 min	X	X	X	X
Week CCI pre-dose	-30 min	X		X	X
Week CCI pre-dose	-30 min	X		X	X
Week CCI pre-dose	-30 min	X	X	X	X

Abbreviations: ADA, anti-drug antibody; PK, pharmacokinetic; CCI [redacted]
Note: Substudy will be conducted in the CCI [redacted] that consent to these collections.
a CCI [redacted] also includes measurement of CCI [redacted]

Appendix 5-2. Ghana-Specific Amendment

3.1. Study Design

This multicenter, global multicenter, global, open-label extension study is designed to assess the safety of long-term treatment with inclacumab in participants with SCD. The study will be conducted globally and will be available to eligible participants enrolled in a prior GBT-Sponsored inclacumab clinical study (originating study). Participants must have completed participation in their originating clinical study and must meet the entry criteria for this study to be eligible for enrollment (see Section 3.3). The study will be conducted at up to 150 global clinical sites, and CCI [redacted]

Eligible participants will receive inclacumab CCI [redacted] Q12W if they continue to receive clinical benefit that outweighs risk, as determined by the Investigator for up to 5 years or until the participant has access to inclacumab from an alternative source (eg, through commercialization or a managed-access program, or whichever comes earlier).

All participants will undergo safety and outcome assessments at Baseline (Day 1), CCI [redacted] and every 12 weeks thereafter. Visits to the clinical site for infusion of study drug will occur at Baseline (Day 1) and every 12 weeks CCI [redacted].

A Data Monitoring Committee (DMC) will regularly review the totality of accumulated safety data from all ongoing inclacumab studies on an ongoing, unblinded basis with

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additional emphasis on adolescent participants. DMC review will continue until the originating studies have been completed and the randomization assignments are unblinded. Details will be provided in the DMC Charter.

3.4. Study Duration

The study will continue until all participants are no longer participating in the study or until the Sponsor determines that the study should be discontinued due to safety or other reasons (Section 5.4.1). Participants may receive study drug if they continue to receive clinical benefit that outweighs risk, as determined by the Investigator for up to 5 years or until the participant has access to inclacumab from an alternative source (eg, through commercialization or a managed-access program, or whichever comes earlier).

Appendix 5-3. UK-Specific Amendment

3.1. Study Design

This multicenter, global, open-label extension study is designed to assess the safety of long-term treatment with inclacumab in participants with SCD. The study will be conducted globally and will be available to eligible participants enrolled in a prior GBT-Sponsored inclacumab clinical study (originating study). Participants must have completed participation in their originating clinical study and must meet the entry criteria for this study to be eligible for enrollment (see Section 3.3). The study will be conducted at up to 150 global clinical sites, and CCI

Eligible participants will receive inclacumab CCI Q12W if they continue to receive clinical benefit that outweighs risk, as determined by the Investigator, until the participant has access to inclacumab from an alternative source (eg, through commercialization or a managed-access program).

All participants will undergo safety and outcome assessments at Baseline (Day 1), CCI , and every 12 weeks thereafter. Visits to the clinical site for infusion of study drug will occur at Baseline (Day 1) and every 12 weeks CCI . WOCBP will be contacted monthly to assess the outcome of a monthly urine pregnancy test (UPT).

A Data Monitoring Committee (DMC) will regularly review the totality of accumulated safety data from all ongoing inclacumab studies on an ongoing, unblinded basis with additional emphasis on adolescent participants. DMC review will continue until the originating studies have been completed and the randomization assignments are unblinded. Details will be provided in the DMC Charter.

3.3.1.2. Exclusion Criteria

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

1. Female participant who is breastfeeding or pregnant.
2. Participant had an infusion-related reaction (IRR) in the originating inclacumab clinical study, or the participant discontinued treatment due to Investigational Medicinal Product (IMP)-related toxicity, worsening of disease, or disease

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progression that required initiation of standard of care treatment prohibited in the originating study.

3. Participant withdrew consent from the originating inclacumab clinical study.
4. Participant was lost to follow-up from the originating inclacumab clinical study.
5. Participant has any medical, psychological, safety, or behavioral conditions that, in the opinion of the Investigator, may confound safety interpretation, interfere with compliance, or preclude informed consent.

3.3.2.1.1. Discontinuation of Study Treatment

Participants may be discontinued from study treatment for any of the following reasons:

- Participant is lost to follow-up
- AE(s)
- Discretion of the Investigator
- In case of worsening of disease or disease progression, if the Investigator considers it is in the best interest of the participant to initiate any standard of care treatment prohibited in Section 6.1.1.
- Discretion of the Sponsor
- Pregnancy

The participant should return to the study site for an End of Study (EOS) Visit 15 weeks (105 days +7 days) after the last dose of study drug, as indicated in Appendix 1 (A).

4.5. Management of Infusion-Related Reactions

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, see Section 7.3) or hypersensitivity reaction of Grade 3 or higher (Section 7.2.1 and Appendix 3 [Appendix C]) occurs during study drug administration, the infusion will be discontinued, and the participant should be treated for the reaction using best clinical practices as indicated. The participant will not be eligible to receive further treatment with study drug (as study drug would be permanently discontinued); however, the participant will continue on study until the EOS/early termination (ET) Visit. The exact date and time of when the infusion was stopped must be recorded.

If a Grade 1 or Grade 2 (mild or moderate) IRR occurs, the study drug infusion may be temporarily interrupted at the discretion of the Investigator. Upon re-initiation of infusion, the infusion rate should be reduced, and the new rate, as well as the stop and re-start times for the infusion will be recorded. Specific instructions for re-initiation of infusion are provided in the Pharmacy Manual.

All IRRs will be recorded as an adverse event of special interest (AESI, Section 7.3).

5.2. Pregnancy Screen

Pregnancy tests will be performed on female participants of child-bearing potential at Screening, Baseline and monthly thereafter, including the clinic visits every 12 weeks,

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through the EOS Visit. A UPT will be conducted on Day 1. If the Day 1 urine test result is positive, it should be confirmed per local standard of care (eg, ultrasound or serum pregnancy test), and dosing should be postponed until a negative result is confirmed; if positive, the participant will not be enrolled in this study.

Female participants of child-bearing potential will be provided with UPT kits at each visit. Participants will be contacted with a monthly telephone call at which the clinical site will query the participant for the results of the monthly UPT. If a monthly UPT is positive, the participant will visit the clinical site to have a blood draw to confirm the UPT result with a serum pregnancy test. Study drug infusions will be delayed until confirmation of the serum pregnancy test result. If the serum pregnancy test result is positive, the participant will be discontinued from the treatment (Section 3.3.2) and will be followed as described in Section 7.6.1.

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).

5.3. 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 have their study drug discontinued or to be withdrawn from study. However, the decision to have the participant remain on study and/or treatment with study drug is at the discretion of the Investigator after performing a risk/benefit assessment of the participant.

6.1.2. Prohibited Medications and Therapies

Treatment with the following is not allowed during the study:

- Treatment with crizanlizumab.
- A stem cell transplant.
- Active treatment on another investigational trial, including gene therapy for SCD.

If the Investigator believes that treatment with any of these prohibited medications and therapies during the study is in the best interest of the participant, treatment with these medications should be initiated and discontinuation of the participant from further treatment with study drug or discontinuation of the participant from the study should be considered (Section 3.3.2).

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Appendix 1 (A) Schedule of Assessments

Study Day/Week	Treatment Period				EOS + 7 days [b]
	Day 1 [a]	Week 6 ± 5 days	Week 12 ± 5 days	Every 12 Weeks after Week 12 ± 10 days/ ET Visit	
Informed consent/assent	X				
Review eligibility criteria	X				
Medication and medical history	X				
Weight and height [c]	X		X	X	
Abbreviated physical examination [d]	X	X	X	X	X
Vital signs [e]	X	X	X	X	X
Hematology	X	X	X	X	X
Serum chemistry	X	X	X	X	X
Coagulation	X	X	X	X	X
Urine pregnancy test [f]	X	X	X	X	X
Chest X-ray [g]	◄-----	----------	----------	------►	
Inclacumab administration	X		X	X	
PGI-C [h]			X	X	
CGI-C [h]			X	X	
ASCQ-Me and missed school/work [i]	◄-----	----------	----------	------►	
Assessments of VOCs [j]	◄-----	----------	----------	------►	
Schedule for assessments for substudy of PK, ADA, and PD is provided in Appendix 2 (Appendix B).					
Adverse events	X	X	X	X	X
Concomitant medications	X	X	X	X	X

Abbreviations: ADA, anti-drug antibodies; ASCQ-Me, Adult Sickle Cell Quality of Life Measurement; CGI-C, Clinician's Global Impression of Change; EOS, end of study; ET, early termination; PD, pharmacodynamics; PGI-C, Patient's Global Impression of Change; PK, pharmacokinetics; UPT, urine pregnancy test; VOC, vaso-occlusive crisis.

a Day 1 assessments will be performed prior to dosing. If any of the Day 1 assessments were performed on the same date or within 7 days following the last study visit in the originating GBT-Sponsored clinical study, the tests do not need to be repeated. If Day 1 for this study is greater than 7 days from the completion of the originating study, new Baseline assessments will be obtained. Enrollment must occur within 30 calendar days of the last study visit in the originating study.

b The participant should return to the study site for an EOS visit 15 weeks (105 days) after the last dose of study drug (+ 7-day window).

c Weight will be collected at each study drug administration visit and used for determination of dosing. Height will be collected every 6 months (Week 24 for first post-Baseline measurement).

d Abbreviated physical examination will include general appearance; examination of eyes, skin, cardiovascular system, and respiratory system; abdominal examination; and a symptom-directed examination.

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. On inclacumab administration days, vital signs will be collected prior to inclacumab administration, at the completion of infusion, and at 1 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 repeat measurement of any of the vital sign parameters will be taken within 5 minutes if the first reading is

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Study Day/Week	Treatment Period				EOS + 7 days [b]
	Day 1 [a]	Week 6 ± 5 days	Week 12 ± 5 days	Every 12 Weeks after Week 12 ± 10 days/ ET Visit	

outside the normal range and deemed clinically significant. When scheduled at the same time as a blood draw, vital signs will be performed prior to the blood collection.

f Female participants of childbearing potential are required to have a negative urine pregnancy (UPT) test within 7 days prior to dosing on Day 1. A UPT will be performed monthly for female participants of childbearing potential including during clinic visits every 12 weeks. The site will query the participant for results of the monthly UPT during a monthly telephone call. If the UPT is positive, the result must be confirmed per local standard of care (eg, ultrasound or serum pregnancy test). Participants with a confirmed positive test will be discontinued from 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).

g Chest X-ray required for all suspected cases of acute chest syndrome (ACS).

h The PGI-C and CGI-C will be collected every 12 weeks through Week 96.

i The participant will complete the ASCQ-Me questionnaire and record days of missed school/work weekly. The ASCQ-Me and days of missed school/work will be collected during the participant's visits to the clinical site through Week 48. Administration of the ASCQ-Me may occur over the phone with the clinic staff and will only be administered when available in local language.

j The incidence of VOC events will be collected at each visit. Participants will be queried to determine if a VOC event leading to contact with a healthcare provider without a visit to a medical facility has occurred, to collect adverse events (AEs), and record changes to concomitant medications.

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Appendix 5-4. France-Specific Amendment

Appendix 4 (D) BLOOD VOLUMES

Sample Type	Volume Required per Sample (mL)	Day 1	Week 6	Week 12	Week 24 & Week 36	Week 48	Q12 Weeks & EOS
CBC/diff & Chemistry Panel (includes Serum Pregnancy/FSH and Hematology Panel)	13	13	13	13	13	13	13
Coagulation (including PT/INR, aPTT, D-Dimer, and Fibrinogen)	5.4	5.4	5.4	5.4	5.4	5.4	5.4
PK	2.7	2.7	2.7	2.7	2.7	2.7	0
ADA	2.7	2.7	0	2.7	0	2.7	0
CCI Day 1 Pre-Dose	8.5	8.5	0	0	0	0	0
CCI	3.5	0	3.5	3.5	3.5	3.5	0
CCI	2.9	2.9	0	2.9	2.9	2.9	0
Total Blood Volume (mL)/Visit		35.2	24.6	30.2	27.5	30.2	18.4
mL/kg[a]		0.9	0.6	0.8	0.7	0.8	0.5
% Total Blood Volume[b]		1.1%	0.8%	1%	0.9%	1%	0.6%
Number of Collection Tubes		9	7	9	8	9	5

Abbreviations: ADA, anti-drug antibodies; CBC, complete blood count; diff, differential; FSH, follicle-stimulating hormone; INR, international normalized ratio; CCI PK, pharmacokinetics; PT, prothrombin time; PTT, partial thromboplastin time; CCI CCI

a Based on body weight of 40kg in an average 12-year old child.
b Based on estimated total blood volume in children ~ 80mL/kg.

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Appendix 5-5. Egypt-Specific Amendment

5.4.4. 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 local laboratory. All clinically significant laboratory value abnormalities are to be recorded as AEs.

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 may be repeated once at the discretion of the Investigator.

Laboratory safety testing will be performed by a local laboratory.

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

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