CLINICAL STUDY PROTOCOL

Study Number	GBT2104-131 (C5361001)
Study Title	A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Assess the Safety and Efficacy of Inclacumab in Participants with Sickle Cell Disease Experiencing Vaso-occlusive Crises
Investigational Product	Inclacumab
IND Number	144073
EudraCT Number	2020-005286-13
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** **Amendment 2** **Amendment 3** **Amendment 4**	06 November 2020, Version 1.0 17 December 2020, Version 2.0 21 January 2021, Version 3.0 11 April 2022, Version 4.0 13 July 2023, Version 5.0

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 4 (13 July 2023)

Overall Rationale for the Amendment:

To add a futility analysis and align the protocol with language in 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	Deleted	To align with Pfizer Protocol Template following the acquisition of Global Blood Therapeutics (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. Investigational Plan • 3.1 (Study Design) • 7.2.3 (Abnormal Laboratory Values) • 7.2.1 (General – Adverse Event Reporting) • 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* • 7.5 (Adverse Events that are VOC Endpoint Events)	Added and/or revised language	To align with Pfizer Protocol Template following the acquisition of Global Blood Therapeutics (GBT) by Pfizer	Y

Section	Change	Brief Rationale	Substantial (Y/N)
• 7.6 (Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure) - *new section* • 7.8 (Follow-up of AEs and SAEs) • 7.6.5 (Medication Errors) – *new section* • 9.4 (Sponsor's Medically Qualified Individual) - *new section* • 9.5.1 (Regulatory and Ethical Considerations) • 9.5.2 (Reporting of Safety Issues and Serious Breach of the Protocol or ICH GCP) - *new section* • 9.5.3 (Informed Consent/Assent Process) • 9.5.5 (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 (Investigational Plan) • 3.1 (Study Design) • 3.2.5 (Exploratory Pharmacology Endpoints) • 3.3.1.1 (Inclusion Criteria) • 3.3.1.2 (Exclusion Criteria) • 3.3.3.1.1 (Early Discontinuation of Study Treatment) • 4.8.3 (Blinding Procedures)	Integrated country specific instructions and guidelines into the global protocol	To align with Pfizer Protocol Template following the acquisition of GBT by Pfizer	N

Section	Change	Brief Rationale	Substantial (Y/N)
• 5 (Study Assessments) • 5.3.4 (Clinical Laboratory Tests) • 5.4.2 (Pregnancy Screen) • 5.5 (Pharmacology Assessments (PK, ADA, PD, Biomarkers) • 6.1.2 (Prohibited Medications and Therapies) • 7.2.1 (General – Adverse Events Reporting) • 7.2.3 (Abnormal Laboratory Values) • 7.5 (Adverse Events That are VOC Endpoint Events) • 7.7 (Data Monitoring Committee) • 8.4.4 (PK, ADA, and PD Analyses) • 8.4.4.1 (Pharmacokinetic Analyses) Appendices: • 1 (Schedule of Assessments) • 5 (Liver Safety) – *new section* • 6 (Country-Specific Amendments) – *new section*			
Synopsis Section 3.3.1.2 (Exclusion Criteria)	Updated the unit for estimated glomerular filtration rate (eGFR) from absolute (ie, mL/min) to adjusted for body surface area (BSA; ie, mL/min/1.73 m^2)	eGFR adjusted for BSA is more commonly reported by local laboratories.	N
Synopsis Section 8.4.3.4 (Interim Futility Analysis)	Added a futility analysis	To allow the potential to stop the trial early if futile	Y

Section	Change	Brief Rationale	Substantial (Y/N)
Section 1.3 (Rationale for Inclacumab in SCD)	Removed reference to safety and efficacy of crizanlizumab	In January 2023, Novartis, the manufacturer of crizanlizumab reported lack of the drug's efficacy (annualized rates of vaso-occlusive crises) in patients with sickle cell disease relative to placebo.	N
Sections: • 3.3.4 (Lost to Follow-up) • 4.9 (Assessment of Treatment Compliance) • 5.4.4 (Quality of Life Assessments) • 5.4.5 (VOC Incidence) • 7 (Assessment of Safety) • 7.1.1 (Definition of Adverse Events) • 7.2.1 (General – Adverse Events Reporting) • 7.5 (Reporting Overdose) Appendix 1 (Schedule of Assessments)	Added the following two sentences, where applicable: "(and/or their parent or legal guardian for participants under 18 years of age)" "Collect at presentation for VOC as feasible."	Clarification	N
Appendix 1 (Schedule of Assessments)	Specified that laboratory assessments that are not routinely collected as part of management of a VOC (ie, unscheduled visits for a VOC) will be requested, as feasible.	Clarification	N

SYNOPSIS

Study Number:	**GBT2104-131 (C5361001)**
Study Title:	**A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Assess the Safety and Efficacy of Inclacumab in Participants with Sickle Cell Disease Experiencing Vaso-occlusive Crises**
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
Phase:	Phase 3 Note: In France, this study is considered Phase 2.
Number of Sites	The study will be conducted at up to approximately 75 clinical sites.
Number of Study Participants:	Approximately 240 participants will be enrolled.
Duration of Treatment:	The total duration of treatment for each participant will be 48 weeks. Doses will be administered at Day 1 and Weeks 12, 24, and 36 with blood levels expected to be in the target range through at least Week 48.
Objective:	The primary objective of this study is to evaluate the safety and efficacy of treatment every 12 weeks (Q12W) with inclacumab to reduce the incidence of vaso-occlusive crises (VOCs) in participants with sickle cell disease (SCD). Additional objectives of the study are to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of inclacumab, the presence of anti-drug antibodies (ADAs), and changes in quality of life (QOL).
Endpoints:	**Primary Efficacy Endpoint:** The primary efficacy endpoint of the study is the rate of VOCs during the 48-week treatment period. A VOC is defined as an acute episode of pain that: • Has no medically determined cause other than a vaso-occlusive event, and • Results in a visit to a medical facility (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 in the primary endpoint. To ensure consistency across study sites, all on-study VOCs reported by the study investigators will be adjudicated by an independent, blinded panel comprised of experts in SCD. The primary efficacy analysis will be performed on adjudicated data.

	Secondary Efficacy Endpoints:
	The secondary efficacy endpoints of the study are the following:
	• Time to first VOC during the 48-week treatment period.
	• Time to second VOC during the 48-week treatment period.
	• Proportion of participants with no VOCs during the 48-week treatment period.
	• Rate of VOCs that required admission to a healthcare facility and treatment with parenteral pain medication during the 48-week treatment period where 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, or
	• Number of days of inpatient hospitalization for a VOC during the 48-week treatment period.
	Safety Endpoints:
	The safety endpoints of the study are the following:
	• Incidence of treatment-emergent adverse events (TEAEs).
	• Change from Baseline in laboratory assessments (complete blood count [CBC], chemistry, and coagulation).
	Exploratory Endpoints:
	The exploratory endpoints of the study are the following:
	• Rate of all SCD-related urgent care visits to the clinic, emergency room, and hospital during the 48-week treatment period.
	• Proportion of total days missed from school or work due to SCD during the 48-week treatment period.
	• Rate of complicated VOCs during the 48-week treatment period.
	• Rate of red blood cell (RBC) transfusions during the 48-week treatment period.
	• Rate of inpatient hospital admissions for any reason during the 48-week treatment period.
	• Number of days of inpatient hospitalization for any reason during the 48-week treatment period.
	• Proportion of participants rated as “very much improved” or “much improved” based on the Patient’s Global Impression of Change (PGI-C) at Weeks 12, 24, 36, and 48.
	• Proportion of participants rated as “very much improved” or “much improved” based on the Clinician’s Global Impression of Change (CGI-C) at Weeks 12, 24, 36, and 48.
	• Change from Baseline in the cumulative score for the Adult Sickle Cell Quality of Life Measurement (ASCQ-Me) Pain Impact – Short Form over time to Week 48.

	Exploratory Pharmacology Endpoints: • Plasma PK of inclacumab as assessed by population PK analysis using nonlinear mixed-effects modeling. • Incidence of ADA to inclacumab. • Pharmacodynamics including changes in non-activated and thrombin receptor activating peptide (TRAP)-activated platelet leukocyte aggregates (PLAs), platelet (PLT) P-selectin expression, serum P-selectin inhibition measured by surface plasmon resonance (SPR), and plasma total and free soluble P-selectin (sP-selectin-) over time. • Biomarkers including changes in RBC adhesion (selected sites), genomic markers (optional), protein markers in the blood, urine markers of kidney function, and voxelotor plasma and whole blood concentrations (as applicable) Relationships between PK, PD, biomarkers, clinical labs, safety, and efficacy will be explored. Note: In Egypt, blood samples for PK, PD, ADA, and biomarker endpoints samples will not be collected.
Study Design:	This study will be a randomized, placebo-controlled, double-blind, multicenter, parallel-group study to assess the safety and efficacy of inclacumab in reducing the frequency of VOCs in approximately 240 adult and adolescent participants (≥ 12 years of age) with SCD globally. Initial enrollment will include participants ≥ 16 years of age until the Data Monitoring Committee (DMC) recommends to the Sponsor that adequate safety and PK data support the enrollment of participants 12 to 15 years of age. Eligible participants will be randomized with a 1:1 ratio into one of two treatment arms as follows: • Inclacumab 30 mg/kg administered intravenously (IV) Q12W (Day 1, Week 12, Week 24, and Week 36); or • Placebo administered IV Q12W (Day 1, Week 12, Week 24, and Week 36). At the time of randomization, participants will be stratified by Baseline hydroxyurea (HU) use (yes; no), number of VOCs (2 to 4; 5 to 10) in the preceding 12 months, and geographic region (North America; sub-Saharan Africa; Europe/rest of world). An independent DMC will regularly review the totality of accumulated safety data from all ongoing inclacumab studies on an ongoing, unblinded basis, with specific emphasis on adolescent participants. Details are provided in the DMC Charter. Participants that complete the study through Week 48 will be provided the opportunity to enroll in an open-label extension (OLE) study. Note: For France-, Germany-, UK-, and Egypt-specific study design, refer to Appendix 6-1, Appendix 6-2, Appendix 6-3, and Appendix 6-5, respectively, in the body of the protocol.
Investigational Product, Dose, and Mode of Administration:	Inclacumab drug product is a sterile, clear to opalescent liquid concentrate for infusion with an approximate pH of 5.5 provided in colorless, 10 mL single-use vials. Each vial contains 500 mg of inclacumab and the following excipients: L-histidine-acetate, sucrose, and poloxamer 188. An inclacumab

	dose of 30 mg/kg will be administered IV. Participants will be monitored for 60 minutes after completion of study drug infusion for adverse reactions.
Comparator Product:	The comparator product is a placebo for inclacumab containing the same ingredients without the active drug. Placebo will be prepared and administered in the same manner as active study drug.
Eligibility Criteria:	**Inclusion Criteria:** 1. Participant has a confirmed diagnosis of SCD (HbSS, HbSC, HbSβ^0 thalassemia, or HbSβ^+ thalassemia genotype). Documentation of SCD genotype is required and may be based on documented history of laboratory testing or confirmed by laboratory testing during Screening. 2. Participant is male or female, ≥ 12 years of age at the time of informed consent. NOTE: Initial study enrollment will include participants ≥ 16 years of age until the DMC recommends to the Sponsor that adequate safety and PK data support the enrollment of participants 12 to 15 years of age. Sites will be informed by the Sponsor when participants 12 to 15 years of age may be enrolled. Note: For France-, Germany-, and UK-specific study design, refer to Appendix 6-1, Appendix 6-2, and Appendix 6-3, respectively, in the body of the protocol. 3. Participant has experienced between 2 and 10 VOCs within the 12 months prior to the Screening Visit as determined by documented medical history. A prior VOC is defined as an acute episode of pain which: • Has no medically determined cause other than a vaso-occlusive event, and • Results in a visit to a medical facility (hospital, emergency department, urgent care center, outpatient clinic, or infusion center) or results in a remote contact with a healthcare provider; and • Requires parenteral narcotic agents, parenteral NSAIDs, or an increase in treatment with oral narcotics. 4. Participants receiving erythropoiesis-stimulating agents (ESA, eg, erythropoietin [EPO]) must be on a stable dose for at least 90 days prior to the Screening Visit and expected to continue with the stabilized regimen throughout the course of the study. 5. Participants receiving HU, L-glutamine, or voxelotor must be on a stable dose for at least 30 days prior to the Screening Visit and expected to continue with the stabilized regimen throughout the course of the study. 6. Participant has adequate venous access, in the opinion of the Investigator, to comply with study procedures. 7. Participant understands the study procedures and agrees to participate in the study by giving written informed consent or parental permission/written assent.

	Note: For the France-specific criterion, Appendix 6-1 in the body of the protocol. 8. Women of childbearing potential (WOCBP) are required to have a negative serum pregnancy test at the Screening visit and negative urine pregnancy test on all subsequent clinic visits and must agree to use a highly effective method of contraception throughout the study period and for at least 165 days after dosing. Female participants will not be considered of childbearing potential if they are pre-menarchal, surgically sterile (hysterectomy, bilateral salpingectomy, tubal ligation, or bilateral oophorectomy) or postmenopausal (no menses for 12 months without an alternative medical cause, confirmed by follicle-stimulating hormone test results). Note: For the UK-specific criterion, Appendix 6-3 in the body of the protocol. **Exclusion Criteria:** 1. Participant is receiving regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventative transfusion). 2. Participant is taking or has received crizanlizumab (ADAKVEO®) within 90 days prior to the Screening Visit. 3. Participant weighs > 133 kg (292 lbs). 4. Participant has a significant active and poorly controlled (unstable) hepatic disorder clearly unrelated to SCD. Note: For UK-specific criterion, refer to Appendix 6-3 in the body of the protocol. 5. Participant has any of the following laboratory values at Screening: a. Absolute neutrophil count (ANC) < 1.0×10^9/L b. Platelet count < 80×10^9/L c. Hemoglobin < 4.0 g/dL for adults and < 5.0 g/dL for participants ages 12 to < 18 d. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 using Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula in adults, and Schwartz formula in adolescents Note: For France- and Germany-specific criterion, refer to Appendix 6-1 and Appendix 6-2, respectively, in the body of the protocol. 6. Participant has known active (symptomatic) coronavirus disease 2019 (COVID-19) infection or tests positive for COVID-19 during Screening. 7. Participant has a history of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to consent including severe or unstable pulmonary hypertension. 8. Participant has had treatment for a malignancy within the 12 months prior to the Screening Visit (except non-melanoma skin cancer and in situ cervical cancers).

	9. Participant has had a stroke within the 2 years prior to the Screening Visit. 10. Participant has a positive test indicative of active malaria infection at Screening. Testing to be conducted at local laboratories in malaria -endemic regions at the discretion of the Investigator. 11. Participant has any confirmed clinically significant drug allergy and/or known hypersensitivity to monoclonal antibody therapeutics or formulation components of the study drug or a related drug. 12. Participant has been in another investigational trial within 30 days or 5 half-lives of the investigational agent (whichever is greater) prior to the Screening Visit. 13. Participant has had a major surgery within 8 weeks prior to the Screening Visit. 14. Participant is pregnant, breastfeeding, or planning to become pregnant during the 48-week treatment period. 15. Participant, parent, or legal guardian are unlikely to comply with the study procedures. Note: For France-specific criterion, refer to Appendix 6-1 in the body of the protocol. 16. Participant has any other medical, or psychological, or behavioral conditions that, in the opinion of the Investigator, would confound or interfere with evaluation of safety, efficacy, and/or PK of the investigational drug; prevent compliance with the study protocol; preclude informed consent; or render the participant, parent, or caretaker unable/unlikely to comply with the study procedures. Note: For the France-specific criterion, Appendix 6-1 in the body of the protocol.
Outcomes Measures:	**Efficacy:** The outcome measure for efficacy is the incidence of VOCs as defined for the primary endpoint along with requirements for hospitalizations, RBC transfusions, and QOL assessments. **Safety:** Participants will be monitored from the time the informed consent is signed through the end of study (EOS) for TEAEs. Severity of TEAEs will be determined based on the Common Terminology Criteria for Adverse Events (CTCAE). Safety assessments also include physical examinations (PEs), vital signs measurements (blood pressure (BP), heart rate (HR), and body temperature), clinical laboratory evaluations including a chemistry panel and CBC, additional laboratory evaluations including prothrombin time, activated partial thromboplastin time (aPTT), and reticulocyte count, pregnancy tests as appropriate, and concomitant medications. Additional assessments for safety will be collected when a participant presents with VOC on a non-study visit day, as feasible. **Pharmacokinetics:** In all participants, plasma samples will be collected for measurement of inclacumab concentrations before and after each dose, at the Week 6 visit, and at the end of the Treatment Period (Week 48). Samples will also be collected at

	the Week 60 EOS Visit in all participants not proceeding to the OLE study. Additional samples for PK will be collected when a participant presents with VOC on a non-study visit day, as feasible. Population PK analysis using nonlinear mixed effects modeling will be performed to characterize inclacumab PK in plasma. **Anti-Drug Antibodies:** In all participants, plasma samples will be collected for characterization of ADA incidence on Day 1 (pre-dose), Week 12 (pre-dose), Week 24 (pre-dose), and the Week 48 Study Visit. Samples will also be collected at the Week 60 EOS Visit in all participants not proceeding to the OLE study. **Pharmacodynamics:** At selected study visits (Appendix 2), whole blood samples will be collected for assessment of non-activated and TRAP-activated PLA formation and PLT P selectin expression. Serum samples will be collected for assessment of P-selectin inhibition by SPR. Plasma samples will be collected for assessment of circulating soluble free and total P-selectin. Additional samples for PD will be collected when a participant presents with VOC on a non-study visit day, as feasible. Biomarkers including changes in red blood cell (RBC) adhesion (selected sites), genomic markers (optional), protein markers in the blood, urine markers of kidney function, and voxelotor plasma and whole blood concentrations (as applicable) will be collected. The relationships between PK, PD, clinical labs, safety, and efficacy will be explored. Note: In Egypt, blood samples for PK, PD, ADA, and biomarker endpoints samples will not be collected.
Study Procedures:	The Schedule of Assessments is provided in Appendix 1 and the schedule for collection of PK, ADA, and PD samples is provided in Appendix 2. The schedule for collection of biomarkers is provided in Appendix 3. Participants will be screened for eligibility for up to 28 days prior to randomization. Eligible participants will be randomized on Day 1 (Baseline) and receive the first dose of study drug. Participants will return to the clinical site at Week 6, Week 12, then Q12W for safety, pharmacology, and efficacy assessments. Infusion of study drug will occur at Week 12, Week 24, and Week 36. The majority of participants receiving active study drug are expected to maintain target concentrations through Week 48. Participants will record responses to the ASCQ-Me questionnaire weekly, when available. Each month between study visits, the participant will be contacted to assess VOCs, pain crises events, adverse events (AEs), and changes in concomitant medications. Participants that complete the 48-week treatment period will be provided the opportunity to enroll the OLE study at Week 48. For participants enrolling in the OLE study, the Week 48 Visit will be the EOS Visit and participants will receive the first dose of open-label inclacumab at this same visit. For participants not enrolling in the OLE study, an additional required Follow-up Visit at Week 60 will be the EOS Visit. Note: For UK- and Egypt-specific procedures, refer to Appendix 6-3 and Appendix 6-5, respectively, in the body of the protocol.

Statistical Methods:	Detailed specifications of the methods for summary and analyses of the data collected in this study will be documented in the Statistical Analysis Plan (SAP). **Sample Size:** A sample size of approximately 240 participants (120 participants per treatment arm [inclacumab and placebo]) provides approximately 90% power to detect a targeted 45% reduction in the rate of VOCs, from an average rate of 3.0 VOCs per year on placebo to 1.65 VOCs per year on inclacumab, using a 2-sided test at an overall $\alpha = 0.05$ level. Calculations assume the number of VOCs per year follows a negative binomial distribution with a dispersion parameter of 1.04. For the purposes of sample size calculation, a drop-out rate of 25% by Week 48 was assumed. **Efficacy Populations and Analysis:** Efficacy analyses will be based on an intent-to-treat (ITT) population consisting of all randomized participants, with participants grouped according to the treatment assigned at randomization. **Primary Efficacy Endpoint:** For the primary efficacy endpoint, the rate of VOCs during the 48-week treatment period will be compared between the inclacumab and placebo arms with the use of negative binomial regression model. The regression model will include covariates for treatment group (inclacumab, placebo) and the randomization stratification factors. The logarithm of observed patient-time at risk will be used as an offset term in the model. The rate of VOCs adjusted for the specified Baseline covariates will be estimated for each treatment arm based on the regression model. Similarly, the ratio of the VOC rate (inclacumab versus placebo) along with the associated 95% confidence interval (CI) and p-value will be estimated from the regression model. The regression model will be fit based on all observed data from randomized participants, regardless of adherence to study drug or to the protocol. Sensitivity analyses will be performed to assess the robustness of the primary analysis results. Details will be specified in the SAP. **Secondary Efficacy Endpoints:** For the secondary endpoints of time to first VOC and time to second VOC, treatment comparison between inclacumab and placebo will be performed based on a stratified log-rank test. Kaplan-Meier plots will be generated. Time to first and time to second VOC will be measured from randomization (Day 1) to onset date of the corresponding VOC event. A Cox regression model will be used to estimate the hazard ratio between the inclacumab and placebo groups, as appropriate. For the proportion of participants with no VOCs during the 48-week treatment period, the exact Cochran-Mantel-Haenszel (CMH) general association test, stratified by the randomization stratification factors, will be used. For the rate of VOCs that required admission to a healthcare facility and treatment with parenteral pain medication during the 48-week treatment period and number of days of inpatient hospitalization for VOC during the 48-week treatment period, the same statistical method used for the primary endpoint will be used.

	Interim Futility Analysis: One interim analysis for futility will be performed at an information fraction of approximately 48%. The futility analysis will include subjects who have the potential for at least 24 weeks of treatment (ie, 2 doses of study drug) by the selected data cutoff date. For the futility analysis, the primary efficacy endpoint will be evaluated by the independent DMC. The study team will remain blinded. A Gamma family (-1) β-spending function will be used to determine the futility boundary. The futility boundary is non-binding. Additional details will be provided in the SAP. **Adjustment for Multiple Comparisons:** A fixed sequence hierarchical test procedure will be used to control Type I error when evaluating the treatment effect of inclacumab compared with placebo for the primary and secondary efficacy endpoints. The endpoints will be tested in a pre-specified order, with formal testing of endpoints continuing until the first non-significant result. **Safety Population and Analysis:** Safety analysis will be based on all randomized participants receiving treatment with study drug. Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of TEAEs, defined as events that occur on or after Day 1 of study treatment or the worsening of a pre-existing condition on or after Day 1 of study treatment, will be tabulated by System Organ Class and Preferred Term. Additional summaries for TEAEs by severity, relationship to study drug, and leading to study drug discontinuation, as well as for adverse events of special interest (AESIs), serious adverse events (SAEs), and deaths will be generated. Vaso-occlusive crises events will be collected and summarized separately (including ACS, hepatic sequestration, splenic sequestration, and priapism). Changes in laboratory parameters (hematology, serum chemistry, and coagulation) and vital signs (eg, blood pressure, heart rate, and body temperature) over time will be summarized descriptively.

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APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACS	acute chest syndrome
ADA	anti-drug antibodies
CCI	[redacted]
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCQ-Me	adult sickle-cell quality of life measurement
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
CGI-C	Clinician's Global Impression of Change
CHO	Chinese hamster ovary
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	chronic kidney disease – epidemiology collaboration
ClinRO	clinician reported outcomes
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CRO	clinical contract research organization
CRP	C-reactive protein
CSR	clinical study report
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trials Information System
DMC	Data Monitoring Committee
DCT	data collection tool
DILI	drug-induced liver injury
EC	Ethics Committee
ECC	emergency contact card
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDC	electronic data capture
EDP	exposure during pregnancy

Abbreviation	Definition
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
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 Practices
GMP	Good Manufacturing Practice
HC	hydrocarbamide
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HR	heart rate
hs-CRP	high sensitivity C-Reactive protein
HSCT	hematopoietic stem cell transplantation
HU	hydroxyurea
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identifier
IgG	immunoglobulin G
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
LDL	Low density lipoprotein
MedDRA	Medical dictionary for regulatory activities
MQI	Medically Qualified Individual
NCI	National Cancer Institute

Abbreviation	Definition
NSAID	non-steroidal anti-inflammatory drug
OLE	open-label extension
PAD	peripheral arterial disease
PD	pharmacodynamics
PE	physical examination
PGI-C	Patient's Global Impression of Change
PK	pharmacokinetics
PLA	platelet-leukocyte aggregate
PLT	platelet
PNH	paroxysmal nocturnal hemoglobinuria
PRO	patient reported outcome
PSGL-1	P-selectin glycoprotein ligand-1
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
SOC	standard of care
sP-selectin	soluble P-selectin
SPR	surface plasmon resonance
sRBC	sickled red blood cell
SRSD	Single Reference Safety Document
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TIBC	total iron binding capacity
TRAP	thrombin receptor activating peptide
ULN	upper limit of normal
UK	United Kingdom
US	United States
WHO	World Health Organization
WOCBP	women of child-bearing potential
VOC	vaso-occlusive crisis

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 (sRBCs), 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 SCD patients.

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

1.2. Current Therapy for Sickle Cell Anemia

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

Three therapies, hydroxyurea (HU [DROXIA®, 2017]; also known as hydroxycarbamide), L-glutamine (ENDARI, 2017) and crizanlizumab (ADAKVEO®, 2019), have been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) 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).

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

Crizanlizumab, a monoclonal antibody directed against human P-selectin, can be used alone and in combination with HU to reduce the frequency of VOCs in patients with SCD. However, patients are required to travel to an infusion center for drug administration once every 4 weeks, a potentially limiting factor in continued adherence to a life-long therapy. Treatment adherence is essential for quality care and non-adherence leads to poor health outcomes and increased healthcare costs, especially among patients with chronic conditions (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 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 and work absence required from both for such infusions. One recent study demonstrated that PNH patients receiving eculizumab every 2 weeks had three times higher productivity losses compared to PNH patients treated every 8 weeks with ravulizumab solely due to more frequent dosing (Levy, 2019). Moreover, patients report that therapies with less frequent dosing regimens enable them to feel independent, better plan future activities, and lead more active lives, all important considerations in developing treatments for SCD, which is a debilitating disease characterized by idiosyncratic and unpredictable exacerbations (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. CCI [redacted]

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 leukocytes recruitment by PLTs or endothelial cells. The same mechanism is also responsible for abnormal adhesion of sRBC to the endothelium, initiating acute vascular occlusion and chronically impairing microvascular blood flow in patients with SCD. Inclacumab binding of P-selectin and prevention of P-selectin binding to its ligands is the putative mechanism by which inclacumab effectively blocks interactions between endothelial cells, PLTs, sRBCs and leukocytes, thereby preventing VOCs.

Nonclinical studies 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 a randomized, placebo-controlled, double-blind study to evaluate the safety and efficacy of inclacumab compared to placebo when administered once every 12 weeks (Q12W) (Day 1, Week 12, Week 24, and Week 36) to patients with a diagnosis of SCD who have experienced between 2 and 10 VOCs in the 12 months preceding enrollment in this study. Given the long half-life of inclacumab (terminal half-life of 21 to 28 days) at the dose to be evaluated in this study, the majority of participants receiving active study drug are expected to maintain target concentrations through Week 48.

The primary endpoint of the study is the rate of VOCs occurring over a 48-week treatment period. The safety of treatment with inclacumab over the 48-week period will also be assessed. This study builds on experience from previous clinical studies in patients with SCD in reducing the incidence of VOCs.

A placebo-controlled trial represents the most common and acceptable approach for determining the safety and efficacy for a therapeutic through a well-designed, controlled study. Some notable distinctions from prior studies include the definition of a VOC that allows for telemedicine in addition to the previous definitions which required a visit to a healthcare facility. This distinction has been incorporated 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 crisis on the part of the patient that requires intervention by a healthcare practitioner. Use of a telemedicine-based VOC is therefore justified.

1.3.2. Rationale for Dose Regimen

In this study, an IV dose of 30 mg/kg will be administered Q12W for a total of 4 doses over a 48-week period to reduce the frequency of VOCs in patients with SCD. More than 700 participants in prior studies (healthy or cardiovascular disease patients) have been exposed to inclacumab; a maximum tolerated dose was not identified. The maximum single dose tested, 40 mg/kg, has not demonstrated any drug-related safety or tolerability signals in a Phase 1 study in healthy participants. Chronic IV dosing of inclacumab (20 mg/kg every 4 weeks for 32 weeks) 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.

In a recent Phase 1 study in healthy participants, the safety and tolerability of a single IV dose of up to 40 mg/kg of inclacumab was consistent with the safety profile of previous studies with inclacumab at doses up to 20 mg/kg IV performed in healthy participants and in individuals with cardiovascular disease (refer to the current version of the IB for details).

Inclacumab plasma concentrations above 10 µg/mL have been associated with maximal inhibition of ex vivo thrombin receptor activating peptide (TRAP)-induced platelet leukocyte aggregate (PLA) formation in healthy volunteers and patients with peripheral arterial disease (PAD) from prior clinical studies. Chronic dosing to maintain inclacumab plasma concentrations above 10 µg/mL is expected to be required for maximal sustained benefit.

Population PK simulations project that the inclacumab dose regimen of 30 mg/kg Q12W will maintain concentrations above 10 µg/mL throughout the 48-week study period in the majority of participants, thereby maximizing the pharmacology required for effective reduction of VOC in the SCD population.

1.3.3. Use of a Placebo Control

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

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

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

2. OBJECTIVES

The primary objective of this study is to evaluate the safety and efficacy of treatment every 12-week with inclacumab to reduce the incidence of VOCs in participants with SCD.

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

3. INVESTIGATIONAL PLAN

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

Note: In France, this study is considered Phase 2.

3.1. Study Design

This study will assess the safety and efficacy of inclacumab in reducing the frequency of VOCs in approximately 240 adult and adolescent participants (≥ 12 years of age) with SCD globally. Initial enrollment will include participants ≥ 16 years of age until the independent Data Monitoring Committee (DMC) recommends to the Sponsor that adequate safety and PK data support the enrollment of participants 12 to 15 years of age.

Eligible participants will be randomized with a 1:1 ratio into one of two treatment arms as follows:

- Inclacumab 30 mg/kg administered IV Q12W; or
- Placebo administered IV Q12W.

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

All participants will undergo safety, efficacy, and PK/PD assessments at Baseline and through Week 48. Visits to the clinical site for infusion of study drug will occur at Baseline (Day 1) and Q12W (Weeks 12, 24, and 36) for a total of 4 infusions. An additional visit at Week 6 will occur for safety, PK, and PD monitoring. The incidence of VOC events will be recorded weekly by the participant and collected every 4 weeks, with participants contacted by phone at Weeks 4, 8, 16, 20, 28, 32, 40, and 44.

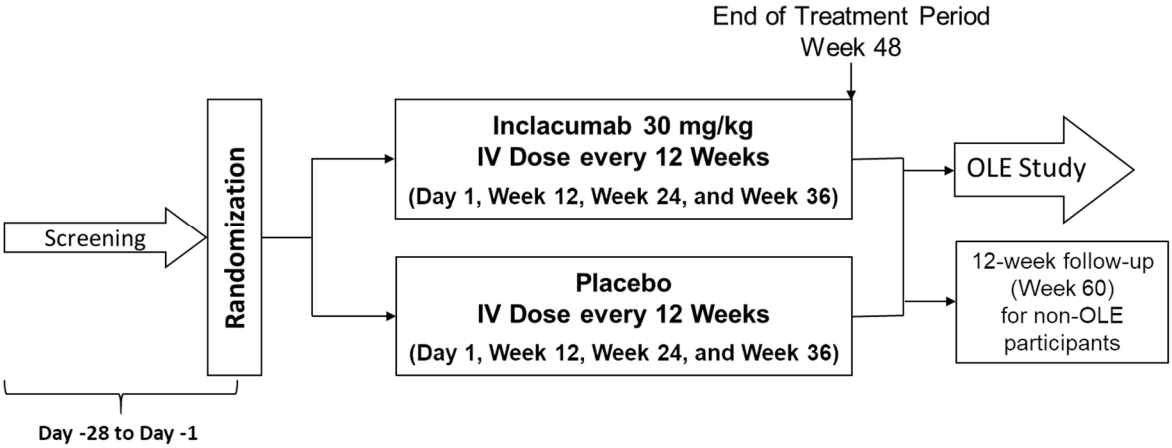
Following completion of the Week 48 Visit, eligible participants will be given the option to enroll in an open-label extension (OLE) study (under a separate protocol) to receive inclacumab. Participants will receive their first dose in the OLE study at the same Week 48 Visit. Participants enrolling in the OLE study will not be required to return to clinic for the Week 60 Visit. Safety, efficacy, and PK/PD assessments will occur at Week 60 for participants not enrolling on the OLE study.

The 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. Details are provided in the DMC Charter.

Note: For France-, Germany-, UK-, Ghana-, and Egypt-specific study design, refer to Appendix 6-1, Appendix 6-2, Appendix 6-3, Appendix 6-4, and Appendix 6-5, respectively.

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

Figure 1: GBT2104-131 Study Design



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

3.2. Study Endpoints

3.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint for the study is the rate of VOCs during the 48-week treatment period. A VOC is defined as an acute episode of pain that:

- Has no medically determined cause other than a vaso-occlusive event, and

- Results in a visit to a medical facility (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 in the primary endpoint.

To ensure consistency across study sites, all VOCs identified will be adjudicated by an independent, blinded panel comprised of experts in SCD. The primary efficacy analysis will be performed on adjudicated data.

3.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints for the study are the following:

- Time to first VOC during the 48-week treatment period.
- Time to second VOC during the 48-week treatment period.
- Proportion of participants with no VOCs during the 48-week treatment period.
- Rate of VOCs that required admission to a healthcare facility and treatment with parenteral pain medication during the 48-week treatment period where 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.
- Number of days of inpatient hospitalization for a VOC during the 48-week treatment period.

3.2.3. Safety Endpoints

Safety endpoints for the study are the following:

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

3.2.4. Exploratory Endpoints

The exploratory endpoints for the study are the following:

- Rate of all SCD-related urgent care visits to clinic, emergency room, and hospital during the 48-week treatment period.

- Proportion of total days missed from school or work due to SCD during the 48-week treatment period.
- Rate of complicated VOCs (defined in Section 5.1) during the 48-week treatment period.
- Rate of red blood cell (RBC) transfusions during the 48-week treatment period.
- Rate of inpatient hospital admissions for any reason during the 48-week treatment period.
- Number of days of inpatient hospitalization for any reason during the 48-week treatment period.
- Proportion of participants rated as "very much improved" or "much improved" based on the Patients Global Impression of Change (PGI-C) at Weeks 12, 24, 36, and 48.
- Proportion of participants rated as "very much improved" or "much improved" based on the Clinician's Global Impression of Change (CGI-C) at Weeks 12, 24, 36, and 48.
- Change from Baseline in the cumulative score for the Adult Sickle Cell Quality of Life Measurement (ASCQ-Me) Pain Impact – Short Form over time to Week 48.

3.2.5. Exploratory Pharmacology Endpoints

The following exploratory pharmacology endpoints will be assessed:

- Plasma PK of inclacumab as assessed by population PK analysis using nonlinear mixed-effects modeling.
- The incidence of ADA to inclacumab.
- Pharmacodynamics including changes in non-activated and TRAP-activated PLAs, PLT P--selectin expression, serum P-selectin inhibition measured by surface plasmon resonance (SPR), and plasma total and free soluble P-selectin (sP-selectin-) over time.
- Biomarkers including changes in RBC adhesion (selected sites), genomic markers (optional), protein markers in the blood, urine markers of kidney function, and voxelotor plasma and whole blood concentrations (as applicable)

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

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

3.3. Selection of Study Population

A total of up to 240 participants (120 per treatment group) at approximately 75 global clinical sites will be enrolled in this study.

3.3.1. Eligibility

Eligibility assessment will be conducted during Screening and prior to receiving study drug on Day 1.

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

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

3.3.1.1. Inclusion Criteria

1. Participant has a confirmed diagnosis of SCD (HbSS, HbSC, HbSβ^0 thalassemia, or HbSβ^+ thalassemia genotype).

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

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

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

   Note: For France-, Germany-, and UK-specific study design, refer to Appendix 6-1, Appendix 6-2, and Appendix 6-3, respectively.

3. Participant has experienced between 2 and 10 VOCs within the 12 months prior to the Screening Visit as determined by documented medical history. A prior VOC is defined as an acute episode of pain that:

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

4. Participants receiving ESA, eg, EPO must be on a stable dose for at least 90 days prior to the Screening Visit and expected to continue with the stabilized regimen throughout the course of the study.

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

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

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

Note: For the France-specific criterion, Appendix 6-1 in the body of the protocol.

8. Women of childbearing potential (WOCBP) are required to have a negative serum pregnancy test at the Screening Visit and negative urine pregnancy test on all subsequent clinic visits and must agree to use a highly effective method of contraception throughout the study period and for at least 165 days after dosing. See Section 6.3 for details on methods of contraception.

   Note: For the UK-specific criterion, refer to Appendix 6-3.

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

3.3.1.2. Exclusion Criteria

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

1. Participant is receiving regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventative transfusion).
2. Participant is taking or has received crizanlizumab (ADAKVEO) within 90 days prior to the Screening Visit.
3. Participant weighs > 133 kg (292 lbs).
4. Participant has a significant active and poorly controlled (unstable) hepatic disorder clearly unrelated to SCD.

   Note: For the UK-specific criterion, refer to Appendix 6-3.
5. Participant has any of the following laboratory values at screening:
   a. Absolute neutrophil count (ANC) < 1.0×10^9/L
   b. Platelet count < 80×10^9/L
   c. Hemoglobin < 4.0 g/dL for adults and < 5.0 g/dL for participants ages 12 to < 18 years of age
   d. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 using Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula in adults, and Schwartz formula in adolescents

   Note: For France- and Germany-specific criterion, refer to Appendix 6-1 and Appendix 6-2, respectively.
6. Participant has known active (symptomatic) COVID-19 infection or tests positive for COVID-19 during Screening.
7. Participant has a history of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to consent including severe or unstable pulmonary hypertension.

8. Participant has had treatment for a malignancy within the 12 months prior to the Screening Visit (except non-melanoma skin cancer and in situ cervical cancers).
9. Participant has had a stroke within the 2 years prior to the Screening Visit.
10. Participant has a positive test indicative of malaria infection at Screening. Testing to be conducted at local laboratories in malaria-endemic regions at the discretion of the Investigator.
11. Participant has any confirmed clinically significant drug allergy and/or known hypersensitivity to monoclonal antibody therapeutics or formulation components of the study drug or a related drug.
12. Participant has been in another investigational trial within 30 days or 5 half-lives of the investigational agent (whichever is greater) prior to the Screening Visit.
13. Participant has had a major surgery within 8 weeks prior to the Screening Visit.
14. Participant is pregnant, breastfeeding, or planning to become pregnant during the 48-week treatment period.
15. Participant, parent, or legal guardian are unlikely to comply with the study procedures.

    Note: For France-specific criterion, refer to Appendix 6-1.
16. Participant has any other medical, psychological, or behavioral conditions that, in the opinion of the Investigator, would confound or interfere with evaluation of safety, efficacy, and/or PK of the investigational drug; prevent compliance with the study protocol; preclude informed consent; or render the participant, parent, or caretaker unable/unlikely to comply with the study procedures.

3.3.2. Participant Completion

Participants not enrolling in the OLE study will complete the study at the time of the last scheduled study procedures at the Week 60 Visit. For participants who enroll into the OLE study, the Week 48 Visit will be the final study visit. Participants will receive their first dose in the OLE study on the same day as the completion of the Week 48 Visit. Participants who terminate the study prior to the Week 48 Visit will be requested to complete the assessments as outlined for the Early Termination (ET) (Week 48) Visit. Participants not enrolling in OLE that complete the Week 48 Visit but terminate prior to the Week 60 Visit will be requested to complete the assessments as outlined for the End of Study (EOS; Week 60) Visit. Participants who require further follow-up for an AE/serious adverse event (SAE) will be followed according to Section 7.8.

3.3.3. Study Discontinuation

The Sponsor has the right to terminate this study at any time. In any instance of ET 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.

3.3.3.1. Early Discontinuation of Individual Participants

3.3.3.1.1. Early Discontinuation of Study Treatment

Participants may discontinue 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 1.1.

Participants who discontinue from study treatment will be encouraged to continue to participate in the study assessments, as applicable. Participants who are discontinued from study treatment due to pregnancy will also be discontinued from the study (Section 1.1). A participant may be discontinued from study treatment at any time at the discretion of the Investigator in accordance with his or her clinical judgment.

Note: For UK-specific guidelines, refer to Appendix 6-3.

3.3.3.1.2. Withdrawal of Consent

Participants will be informed that they are free to withdraw from the study at any time and for any reason. The Investigator must withdraw from the study any participant who requests to be withdrawn. Participants who ask to leave the study early (withdraw consent) should be encouraged to undergo the tests and evaluations listed for the ET Visit (ie, ET is intended for participants who withdraw consent). If a participant withdraws before completing the study, the date and reason for withdrawal is to be documented on the electronic case report form (eCRF).

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

3.3.4. Lost to Follow-up

Participants (and/or their parent or legal guardian for participants under 18 years of age) 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 under 18 years of age) through a minimum of 2 telephone calls. If the participant (and/or their parent or legal guardian for participants under 18 years of age) still cannot be contacted, the site will send a certified letter to the last known address of the participant. If no contact is made by the participant (and/or their parent or legal guardian for participants under 18 years of age), the site will consider the participant lost to follow-up. All follow-up attempts will be documented and kept with the participant's source documentation, and the applicable eCRFs will be completed.

3.4. Study Duration

The total study duration for each participant will be up to 64 weeks, including a 28-day Screening period, a 48-week treatment period, and a 12-week follow-up period.

Participants who enroll in the OLE study after Week 48 will have a total study duration of 52 weeks, including the 28-day Screening period and 48-week treatment period.

3.5. Treatments

Study drug will be provided to the study sites in a blinded fashion as a solution for IV infusion. All study drug will be administered at the clinical study site.

Participants will be randomized into one of 2 treatment groups: inclacumab or placebo. The active inclacumab and placebo solutions will look identical to maintain the blind. The Investigator, site staff, participant, and Sponsor study personnel (or their designees) will be blinded to the study group to which the participant is randomized. Participants will be dosed as follows:

- **Inclacumab:** 30 mg/kg inclacumab administered IV Q12W (Day 1, Week 12, Week 24, and Week 36)
- **Placebo:** placebo administered IV Q12W (Day 1, Week 12, Week 24, and Week 36)

4. STUDY DRUG INFORMATION

4.1. Description of Active Study Drug – Inclacumab

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

Inclacumab drug product is a sterile, clear to opalescent liquid concentrate for infusion with an approximate pH of 5.5 provided in colorless, 10 mL single-use vials. Each vial contains 500 mg of inclacumab and the following excipients: L-histidine-acetate, sucrose, and Poloxamer 188.

4.2. Description of Placebo for Inclacumab

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

4.3. Packaging and Labeling

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

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

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

4.4. Storage and Handling

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

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

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

4.5. Instructions for Use and Administration

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

4.6. Management of Infusion-Related Reactions (IRR)

Participants will be monitored throughout the infusion and for 60 minutes after completion of study drug infusion for adverse reactions. If an infusion-related reaction (IRR) or hypersensitivity reaction of Grade 3 or higher (Appendix 4) occurs during study drug administration, the infusion will be discontinued, and the participant should be treated for the reaction per site standard operating procedures as indicated. The participant will not receive further treatment with study drug but will continue on study until the EOS/ET (Week 60) 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 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 SAE (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 48. However, the participant will be ineligible for the OLE study.

4.7. Accountability

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

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

The Investigator must return all used and unused vials of study drug as instructed by the Sponsor, or designee, unless approved for onsite destruction. If any study drug supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from the Sponsor, or designee, by providing, in writing, the destruction policy or

details of the method of destruction. After such destruction, the Sponsor, or designee, must be notified, in writing, of the details of the study drug destruction (eg, lot or kit numbers, quantities).

4.8. Methods of Assigning Participants to Treatment Groups

4.8.1. Participant Screening

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

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

The Screening Period for a particular participant will commence when the participant undergoes the first study-specific Screening assessment and must be completed within 28 days after signing the informed consent/assent document (ICD).

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

4.8.2. Randomization Method

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

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

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

4.8.3. Blinding Procedures

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

The Investigator must contact the Medical Monitor prior to unblinding of study drug for any participant. In an emergency, however, where knowledge of the study drug is critical to participant safety, the code may be broken. In cases where the Investigator is unable to contact the Medical Monitor prior to unblinding, the Investigator must notify the Sponsor, or

designee, as soon as possible (ie, within 24 hours) after unblinding. In addition, the Investigator must record the date, time, and reason for unblinding the study drug treatment in the source documentation.

Note: For UK-specific guidelines, refer to Appendix 6-3.

4.9. 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 under 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.

5. STUDY ASSESSMENTS

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

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

5.1. Primary Efficacy Assessment

Efficacy will be assessed through collection of VOCs during the 48-week treatment period. A VOC is defined as an acute episode of pain that:

- Has no medically determined cause other than a vaso-occlusive event, and
- Results in a visit to a medical facility (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.

Complicated VOCs of ACS, hepatic sequestration, splenic sequestration, and priapism, that meet the requirements listed above will be included in the primary endpoint.

Participants 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 their VOCs, (eg, emergency room, hospital, urgent care center, outpatient clinic or infusion center), participants 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.

To ensure consistency across study sites, all on-study VOCs reported by the study investigators will be adjudicated by an independent, blinded panel comprised of experts in SCD (See Section 7.4.2). The primary efficacy analysis will be performed on adjudicated data.

5.2. Secondary and Exploratory Efficacy Assessments

The secondary efficacy endpoints are based on collection of the incidence and timing of VOCs (per the definition in the primary endpoint) after randomization, QOL assessments and on hospital durations.

For the exploratory efficacy endpoints, in addition to incidence and timing of VOCs, the following will be collected:

- All visits to healthcare facilities for a VOC regardless of treatment administered.
- Number of days with a VOC leading to a healthcare visit.
- Total days missed from school or work due to SCD.
- Red blood cell (RBC) transfusions.

For all VOCs, the medications and doses used to treat the VOC will be collected. This includes:

- IV/oral opioid analgesics,
- IV/oral non-opioid analgesics,
- Transfusions, and
- Volume replacement/hydration.

Quality of life (QOL) assessments will be collected as patient reported outcomes (PROs) or clinician reported outcomes (ClinRO), when available in local language, including:

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

5.3. Safety Assessments

5.3.1. Adverse Events

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

5.3.2. Physical Examination

A full physical examination (PE) will be performed at each visit. A full PE will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system.

5.3.3. Vital Signs

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

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

At visits where participants receive study drug vital signs will be measured prior to study drug administration. When scheduled at the same time as a blood draw, vital signs will be performed prior to the blood collection.

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.

5.3.4. Clinical Laboratory Tests

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

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

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

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

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

Note: For Egypt-specific guidelines, refer to Appendix 6-5.

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, TIBC, ferritin) • Platelet count **Coagulation** • Prothrombin time • Activated partial thromboplastin time • D-dimer • Von Willebrand factor • Fibrinogen	**Serum Chemistry** • Blood Urea Nitrogen • Bilirubin (total, direct, and indirect) • Alkaline phosphatase • Aspartate aminotransferase • Alanine aminotransferase • Albumin • Sodium • Potassium • Magnesium • Calcium • Chloride • Bicarbonate • Glucose • Creatine kinase • Creatinine • Lactate dehydrogenase • CRP • hs-CRP • Total globulin • Total protein • IgG • Cystatin C • Lipid Panel – Total cholesterol – HDL – LDL – Triglycerides
Additional Tests • Hemoglobin genotype (if not previously determined) • Fetal hemoglobin • Serum pregnancy test (WOCBP only) • Urine pregnancy test (WOCBP only) • Follicle-stimulating hormone (FSH) for post-menopausal women	

Abbreviations: CRP, C-reactive protein; HDL, high density lipoprotein; hs-CRP, High sensitivity C-Reactive protein; LDL, low density lipoprotein; TIBC, total iron binding capacity; WOCBP, women of child-bearing potential.

5.4. Clinical Assessments

5.4.1. Demographic/Medical History

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

5.4.2. Pregnancy Screen

Pregnancy tests will be performed on female participants of childbearing potential as indicated in the Schedule of Assessments (Appendix 1). A serum pregnancy test will be conducted at Screening with urine pregnancy tests conducted thereafter. If the Day 1 urine test is positive, a pre-dose serum pregnancy test should be performed and dosing should be postponed until a negative result is confirmed; if positive, the participant will be considered a screen failure.

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

Note: For UK-specific study design, refer to Appendix 6-3.

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

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

5.4.4. Quality of Life Assessments

Participants (and/or their parent or legal guardian for participants under 18 years of age) will be asked to provide responses to 2 QOL surveys (PGI-C and ASCQ-Me) as well as to track their pain medication intake and any school or work missed due to their SCD symptoms. Participants (and/or their parent or legal guardian for participants under 18 years of age) will complete the ASCQ-Me questionnaire weekly, when available. Administration of some of these surveys 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) on their global impression of participant change in QOL.

5.4.5. VOC Incidence

The incidence of VOC events will be recorded weekly by the participant (and/or their parent or legal guardian for participants under 18 years of age) and collected every 4 weeks. Each month on non-treatment visit days, participants (and/or their parent or legal guardian for participants under 18 years of age) will be contacted by phone to determine if a VOC event or a pain crisis leading to contact with a healthcare provider without a visit to a medical facility has occurred, to collect AEs, and to record changes to concomitant medications.

Note: For France-, Germany-, UK-, and Ghana-specific guidelines, refer to Appendix 6-1, Appendix 6-2, Appendix 6-3, and Appendix 6-5, respectively.

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

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

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

5.5.1. Pharmacokinetics

In all participants, plasma samples will be collected for measurement of inclacumab concentrations at a central laboratory using a validated ligand-binding assay under the supervision of the Sponsor. Plasma concentrations of inclacumab will be measured before and after each dose, at the Week 6 Visit, at the end of the treatment period (Week 48), and – in all participants not enrolling in the OLE – at the Week 60 EOS Visit. Population PK analysis using nonlinear mixed effects modeling will be performed to characterize inclacumab PK in plasma.

5.5.2. Anti-drug Antibodies

In all participants, plasma samples will be collected for characterization of ADA on Day 1 (pre-dose), Week 12 (pre-dose), Week 24 (pre-dose), at Week 48, and – in all participants not enrolling in the OLE – at the Week 60 EOS Visit. The detection and characterization of anti-inclacumab antibodies will be performed at a central laboratory using validated bridging ADA assays under the supervision of the Sponsor. Other analyses may be performed to further characterize the immunogenicity of inclacumab, including assessment of neutralizing antibodies.

5.5.3. Pharmacodynamics

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

- Whole blood samples for PD assessment of non-activated and TRAP-activated PLA formation and PLT P-selectin expression by flow cytometry.
- Serum samples for PD assessment of P-selectin inhibition by SPR.
- Plasma samples for PD assessment of circulating soluble free and total P-selectin.

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

5.5.4. Biomarkers

Biomarkers to be evaluated include:

- Whole blood samples for assessment of RBC adhesion by microfluidic channels (at selected sites)
- Whole blood samples for genomic analysis (optional)
- Serum samples for assessment of protein markers by multiplex assay
- Urine samples for assessment of kidney function
- Plasma and whole blood samples for assessment of voxelotor concentrations (as applicable)

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

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

Note: For Egypt-specific assessments, refer to Appendix 6-5.

5.6. Unscheduled Visits for a VOC

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

5.7. Additional Unscheduled Visits

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

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

5.8. Missed Visits

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

5.9. Post-study Follow-up

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

5.10. Study Completion

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

5.10.1. Early Study Termination

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

6. CONCOMITANT MEDICATIONS AND PROCEDURES

6.1. Concomitant Medications

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

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

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

Other than the medications listed in Section 6.1.1, medications that are used as the standard of care for SCD will be allowed during the study.

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

6.1.1. Prohibited Medications and Therapies

Treatment with the following is not allowed during the study:

- Initiation of treatment with HU, ESA, (eg, EPO), voxelotor, crizanlizumab, or L-glutamine.
- Stem cell transplant.
- Active treatment on another investigational trial, including gene therapy for SCD.

- Initiation of a chronic transfusion program (pre-planned series of transfusions for prophylactic purposes).

Note: For UK-specific guidelines, refer to Appendix 6-3.

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/ET Visit.

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

6.3. Contraception Requirements

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

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

6.3.1. Instructions for Female Participants of Childbearing Potential

For female participants of childbearing potential (post-menarche) who are sexually active, pregnancy should be avoided by the use of a highly effective method of contraception (as outlined in Section 6.3.3) consistently throughout the study and for at least 165 days after dosing.

Female participants who become pregnant during the study will be withdrawn from the study. Pregnancy reporting requirements are outlined in Section 1.1.

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

For Male Participants with Female Partners Capable of Reproduction:

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

Pregnancy reporting is described in Section 1.1.

6.4. Continuation of Treatment

Participants who complete the treatment and study through Week 48 will not receive any further treatment with the study drug on this study. Participants who complete the study, and meet eligibility requirements, will be provided with the opportunity to receive open-label inclacumab in the OLE study. The first dose administered in the OLE study will occur after completion of the end-of-study evaluations at the Week 48 Visit.

7. ASSESSMENT OF SAFETY

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

The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in this section. At each visit, the study participant or participant caregiver (and/or their parent or legal guardian for participants under 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 and during monthly phone calls. See Section 7.2 for details regarding the required time periods for AE reporting.

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

7.1. Adverse Events

7.1.1. Definition of Adverse Events

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

7.1.2. Definition of Serious Adverse Events

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

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

NOTE: Hospitalization planned prior to study enrollment (eg, for elective surgeries) is not considered to be an SAE. Any complications arising from a planned hospitalization may be considered an 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: 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)

Table 2: 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.

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 under 18 years of age) signs the ICD/assent form until 3 months after last dose (Week 48)/or 6 months after last dose (Week 60) EOS Visit or ET Visit, whichever comes first. 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

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.

Note: For UK-specific information, refer to Appendix 6-3.

7.2.2. Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded separately on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

7.2.3. Abnormal Laboratory Values

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

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia".

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

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 5.

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 AESIs or SAEs, regardless of causal attribution, must be reported by the Investigator or designee or site personnel within 24 hours of AESI or SAE awareness. The AESI or SAE will be reported by completing the SAE eCRF. AESIs will be recorded on the SAE eCRF within 24 hours of the site's awareness of them, even if they do not meet criteria for an SAE. 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 as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than 7 calendar days of the Sponsor's or designee's first knowledge of the event and follow-up information submitted within an additional 8 calendar days, or as otherwise required per local laws and regulations. All other SUSARs will be submitted within 15 calendar days of the Sponsor's or designee's first knowledge of the event. The Investigator is responsible for notifying the local IRBs or ECs of all SAEs that occur at his or her site as required by local regulations or IRB/EC policies, if this responsibility resides with the site.

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

1.1. 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 under 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**.

7.4. Adverse Events That are VOC Endpoint Events

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

Note: For UK-specific guidelines, refer to Appendix 6-3.

Table 3: VOC Events Not Requiring AE/SAE Reporting

Uncomplicated VOC*
ACS
Hepatic sequestration

Table 3: VOC Events Not Requiring AE/SAE Reporting

Uncomplicated VOC*
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.

7.4.1. Procedures for Reporting and Documenting VOC Event Data

All VOCs, as defined in Section 5.1, are to be documented within the eCRF within **5 days** of a site becoming aware of such event. Each VOC is to be recorded only once on the "Vaso-Occlusive Event" eCRF page. All VOCs are to be recorded throughout the entire treatment period, up to Week 48, and should continue until the Follow-Up Visit at Week 60 for participants who do not enroll in the OLE study (or earlier if participant discontinues from the study). The Investigator will classify and provide all the following information for each VOC as follows:

- Diagnosis, which will be limited to one of the five pre-defined VOC events as described in Section 5.1:
  - Uncomplicated VOCs
  - Acute chest syndrome
  - Hepatic sequestration
  - Splenic sequestration
  - Priapism (requiring a visit to a medical facility)
- Onset date,
- Stop date,
- Action taken (None, Required concomitant medication, Temporarily withheld study drug, Permanent discontinuation of study drug, or Other [explain]),
- Whether or not hospitalization or a visit to emergency department, urgent care center, outpatient clinic, or infusion center was required,
- Concomitant medications given, and
- Outcome (Recovered without sequelae, Resolved with sequelae, Ongoing, Unknown, Death).

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

7.4.2. Source Document Collection for VOC Event Adjudication

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

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

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

Any SAE that is adjudicated by the endpoint adjudication committee NOT to meet endpoint criteria is reported back to the Investigator site of incidence. The Investigator must report the SAE to Sponsor Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The Investigator's SAE awareness date is the date on which the Investigator site of incidence receives the SAE back from the endpoint adjudication committee.

7.5. 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 Pfizer Safety or designee within 24 hours of Investigator awareness.

7.5.1. 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 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 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 Pfizer Safety. Since the exposure information does not pertain to the 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.

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 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.

7.5.2. 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.

The Investigator must report EDB to Pfizer Safety within 24 hours of the Investigator's awareness, irrespective of whether an SAE has occurred. 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.

7.5.3. Occupational Exposure

The Investigator must report any instance of occupational exposure to Pfizer Safety 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.

7.5.4. 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**.

7.5.5. 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; CRF, 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;
- 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 a SAE should be reported to Pfizer Safety within 24 hours.

7.6. Data Monitoring Committee

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

Initial enrollment of study participants will be limited to adults and adolescents 16 years of age or older. The DMC will review all available safety data and PK/PD data (as applicable)

from the first 20 participants who have completed a minimum of 12 weeks of study participation in the Phase 3 program in order to make a recommendation about enrollment of participants 12 to 15 years of age. Should the DMC recommend enrollment of participants 12 to 15 years of age, sites will be informed by the Sponsor. The DMC will continue close monitoring by meeting to review data of each 20 participants 12 to 15 years of age, or every 6 months, whichever occurs first. The DMC may also schedule ad hoc meetings at their discretion or at the Sponsor's request.

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

Note: For France-, Germany-, UK-specific guidelines, refer to Appendix 6-1, Appendix 6-2, and Appendix 6-3.

7.7. 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 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 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 originally completed SAE eCRF form with all changes signed and dated by the Investigator or designee. By signing the SAE eCRF form, the Investigator or designee attests to the accuracy and completeness of the data and that he/she has reviewed the report being submitted and approved.

Investigators are not obligated to actively seek SAE information from subjects 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 subject has discontinued or completed the study that they judge may be reasonably related to treatment with study drug or study participation.

7.8. Safety Responsibilities

7.8.1. 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.
- Complete the AE/SAE and/or AESI eCRF within 24 hours of the study site staff becoming aware of the event.
- Pursue AESI or SAE follow-up information actively and persistently. Follow-up information must be reported to Sponsor, or designee, within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the participants' medical records and submit documentation (with participant 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.

7.8.2. 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.

7.8.3. 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.
- 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 Clinical Trial (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

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

8.1. Study Endpoints

Study endpoints are provided in Section 3.2.

8.2. Determination of Sample Size

A sample size of approximately 240 participants (120 participants per treatment arm [inclacumab and placebo]) provides approximately 90% power to detect a targeted 45% reduction in the rate of VOCs, from an average rate of 3.0 VOCs per year on placebo to 1.65 VOCs per year on inclacumab, using a 2-sided test at an overall $\alpha = 0.05$ level.

Calculations were based on the methodology of Zhu and Lakkis (Zhu, 2014) and assume the number of VOCs per year follows a negative binomial distribution with a dispersion parameter of 1.04. For the purposes of sample size calculation, a drop-out rate of 25% by Week 48 was assumed.

8.3. Analysis Populations

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

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

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

8.4. Statistical Analysis

8.4.1. Summaries of Study Conduct

The number of participants randomized will be tabulated by region, country, study site, and treatment group. Participant disposition (the number of participants randomized, treated, completing study treatment, and completing the study) will be tabulated by treatment group. 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, number of VOCs in the prior 12 months, concomitant HU/hydrocarbamide (HC) use, prior crizanlizumab use, and geographic region, will be summarized for the ITT population by treatment group. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized. Exposure to study drug (number of study drug treatments) and time on study will also be summarized.

8.4.3. Efficacy Analyses

8.4.3.1. Primary Endpoint

For the primary efficacy endpoint, the rate of VOCs during the 48-week treatment period will be compared between the inclacumab and placebo arms with the use of negative binomial regression model.

The regression model will include covariates for treatment group (inclacumab, placebo) and the randomization stratification factors (Baseline HU use [yes; no], number of VOCs [2 to 4; 5 to 10] in the preceding 12 months, and geographic region [North America; sub-Saharan Africa; Europe/rest of world]). The logarithm of observed patient-time at risk will be used as an offset term in the model. The rate of VOCs adjusted for the specified Baseline covariates will be estimated for each treatment arm based on the regression model. Similarly, the ratio of the VOC rate (inclacumab versus placebo) along with the associated 95% confidence interval (CI) and p-value will be estimated from the regression model.

The regression model will be fit based on all observed data from randomized participants, regardless of adherence to study drug or to the protocol. Sensitivity analyses will be performed to assess the robustness of the primary analysis results. Details will be specified in the SAP.

8.4.3.2. Secondary Endpoints

For the secondary endpoints of time to first VOC and time to second VOC, treatment comparison between inclacumab and placebo will be performed based on a stratified log-rank test. Kaplan-Meier plots will be generated. Time to first and time to second VOC will be measured from randomization (Day 1) to onset date of the corresponding VOC event. A Cox

regression model will be used to estimate the hazard ratio between the inclacumab and placebo groups, as appropriate.

For the proportion of participants with no VOCs during the 48-week treatment period, the exact Cochran-Mantel-Haenszel (CMH) general association test, stratified by the randomization stratification factors, will be used.

For the rate of VOCs that required admission to a healthcare facility and treatment with parenteral pain medication and number of days of inpatient hospitalization for a VOC during the 48-week treatment period, the same statistical method used for the primary endpoint will be used.

8.4.3.3. Exploratory Endpoints

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

8.4.3.4. Interim Futility Analysis

One interim analysis for futility will be performed at an information fraction of approximately 48%. The futility analysis will include subjects who, by the selected data cutoff date, have the potential for at least 24 weeks of treatment (ie, 2 doses of the study drug).

For the futility analysis, the primary efficacy endpoint will be evaluated by the independent DMC. The study team will remain blinded. A Gamma family (-1) β-spending function will be used to determine the futility boundary. The futility boundary is considered non-binding.

Additional details will be provided in the SAP.

8.4.3.5. Adjustment for Multiple Comparisons

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

1. Rate of VOCs during the 48-week treatment period (primary endpoint)
2. Time to first VOC during the 48-week treatment period
3. Time to second VOC during the 48-week treatment period
4. Proportion of participants with no VOCs during the 48-week treatment period
5. Rate of VOCs that required admission to a healthcare facility and treatment with parenteral pain medication during the 48-week treatment period
6. Number of days of inpatient hospitalization for a VOC during the 48-week treatment period

Each endpoint will be tested at a 2-sided alpha level of 0.05. Formal testing of endpoints will continue until the first non-significant result. Testing of endpoints subsequent to a non-significant result will be considered exploratory in nature.

8.4.3.6. Safety Analyses

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

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of TEAEs, defined as events that occur on or after Day 1 of study treatment or the worsening of a 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 in laboratory parameters (hematology, serum chemistry, and coagulation) and vital signs (eg, BP, HR, and body temperature) over time will be summarized descriptively.

8.4.4. PK, ADA, and PD Analyses

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

8.4.4.1. Pharmacokinetic Analyses

Population PK analysis will include data from all participants who receive active study drug and have at least 1 measurable post-dose concentration. If any participants are found to have incomplete data, protocol deviations, or clinical events affecting PK, a decision will be made on a case-by-case basis as to their inclusion in the analysis. The influence of demographic covariates (such as body weight, sex, age, race) on inclacumab PK parameters will be investigated. If appropriate, the inclacumab PK data may be pooled with PK data from other studies. Results of population PK analyses will be reported separately.

A review of PK/PD data from at least 20 participants in the Phase 3 program for dose confirmation will be performed by the DMC.

Note: For France-specific guidelines, refer to Appendix 6-1.

8.4.4.2. Anti-drug Antibody Analyses

Analysis for ADAs will include data from all participants who receive active study drug and have at least 1 assessment for ADA after the start of dosing. Anti-drug antibody characterization will include but is not limited to, incidence, timing, and persistence of ADA. If any participants are found to have incomplete data, protocol deviations, or clinical events affecting ADA, a decision will be made on a case-by-case basis as to their inclusion in the analysis. The percentage of participants with confirmed ADA positivity during the study out of the total number tested will be summarized. The results of additional characterization will be reported separately. Correlation of ADA with PK, safety, and efficacy observations will be explored.

8.4.4.3. Pharmacodynamic Analyses

Pharmacodynamic results will be displayed graphically over time to observe changes from Baseline. For markers demonstrating correlative trends, population-based analyses, eg,

PK/PD or mechanistic modeling, may be explored to characterize the relationships between PK, PD, clinical labs, safety, and/or efficacy observations. The results of these exploratory analyses will be reported elsewhere.

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.

- 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, PEs, 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

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 Study Binder.

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 Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
- Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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.

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 Code of Federal Regulations (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 under 18 years of age) and answer all questions regarding the study. The participant (and/or their legal guardian for participants under 18 years of age) 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 (or their legally authorized representative [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 legal guardian for participants under 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 (or their legally authorized representative) must be informed that their 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 (or their legally authorized representative).

The participant (and/or their legal guardian for participants under 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 legal guardian for participants under 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 legal guardian for participants under 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 legal guardian for participants under 18 years of age).

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,

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.

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.

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 European Union Drug Regulating Authorities Clinical Trials Database/Clinical Trials Information System (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 the European Union (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

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 Requirement 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

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.

1.2. 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.

9.6. 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-, Ghana- and Egypt-specific schedule of assessments, refer to Appendix 6-3, Appendix 6-4, and Appendix 6-5, respectively.

Study Period	**Screening**	**Treatment Period**						**Follow-up**	**Upon Presentation for VOC**
Procedure	**Day -28 to -1**	**Baseline Day 1** [a]	**Week 6 Day 43 ±7 days**	**Week 12 Day 85 ±7 days**	**Week 24 Day 169 ±7 days**	**Week 36 Day 253 ±7 days**	**Week 48 Day 337 (EOS** [c]**/ET) ±7 days**	**Week 60** [b] **Day 421 EOS** [c] **±7 days**	
Informed consent/assent	X								
Review of eligibility criteria	X	X							
Demographics	X								
Medical history	X								
VOC History	X	X							
Height (cm) & Weight (kg) [d]	X	X		X	X	X	X		
Vital Signs [e]	X	X		X	X	X	X	X	
Physical Examination	X	X		X	X	X	X	X	
Chest X-ray [f]		←	- - - -	- - - -	- - - -	- - - -	- - - -	→	
CBC/diff [g] & Chemistry [h] (w FSH [i])	X	X	X	X	X	X	X	X	X
Hemoglobin Genotype [j]	X								
Fetal Hemoglobin		X							
Coagulation Assessments [k]	X	X	X	X	X		X		X
Pregnancy Test for WOCBP [i]	X	X	X	X	X	X	X	X	
Assessment of VOC & Other Pain Crises Events [l]		←	- - - -	- - - -	- - - -	- - - -	- - - -	→	
Randomization		X							
CGI-C				X	X	X	X		
PGI-C				X	X	X	X		
ASCQ-Me weekly at home by participant (and/or their parent or legal guardian for		X	X	X	X	X	X		

Study Period	Screening	Treatment Period						Follow-up	Upon Presentation for VOC
Procedure	Day -28 to -1	Baseline Day 1 [a]	Week 6 Day 43 ±7 days	Week 12 Day 85 ±7 days	Week 24 Day 169 ±7 days	Week 36 Day 253 ±7 days	Week 48 Day 337 (EOS [c]/ET) ±7 days	Week 60 [b] Day 421 EOS [c] ±7 days	
participants under 18 years of age) [m]									
ASCQ-Me [m]		X	X	X	X	X	X		
Study Drug Infusion		X		X	X	X			
PK, ADA, PD and biomarker sampling – Refer to the Schedule of Assessments in Appendix 2 and Appendix 3.									
Adverse Events	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	

Abbreviations: ACS, acute chest syndrome; ADA, anti-drug antibody; aPTT, activated partial thromboplastin time; ASCQ-Me, Adult Sickle Cell Quality of Life Measurement; CBC, complete blood count; CGI-C, clinician's global impression of change; EOS, end of study; ET, early termination; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein, HIV, human immunodeficiency virus; LDL, low-density lipoprotein; OLE, open-label extension; PD, pharmacodynamics; PGI-C, patient's global impression of change; PK, pharmacokinetics; PLT, platelet; PT, prothrombin time; VOC, vaso-occlusive crisis.

Note: During the treatment period, study assessments are to be collected pre-dose unless otherwise specified.

a. All blood draws for Baseline assessments will be obtained prior to study drug administration.
b. Week 60 (Day 421) Visit will be for participants who choose not to enroll, or are ineligible for, the OLE study. At this visit, safety and efficacy assessments and samples for PK, ADA, PD will be collected.
c. For participants electing to enroll in the OLE study, the Day 337 (Week 48) Visit will be the EOS Visit. For participants not enrolling in the OLE study, an additional required visit will occur on Day 421 (Week 60) for safety and PK/ADA/PD follow-up.
d. Height and weight to be captured at Screening with only weight captured thereafter.
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. Vital signs will also be collected at the completion of infusion and at one hour after completion of infusion. Participants should be clinically well with stable vital signs and without signs or symptoms of an infusion-related reaction prior to release from observation. A 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.
f. Chest X-ray required for all suspected cases of ACS.
g. Hematology assessments include the following: hemoglobin, hematocrit, white blood cells with differential, red blood cells, % and absolute reticulocytes, and PLTs. An iron panel will also be performed (iron, ferritin, total iron binding capacity [TIBC]). Collect at presentation for VOC as feasible.
h. Chemistry assessments include the following: blood urea nitrogen, bilirubin (total, direct and indirect), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, serum albumin, sodium, potassium, magnesium, calcium, chloride, glucose, bicarbonate, creatinine kinase, serum creatinine, total protein, total globulin, IgG. lactate dehydrogenase, cystatin-C, C-reactive protein (CRP), high sensitivity-reactive protein (hs-CRP), and lipid panel (total cholesterol, HDL, LDL, triglycerides). Collect at presentation for VOC as feasible.

Study Period	Screening	Treatment Period						Follow-up	Upon Presentation for VOC
Procedure	Day -28 to -1	Baseline Day 1 [a]	Week 6 Day 43 ±7 days	Week 12 Day 85 ±7 days	Week 24 Day 169 ±7 days	Week 36 Day 253 ±7 days	Week 48 Day 337 (EOS [c]/ET) ±7 days	Week 60 [b] Day 421 EOS [c] ±7 days	

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

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

k. Coagulation parameters are PT, aPTT, D-dimer, von Willebrand factor (vWF), and fibrinogen. Collect at presentation for VOC as feasible.

l. The incidence of VOC events will be recorded weekly by the participant (and/or their parent or legal guardian for participants under 18 years of age) and collected every 4 weeks (±7 days). On non-visit days (Week 4 [Day 29], Week 8 [Day 57], Week 16 [Day 113], Week 20 [Day 141], Week 28 [Day 197], Week 32 [Day 225], Week 40 [Day 281], and Week 44 [Day 309], participants (and/or their parent or legal guardian for participants under 18 years of age) will be contacted by phone to determine if a VOC event or a pain crisis 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.

m. The participant (and/or their parent or legal guardian for participants under 18 years of age) will complete the ASCQ-Me questionnaire weekly, when available. Questionnaires will be distributed to sites once available in local language. The ASCQ-Me questionnaire completed by participants (and/or their parent or legal guardian for participants under 18 years of age) at home will be collected during the participant's visits to the clinical site at Weeks 6, 12, 24, 36, and 48. In addition, the ASCQ-Me questionnaire will be administered during the participant's visits to the clinical site at Weeks 6, 12, 24, 36, and 48.

Appendix 2. Schedule of Assessments for Inclacumab PK, ADA, PD

Timepoint	Time Window	PK	ADA	SPR P-selectin Inhibition	PLA and PLT P-selectin	Free and Total sP-selectin
		Plasma	Plasma	Serum	Whole Blood	Plasma
Day 1 pre-dose	-30 min	X	X	X	X	X
Day 1 EOI	+5 min	X				
Day 1 EOI +45 min	± 15 min	X		X	X	X
Week 6	±7 days	X		X	X	X
Week 12 pre-dose	-30 min	X	X	X	X	X
Week 12 EOI	+5 min	X				X
Week 24 pre-dose	-30 min	X	X	X	X	X
Week 24 EOI	+5 min	X				X
Week 36 pre-dose	-30 min	X		X	X	X
Week 36 EOI	+5 min	X				X
Week 48	±7 days	X	X	X	X	X
Week 60 [a]	±7 days	X	X	X	X	X
Upon presentation for VOC [b]		X			X	X

Abbreviations: ADA, anti-drug antibody; EOI, end of infusion; OLE, open-label extension; PD, pharmacodynamics; PK, pharmacokinetics; PLA, platelet leukocyte aggregate; PLT, platelet; sP-selectin, soluble P-selectin; SPR, surface plasmon resonance; VOC, vaso-occlusive crisis.

a Week 60 (Day 421) Visit will be for participants who choose not to enroll, or are ineligible for, the OLE study.

b As feasible.

Appendix 3. Schedule of Assessments for Biomarkers

Timepoint	Time Window	RBC Adhesion [a]	Genomic Biobank [b]	Protein Multiplex	Urine Panel [c]	Voxelotor PK [d]
		Whole blood	Whole blood	Serum	Urine	Plasma & Whole Blood
Day 1 pre-dose	-30 min	X	X	X	X	X
Day 1 EOI +45m	±15 min	X				
Week 6	±7 days	X				
Week 12 pre-dose	-30 min	X		X		X
Week 48	±7 days	X	X	X	X	X
Upon presentation for VOC [e]				X	X	

Abbreviations: EOI, end of infusion; PK, pharmacokinetics; RBC, red blood cell; VOC, vaso-occlusive crisis.
a The RBC adhesion assay will be performed in a subset of participants at selected sites, if feasible.
b The Genomic Biobank sample is optional and should be performed in consenting subjects.
c A single spot urine will be collected on Day 1 (pre-dose) and Week 48. Urine panel assessments may include but are not limited to albumin, protein, creatinine, hemoglobin.
d Plasma/whole blood for assessment of voxelotor PK should be collected within 30 minutes prior to the dose of voxelotor. Voxelotor PK assessment is only applicable to subjects on a stable dose of voxelotor at Screening.
e As feasible.

Appendix 4. Infusion-Related Reaction Grading

The severity of infusion-related reactions (IRRs)will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0 per Table 5, 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

Table 5: Infusion-related Reactions

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

Appendix 5. 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."

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.

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.

- 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, prothrombin time/international normalized ratio, 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.

Appendix 6. Country-specific amendments

Appendix 6.1. France-Specific Amendment

3. Investigational Plan

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

3.1. Study Design

This study will assess the safety and efficacy of inclacumab in reducing the frequency of VOCs in approximately 240 adult and adolescent participants (≥ 12 years of age) globally with SCD. Initial enrollment will include participants ≥ 16 years of age until the independent Data Monitoring Committee (DMC) determines that adequate safety and PK data support the enrollment of participants 12 to 15 years of age. In France, only participants ≥ 18 years of age will be enrolled.

Eligible participants will be randomized with a 1:1 ratio into one of two treatment arms as follows:

- Inclacumab 30 mg/kg administered IV Q12W; or
- Placebo administered IV Q12W.

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

All participants will undergo safety, efficacy, and PK/PD assessments at Baseline and through Week 48. Visits to the clinical site for infusion of study drug will occur at Baseline (Day 1) and Q12W (Weeks 12, 24, and 36) for a total of 4 infusions. An additional visit at Week 6 will occur for safety, PK, and PD monitoring. The incidence of VOC events will be collected every 4 weeks, with participants contacted by phone at Weeks 4, 8, 16, 20, 28, 32, 40, and 44.

Following completion of the Week 48 visit, eligible participants will be given the option to enroll in an open-label extension (OLE) study (under a separate protocol) to receive inclacumab. Participants will receive their first dose in the OLE study at the same Week 48 visit. Participants enrolling in the OLE study will not be required to return to clinic for the Week 60 visit. Safety, efficacy, and PK/PD assessments will occur at Week 60 for participants not enrolling on the OLE study.

The 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. Details will be provided in the DMC Charter.

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

3.3.1.1. Inclusion Criteria

1. Participant has a confirmed diagnosis of SCD (HbSS, HbSC, HbSβ^0 thalassemia, or HbSβ^+ thalassemia genotype).

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

2. Participant is male or female, ≥ 18 years of age at the time of informed consent.
3. Participant has experienced between 2 and 10 VOCs within the 12 months prior to the Screening Visit as determined by documented medical history. A prior VOC is defined as an acute episode of pain that:

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

4. Participants receiving erythropoiesis-stimulating agents (ESA, eg, EPO) must be on a stable dose for at least 90 days prior to the Screening Visit and expected to continue with the stabilized regimen throughout the course of the study.
5. Participants receiving HU, L-glutamine, or voxelotor must be on a stable dose for at least 30 days prior to the Screening Visit and expected to continue with the stabilized regimen throughout the course of the study.
6. Participant has adequate venous access, in the opinion of the Investigator, to comply with study procedures.
7. Participant understands the study procedures and agrees to participate in the study by giving written informed consent.
8. Women of childbearing potential (WOCBP) are required to have a negative serum pregnancy test at the Screening Visit and negative urine pregnancy test on all subsequent clinic visits and must agree to use a highly effective method of contraception throughout the study period and for at least 165 days after dosing. See Section 6.3 for details on methods of contraception.

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

3.3.1.2 Exclusion Criteria

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

1. Participant is receiving regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventative transfusion).
2. Participant is taking or has received crizanlizumab (ADAKVEO) within 90 days prior to the Screening Visit.
3. Participant weighs > 133 kg (292 lbs.).
4. Participant has a significant active and poorly controlled (unstable) hepatic disorder clearly unrelated to SCD.
5. Participant has any of the following laboratory values at screening:
    a. Absolute neutrophil count (ANC) < 1.0×10^9/L
    b. Platelet count < 80×10^9/L
    c. Hemoglobin < 4.0 g/dL
    d. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 using Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula
6. Participant has known active (symptomatic) COVID infection or tests positive for COVID-19 during Screening.
7. Participant has a history of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to consent including severe or unstable pulmonary hypertension.
8. Participant has had treatment for a malignancy within the 12 months prior to the Screening Visit (except non-melanoma skin cancer and in situ cervical cancers).
9. Participant has had a stroke within the 2 years prior to the Screening Visit.
10. Participant has a positive test indicative of malaria infection at Screening. Testing to be conducted at local laboratories in malaria-endemic regions at the discretion of the Investigator.
11. Participant has any confirmed clinically significant drug allergy and/or known hypersensitivity to monoclonal antibody therapeutics or formulation components of the study drug or a related drug.
12. Participant has been in another investigational trial within 30 days or 5 half-lives of the investigational agent (whichever is greater) prior to the Screening Visit.
13. Participant has had a major surgery within 8 weeks prior to the Screening Visit.
14. Participant is pregnant, breastfeeding, or planning to become pregnant during the 48-week treatment period.

15. Participant is unlikely to comply with the study procedures; OR adult participant is subject to legal protection, unable to express consent or deprived of their liberty by a judicial or administrative decision.
16. Participant has other medical, psychological, or addictive condition that, in the opinion of the Investigator, would confound or interfere with evaluation of safety, efficacy, and/or PK of the investigational drug; prevent compliance with the study protocol; preclude informed consent; or render the participant unable/unlikely to comply with the study procedures.

5.4.5. Incidence of VOCs

The incidence of VOC events will be collected every 4 weeks. Each month on non-treatment visit days, participants will be contacted by phone to determine if a VOC event or a pain crisis leading to contact with a healthcare provider without a visit to a medical facility has occurred, to collect AEs, and to record changes to concomitant medications.

7.7. Data Monitoring Committee

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

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

8.4.4.1. Pharmacokinetic Analyses

Population PK analysis will include data from all participants who receive active study drug and have at least 1 measurable post-dose concentration. If any participants are found to have incomplete data, protocol deviations, or clinical events affecting PK, a decision will be made on a case-by-case basis as to their inclusion in the analysis. The influence of demographic covariates (such as body weight, sex, age, race) on inclacumab PK parameters will be investigated. If appropriate, the inclacumab PK data may be pooled with PK data from other studies. Results of population PK analyses will be reported separately.

A review of PK/PD data from at least 20 participants in the program for preliminary dose confirmation will be performed by the DMC.

9.5.3. Informed Consent/Assent Process

France-specific content is now replaced with new language per Pfizer (refer to Section 9.5.3).

Appendix 6.2. Germany-Specific Amendment

3.1. Study Design

This study will assess the safety and efficacy of inclacumab in reducing the frequency of VOCs in approximately 240 adult and adolescent participants (≥ 12 years of age) globally with SCD. Initial enrollment will include participants ≥ 16 years of age until the independent Data Monitoring Committee (DMC) determines that adequate safety and PK data support the enrollment of participants 12 to 15 years of age. In Germany, only participants ≥ 18 years of age will be enrolled.

Eligible participants will be randomized with a 1:1 ratio into one of two treatment arms as follows:

- Inclacumab 30 mg/kg administered IV Q12W; or
- Placebo administered IV Q12W.

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

All participants will undergo safety, efficacy, and PK/PD assessments at Baseline and through Week 48. Visits to the clinical site for infusion of study drug will occur at Baseline (Day 1) and Q12W (Weeks 12, 24, and 36) for a total of 4 infusions. An additional visit at Week 6 will occur for safety, PK, and PD monitoring. The incidence of VOC events will be collected every 4 weeks, with participants contacted by phone at Weeks 4, 8, 16, 20, 28, 32, 40, and 44.

Following completion of the Week 48 visit, eligible participants will be given the option to enroll in an open-label extension (OLE) study (under a separate protocol) to receive inclacumab. Participants will receive their first dose in the OLE study at the same Week 48 visit. Participants enrolling in the OLE study will not be required to return to clinic for the Week 60 visit. Safety, efficacy, and PK/PD assessments will occur at Week 60 for participants not enrolling on the OLE study.

The 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. Details will be provided in the DMC Charter.

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

3.3.1.1. Inclusion Criteria

1. Participant has a confirmed diagnosis of SCD (HbSS, HbSC, HbSβ^0 thalassemia, or HbSβ^+ thalassemia genotype).

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

2. Participant is male or female, ≥ 18 years of age at the time of informed consent.

3. Participant has experienced between 2 and 10 VOCs within the 12 months prior to the Screening Visit as determined by documented medical history. A prior VOC is defined as an acute episode of pain that:

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

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

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

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

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

8. Women of childbearing potential (WOCBP) are required to have a negative serum pregnancy test at the Screening Visit and negative urine pregnancy test on all subsequent clinic visits and must agree to use a highly effective method of contraception throughout the study period and for at least 165 days after dosing. See Section 6.3 for details on methods of contraception.

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

3.3.1.2. Exclusion Criteria

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

1. Participant is receiving regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventative transfusion).

2. Participant is taking or has received crizanlizumab (ADAKVEO) within 90 days prior to the Screening Visit.

3. Participant weighs > 133 kg (292 lbs.).

4. Participant has a significant active and poorly controlled (unstable) hepatic disorder clearly unrelated to SCD.

5. Participant has any of the following laboratory values at screening:

   a. Absolute neutrophil count (ANC) < 1.0×10^9/L

   b. Platelet count < 80×10^9/L

   c. Hemoglobin < 4.0 g/dL for adults

   d. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 using Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula in adults

6. Participant has known active (symptomatic) COVID infection or tests positive for COVID-19 during Screening.

7. Participant has a history of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to consent including severe or unstable pulmonary hypertension.

8. Participant has had treatment for a malignancy within the 12 months prior to the Screening Visit (except non-melanoma skin cancer and in situ cervical cancers).

9. Participant has had a stroke within the 2 years prior to the Screening Visit.

10. Participant has a positive test indicative of malaria infection at Screening. Testing to be conducted at local laboratories in malaria-endemic regions at the discretion of the Investigator.

11. Participant has any confirmed clinically significant drug allergy and/or known hypersensitivity to monoclonal antibody therapeutics or formulation components of the study drug or a related drug.

12. Participant has been in another investigational trial within 30 days or 5 half-lives of the investigational agent (whichever is greater) prior to the Screening Visit.

13. Participant has had a major surgery within 8 weeks prior to the Screening Visit.

14. Participant is pregnant, breastfeeding, or planning to become pregnant during the 48-week treatment period.

15. Participant are unlikely to comply with the study procedures.

16. Participant has other medical, psychological, or addictive condition that, in the opinion of the Investigator, would confound or interfere with evaluation of safety, efficacy, and/or PK of the investigational drug; prevent compliance with the study protocol; preclude informed consent; or render the participant or caretaker unable/unlikely to comply with the study procedures.

5.4.5. Incidence of VOCs

The incidence of VOC events will be collected every 4 weeks. Each month on non-treatment visit days, participants will be contacted by phone to determine if a VOC event or a pain crisis leading to contact with a healthcare provider without a visit to a medical facility has occurred, to collect AEs, and to record changes to concomitant medications.

7.7. Data Monitoring Committee

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

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

Appendix 6.3. UK-Specific Amendment

3.1. Study Design

This study will assess the safety and efficacy of inclacumab in reducing the frequency of VOCs in approximately 240 adult and adolescent participants (≥ 12 years of age) with SCD. Initial enrollment will include participants ≥ 16 years of age until the independent Data Monitoring

Committee (DMC) determines that adequate safety and PK data support the enrollment of participants 12 to 15 years of age, and the DMC recommendation has been approved by the regulatory authority.
Eligible participants will be randomized with a 1:1 ratio into one of two treatment arms as follows:

- Inclacumab 30 mg/kg administered IV Q12W; or
- Placebo administered IV Q12W.

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

All participants will undergo safety, efficacy, and PK/PD assessments at Baseline and through Week 48. Visits to the clinical site for infusion of study drug will occur at Baseline (Day 1) and Q12W (Weeks 12, 24, and 36) for a total of 4 infusions. An additional visit at Week 6 will occur for safety, PK, and PD monitoring. The incidence of VOC events will be recorded weekly by the participant and collected every 4 weeks, with participants contacted by phone at Weeks 4, 8, 16, 20, 28, 32, 40, and 44.

Following completion of the Week 48 visit, eligible participants will be given the option to enroll in an open-label extension (OLE) study (under a separate protocol) to receive inclacumab. Participants will receive their first dose in the OLE study at the same Week 48 visit. Participants enrolling in the OLE study will not be required to return to clinic for the Week 60 visit. Safety, efficacy, and PK/PD assessments will occur at Week 60 for participants not enrolling on the OLE study.

The 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. Details will be provided in the DMC Charter.

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

3.3.1.1. Inclusion Criteria

1. Participant has a confirmed diagnosis of SCD (HbSS, HbSC, HbSβ^0 thalassemia, or HbSβ^+ thalassemia genotype).

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

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

   NOTE: Initial study enrollment will include participants ≥ 16 years of age until the DMC determines that adequate safety and PK data support the enrollment of participants 12 to 15 years of age, and the DMC recommendation has been approved by the regulatory authority. Sites will be informed by the Sponsor when participants 12 to 15 years of age may be enrolled.

3. Participant has experienced between 2 and 10 VOCs within the 12 months prior to the Screening Visit as determined by documented medical history. A prior VOC is defined as an acute episode of pain that:

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

4. Participants receiving erythropoiesis-stimulating agents (ESA, eg, EPO) must be on a stable dose for at least 90 days prior to the Screening Visit and expected to continue with the stabilized regimen throughout the course of the study.
5. Participants receiving HU, L-glutamine, or voxelotor must be on a stable dose for at least 30 days prior to the Screening Visit and expected to continue with the stabilized regimen throughout the course of the study.
6. Participant has adequate venous access, in the opinion of the Investigator, to comply with study procedures.
7. Participant understands the study procedures and agrees to participate in the study by giving written informed consent or parental permission/written assent.
8. Women of childbearing potential (WOCBP) are required to have a negative serum pregnancy test at the Screening Visit and negative urine pregnancy test monthly on all subsequent clinic or telephone visits and must agree to use a highly effective method of contraception throughout the study period and for at least 165 days after dosing. See Section 6.3 for details on methods of contraception.

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

3.3.1.2. Exclusion Criteria

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

1. Participant is receiving regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventative transfusion).
2. Participant is taking or has received crizanlizumab (ADAKVEO) within 90 days prior to the Screening Visit.
3. Participant weighs > 133 kg (292 lbs.).
4. Participant has severe hepatic impairment unrelated to SCD.
5. Participant has any of the following laboratory values at screening:
   a. Absolute neutrophil count (ANC) < 1.0×10^9/L
   b. Platelet count < 80×10^9/L

c. Hemoglobin < 4.0 g/dL for adults and < 5.0 g/dL for participants ages 12 to < 18 years of age

d. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 using Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula in adults, and Schwartz formula in adolescents

6. Participant has known active (symptomatic) COVID infection or tests positive for COVID-19 during Screening.
7. Participant has a history of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to consent including severe or unstable pulmonary hypertension.
8. Participant has had treatment for a malignancy within the 12 months prior to the Screening Visit (except non-melanoma skin cancer and in situ cervical cancers).
9. Participant has had a stroke within the 2 years prior to the Screening Visit.
10. Participant has a positive test indicative of malaria infection at Screening. Testing to be conducted at local laboratories in malaria-endemic regions at the discretion of the Investigator.
11. Participant has any confirmed clinically significant drug allergy and/or known hypersensitivity to monoclonal antibody therapeutics or formulation components of the study drug or a related drug.
12. Participant has been in another investigational trial within 30 days or 5 half-lives of the investigational agent (whichever is greater) prior to the Screening Visit.
13. Participant has had a major surgery within 8 weeks prior to the Screening Visit.
14. Participant is pregnant, breastfeeding, or planning to become pregnant during the 48-week treatment period.
15. Participant, parent, or legal guardian are unlikely to comply with the study procedures.
16. Participant has other medical, psychological, or addictive condition that, in the opinion of the Investigator, would confound or interfere with evaluation of safety, efficacy, and/or PK of the investigational drug; prevent compliance with the study protocol; preclude informed consent; or render the participant, parent, or caretaker unable/unlikely to comply with the study procedures.

3.3.3.1.1. Early Discontinuation of Study Treatment

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

- Adverse event
- Withdrawal of consent
- 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.
- 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 3.3.3.1.

Participants who discontinue from study treatment will be encouraged to continue to participate in the study assessments, as applicable. Participants who are discontinued from study treatment due to pregnancy will also be discontinued from the study (Section 3.3.3.1). A participant may be discontinued from study treatment at any time at the discretion of the Investigator in accordance with his or her clinical judgment.

4.8.3. Blinding Procedures

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

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

5.4.2. Pregnancy Screen

Pregnancy tests will be performed on female participants of child-bearing potential as indicated in the Schedule of Assessments (Appendix 1). A serum pregnancy test will be conducted at Screening with urine pregnancy tests conducted thereafter. If the Day 1 urine test is positive, a pre-dose serum pregnancy test should be performed and dosing should be postponed until a negative result is confirmed; if positive, the participant will be considered a screen failure.

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

6.1.2. Prohibited Medications and Therapies

Treatment with the following is not allowed during the study:

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

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 3.3.3.1.1).

7.2.1 General (Adverse Events)

All AEs/SAEs will be recorded from the time the study participant (and/or their parent or legal guardian for participants under 18 years of age) signs the ICD/assent form until 3 months after last dose (Week 48)/or 6 months after last dose (Week 60) EOS Visit or ET Visit, whichever is later. 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 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.

7.7. 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, with the support of an independent data coordinating center.

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

Appendix 1. Schedule of Assessments

Study Period	**Screening**	**Treatment Period**						**Follow-up**	**Upon Presentation for VOC**
			Week 6	**Week 12**	**Week 24**	**Week 36**	**Week 48**	**Week 60** [b]	
Procedure	**Day -28 to -1**	**Baseline Day 1** [a]	**Day 43 ±7 days**	**Day 85 ±7 days**	**Day 169 ±7 days**	**Day 253 ±7 days**	**Day 337 (EOS** [c]**/ET) ±7 days**	**Day 421 EOS** [c] **±7 days**	
Informed Consent/Assent	X								
Review of Eligibility Criteria	X	X							
Demographics	X								
Medical History	X								
VOC History	X	X							
Height (cm) & Weight (kg) [d]	X	X		X	X	X	X		
Vital Signs [e]	X	X		X	X	X	X	X	
Physical Examination	X	X		X	X	X	X	X	
Chest X-ray [f]		←---	------	------	------	------	------	---→	
CBC/diff [g] & Chemistry [h] (w FSH [i])	X	X	X	X	X	X	X	X	X
Hemoglobin Genotype [j]	X								
Fetal Hemoglobin		X							
Coagulation Assessments [k]	X	X	X	X	X		X		X
Pregnancy Test for WOCBP [i]	X	X	X	X	X	X	X	X	
Assessment of VOC & Other Pain Crises Events [l]		←---	------	------	------	------	---→		
Randomization		X							
CGI-C				X	X	X	X		
PGI-C				X	X	X	X		
ASCQ-Me [m]		←---	------	------	------	---→			
Study Drug Infusion		X		X	X	X			
PK, ADA, PD and Biomarker Sampling – Refer to the Schedule of Assessments in Appendix 2 and Appendix 3.									
Adverse Events	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	

Study Period	Screening	Treatment Period						Follow-up	Upon Presentation for VOC
Procedure	Day -28 to -1	Baseline Day 1 [a]	Week 6 Day 43 ±7 days	Week 12 Day 85 ±7 days	Week 24 Day 169 ±7 days	Week 36 Day 253 ±7 days	Week 48 Day 337 (EOS [c]/ET) ±7 days	Week 60 [b] Day 421 EOS [c] ±7 days	

Abbreviations: ADA, anti-drug antibody; aPTT, activated partial thromboplastin time; ASCQ-Me, Adult Sickle Cell Quality of Life Measurement; CBC, complete blood count; CGI-C, clinician's global impression of change; EOS, end of study; ET, early termination; FSH, follicle stimulating hormone; HDL, high-density lipoprotein, HIV, human immunodeficiency virus; LDL, low-density lipoprotein; OLE, open-label extension; PD, pharmacodynamics; PGI-C, patient's global impression of change; PK, pharmacokinetics; PT, prothrombin time; VOC, vaso-occlusive crisis.

Note: During the treatment period, study assessments are to be collected pre-dose unless otherwise specified.

a. All blood draws for Baseline assessments will be obtained prior to study drug administration.
b. Week 60 (Day 421) visit will be for participants who choose not to enroll, or are ineligible for, the open-label extension study. At this visit, safety and efficacy assessments and samples for PK, ADA, PD will be collected.
c. For participants electing to enroll in the OLE study, the Day 337 (Week 48) visit will be the EOS Visit. For participants not enrolling in the OLE study, an additional required visit will occur on Day 421 (Week 60) for safety and PK/ADA/PD follow-up.
d. Height and weight to be captured at Screening with only weight captured thereafter.
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. Vital signs will also be collected at the completion of infusion and at one hour after completion of infusion. Participants should be clinically well with stable vital signs and without signs or symptoms of an infusion-related reaction prior to release from observation. A 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.
f. Chest X-ray required for all suspected cases of acute chest syndrome (ACS).
g. Hematology assessments include the following: hemoglobin, hematocrit, white blood cells with differential, red blood cells, % and absolute reticulocytes, and platelets. An iron panel will also be performed (iron, ferritin, total iron binding capacity [TIBC]). **Collect at presentation for VOC, as feasible.**
h. Chemistry assessments include the following: blood urea nitrogen, bilirubin (total, direct and indirect), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, serum albumin, sodium, potassium, magnesium, calcium, chloride, glucose, bicarbonate, creatinine kinase, serum creatinine, total protein, total globulin, IgG. lactate dehydrogenase, cystatin-C, C-reactive protein (CRP), high sensitivity-reactive protein (hs-CRP), and lipid panel (total cholesterol, HDL, LDL, triglycerides). **Collect at presentation for VOC, as feasible.**
i. Pregnancy tests will be performed on women of child-bearing potential (WOCBP). A serum test will be conducted at screening and a urine test at subsequent visits. Urine pregnancy tests will be conducted monthly, including during clinic visits every 12 weeks. The site will query the participant for results of the monthly UPT at each monthly telephone call. A positive urine pregnancy test at any time during the study requires confirmation via a serum pregnancy test. Female participants will not be considered of childbearing potential if they are pre-menarchal, surgically sterile (hysterectomy, bilateral salpingectomy, tubal ligation, or bilateral oophorectomy) or postmenopausal (no menses for 12 months without an alternative medical cause, confirmed by follicle-stimulating hormone test results).
j. Hemoglobin genotyping will be performed if the genotype is unknown.
k. Coagulation parameters are PT, aPTT, D-dimer, von Willebrand factor (vWF), and fibrinogen, as feasible.
l. The incidence of VOC events will be collected every 4 weeks (±7 days). On non-visit days (Week 4 [Day 29], Week 8 [Day 57], Week 16 [Day 113], Week 20 [Day 141], Week 28 [Day 197], Week 32 [Day 225], Week 40 [Day 281], and Week 44 [Day 309], participants will be contacted by phone to determine if a VOC event or a pain crisis 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.
m. The participant will complete the ASCQ-Me questionnaire weekly. Questionnaires will be distributed to sites once available in local language. The ASCQ-Me will be collected during the participant's visits to the clinical site at Weeks 6, 12, 24, 36, and 48.

Appendix 6.4. Ghana-Specific Amendment

Section 3.1. Study Design

This study will assess the safety and efficacy of inclacumab in reducing the frequency of VOCs in approximately 240 adult and adolescent participants (≥ 12 years of age) with SCD globally. Initial enrollment will include participants ≥ 16 years of age until the independent Data Monitoring Committee (DMC) determines that adequate safety and PK data support the enrollment of participants 12 to 15 years of age.

Eligible participants will be randomized with a 1:1 ratio into one of two treatment arms as follows:

- Inclacumab 30 mg/kg administered IV Q12W; or
- Placebo administered IV Q12W.

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

All participants will undergo safety, efficacy, and PK/PD assessments at Baseline and through Week 48. Visits to the clinical site for infusion of study drug will occur at Baseline (Day 1) and Q12W (Weeks 12, 24, and 36) for a total of 4 infusions. An additional visit at Week 6 will occur for safety, PK, and PD monitoring. The incidence of VOC events will be collected every 4 weeks, with participants contacted by phone at Weeks 4, 8, 16, 20, 28, 32, 40, and 44.

Following completion of the Week 48 visit, eligible participants will be given the option to enroll in an open-label extension (OLE) study (under a separate protocol) to receive inclacumab. Participants will receive their first dose in the OLE study at the same Week 48 visit. Participants enrolling in the OLE study will not be required to return to clinic for the Week 60 visit. Safety, efficacy, and PK/PD assessments will occur at Week 60 for participants not enrolling on the OLE study.

The 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. Details will be provided in the DMC Charter.

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

Section 5.4.5. VOC Incidence

The incidence of VOC events will be collected every 4 weeks. Each month on non-treatment visit days, participants will be contacted by phone to determine if a VOC event or a pain crisis leading to contact with a healthcare provider without a visit to a medical facility has occurred, to collect AEs, and to record changes to concomitant medications.

Appendix 1. Schedule of Assessments

Study Period	Screening	Treatment Period						Follow-up	Upon Presentation for VOC
Procedure	Day -28 to -1	Baseline Day 1 [a]	Week 6 Day 43 ±7 days	Week 12 Day 85 ±7 days	Week 24 Day 169 ±7 days	Week 36 Day 253 ±7 days	Week 48 Day 337 (EOS [c]/ET) ±7 days	Week 60 [b] Day 421 EOS [c] ±7 days	
Informed consent/assent	X								
Review of eligibility criteria	X	X							
Demographics	X								
Medical history	X								
VOC History	X	X							
Height (cm) & Weight (kg) [d]	X	X		X	X	X	X		
Vital Signs [e]	X	X		X	X	X	X	X	
Physical Examination	X	X		X	X	X	X	X	
Chest X-ray [f]		←	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	→	
CBC/diff [g] & Chemistry [h] (w FSH [i])	X	X	X	X	X	X	X	X	X
Hemoglobin Genotype [j]	X								
Fetal Hemoglobin		X							
Coagulation Assessments [k]	X	X	X	X	X		X		X
Pregnancy Test for WOCBP [i]	X	X	X	X	X	X	X	X	
COVID-19 Test	X								
Malaria Test [l]	X								
Assessment of VOC & Other Pain Crises Events [m]		←	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	→	
Randomization		X							
CGI-C				X	X	X	X		
PGI-C				X	X	X	X		
ASCQ-Me weekly at home by participant (and/or their parent or legal guardian for participants under 18 years of age) [n]		X	X	X	X	X	X		
Study Drug Infusion		X		X	X	X			

Study Period	Screening	Treatment Period						Follow-up	Upon Presentation for VOC
Procedure	Day -28 to -1	Baseline Day 1 [a]	Week 6 Day 43 ±7 days	Week 12 Day 85 ±7 days	Week 24 Day 169 ±7 days	Week 36 Day 253 ±7 days	Week 48 Day 337 (EOS [c]/ET) ±7 days	Week 60 [b] Day 421 EOS [c] ±7 days	
PK, ADA, PD and Biomarker Sampling – Refer to the Schedule of Assessments in Appendix 2 and Appendix 3.									
Adverse Events	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	

Abbreviations: ACS, acute chest syndrome; ADA, anti-drug antibody; aPTT, activated partial thromboplastin time; ASCQ-Me, Adult Sickle Cell Quality of Life Measurement; CBC, complete blood count; CGI-C, clinician's global impression of change; COVID-19, corona virus disease 2019; EOS, end of study; ET, early termination; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein, HIV, human immunodeficiency virus; LDL, low-density lipoprotein; OLE, open-label extension; PD, pharmacodynamics; PGI-C, patient's global impression of change; PK, pharmacokinetics; PLT, platelet; PT, prothrombin time; VOC, vaso-occlusive crisis.

Note: During the treatment period, study assessments are to be collected pre-dose unless otherwise specified.

a. All blood draws for Baseline assessments will be obtained prior to study drug administration.
b. Week 60 (Day 421) Visit will be for participants who choose not to enroll, or are ineligible for, the OLE study. At this visit, safety and efficacy assessments and samples for PK, ADA, PD will be collected.
c. For participants electing to enroll in the OLE study, the Day 337 (Week 48) Visit will be the EOS Visit. For participants not enrolling in the OLE study, an additional required visit will occur on Day 421 (Week 60) for safety and PK/ADA/PD follow-up.
d. Height and weight to be captured at Screening with only weight captured thereafter.
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. Vital signs will also be collected at the completion of infusion and at one hour after completion of infusion. Participants should be clinically well with stable vital signs and without signs or symptoms of an infusion-related reaction prior to release from observation. A 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.
f. Chest X-ray required for all suspected cases of ACS.
g. Hematology assessments include the following: hemoglobin, hematocrit, white blood cells with differential, red blood cells, % and absolute reticulocytes, and PLTs. An iron panel will also be performed (iron, ferritin, total iron binding capacity [TIBC]). Collect at presentation for VOC as feasible.
h. Chemistry assessments include the following: blood urea nitrogen, bilirubin (total, direct and indirect), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, serum albumin, sodium, potassium, magnesium, calcium, chloride, glucose, bicarbonate, creatinine kinase, serum creatinine, total protein, total globulin, IgG. lactate dehydrogenase, cystatin-C, C-reactive protein (CRP), high sensitivity-reactive protein (hs-CRP), and lipid panel (total cholesterol, HDL, LDL, triglycerides). Collect at presentation for VOC as feasible.
i. Pregnancy tests will be performed on women of child-bearing potential (WOCBP). A serum test will be conducted at screening and a urine test at subsequent visits. A positive urine pregnancy test at any time during the study requires confirmation via a serum pregnancy test. Female participants will not be considered of childbearing potential if they are pre-menarchal, surgically sterile (hysterectomy, bilateral salpingectomy, tubal ligation, or bilateral oophorectomy) or postmenopausal (no menses for 12 months without an alternative medical cause, confirmed by follicle-stimulating hormone test results).
j. Hemoglobin genotyping will be performed if the genotype is unknown.
k. Coagulation parameters are PT, aPTT, D-dimer, von Willebrand factor (vWF), and fibrinogen. Collect at presentation for VOC as feasible.
l. Testing to be conducted at local laboratories in malaria-endemic regions at the discretion of the Investigator.
m. The incidence of VOC events will be collected every 4 weeks (±7 days). On non-visit days (Week 4 [Day 29], Week 8 [Day 57], Week 16 [Day 113], Week 20 [Day 141], Week 28 [Day 197], Week 32 [Day 225], Week 40 [Day 281], and Week 44 [Day 309], participants (and/or their parent or legal guardian for participants under 18 years of

Study Period	Screening	Treatment Period						Follow-up	Upon Presentation for VOC
Procedure	Day -28 to -1	Baseline Day 1 [a]	Week 6 Day 43 ±7 days	Week 12 Day 85 ±7 days	Week 24 Day 169 ±7 days	Week 36 Day 253 ±7 days	Week 48 Day 337 (EOS [c]/ET) ±7 days	Week 60 [b] Day 421 EOS [c] ±7 days	

age) will be contacted by phone to determine if a VOC event or a pain crisis 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.

n. The participant (and/or their parent or legal guardian for participants under 18 years of age) will complete the ASCQ-Me questionnaire weekly, when available. Questionnaires will be distributed to sites once available in local language. The ASCQ-Me questionnaire completed by participants (and/or their parent or legal guardian for participants under 18 years of age) at home will be collected during the participant's visits to the clinical site at Weeks 6, 12, 24, 36, and 48. In addition, the ASCQ-Me questionnaire will be administered during the participant's visits to the clinical site at Weeks 6, 12, 24, 36, and 48.

Appendix 6.5. Egypt-Specific Amendment

3.1. Study Design

This study will assess the safety and efficacy of inclacumab in reducing the frequency of VOCs in approximately 240 adult and adolescent participants (≥ 12 years of age) with SCD globally. Initial enrollment will include participants ≥ 16 years of age until the independent Data Monitoring Committee (DMC) recommends to the Sponsor that adequate safety and PK data

support the enrollment of participants 12 to 15 years of age. Eligible participants will be randomized with a 1:1 ratio into one of two treatment arms as follows:

- Inclacumab 30 mg/kg administered IV Q12W; or
- Placebo administered IV Q12W.

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

All participants will undergo safety and efficacy assessments at Baseline and through Week 48. Visits to the clinical site for infusion of study drug will occur at Baseline (Day 1) and Q12W (Weeks 12, 24, and 36) for a total of 4 infusions. The incidence of VOC events will be recorded weekly by the participant and collected every 4 weeks, with participants contacted by phone at Weeks 4, 8, 16, 20, 28, 32, 40, and 44.

Following completion of the Week 48 Visit, eligible participants will be given the option to enroll in an open-label extension (OLE) study (under a separate protocol) to receive inclacumab. Participants will receive their first dose in the OLE study at the same Week 48 Visit. Participants enrolling in the OLE study will not be required to return to clinic for the Week 60 Visit. Safety and efficacy assessments will occur at Week 60 for participants not enrolling on the OLE study.

The 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. Details are provided in the DMC Charter.

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

3.2.5. Exploratory Pharmacology Endpoints

The following exploratory pharmacology endpoints will be assessed:

- Plasma PK of inclacumab as assessed by population PK analysis using nonlinear mixed-effects modeling.
- The incidence of ADA to inclacumab.
- Pharmacodynamics including changes in non-activated and TRAP-activated PLA, PLT P-selectin expression, serum P-selectin inhibition measured by surface plasmon resonance (SPR), and plasma total and free soluble P-selectin (sP-selectin) over time.

- Biomarkers including changes in RBC adhesion (selected sites) genomic markers (optional), protein markers in the blood, urine markers of kidney function, and voxelotor plasma and whole blood concentrations (as applicable).

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

Note: blood samples for the determination of PK, PD, ADA, and biomarker endpoints will not be collected at sites located in Egypt.

3.3.1.2. Exclusion Criteria

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

1. Participant is receiving regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventative transfusion).
2. Participant is taking or has received crizanlizumab (ADAKVEO) within 90 days prior to the Screening Visit.
3. Participant weighs > 133 kg (292 lbs).
4. Participant has a significant active and poorly controlled (unstable) hepatic disorder clearly unrelated to SCD.
5. Participant has any of the following laboratory values at screening:
    a. Absolute neutrophil count (ANC) < 1.0×10^9/L
    b. Platelet count < 80×10^9/L
    c. Hemoglobin < 4.0 g/dL for adults and < 5.0 g/dL for participants ages 12 to < 18 years of age
    d. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 using Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula in adults, and Schwartz formula in adolescents
6. Participant has known active (symptomatic) COVID-19 infection or tests positive for COVID-19 during Screening.
7. Participant has a history of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to consent including severe or unstable pulmonary hypertension.
8. Participant has had treatment for a malignancy within the 12 months prior to the Screening Visit (except non-melanoma skin cancer and in situ cervical cancers).
9. Participant has had a stroke within the 2 years prior to the Screening Visit.
10. Participant has a positive test indicative of malaria infection at Screening. Testing to be conducted at local laboratories in malaria-endemic regions at the discretion of the Investigator.

11. Participant has any confirmed clinically significant drug allergy and/or known hypersensitivity to monoclonal antibody therapeutics or formulation components of the study drug or a related drug.
12. Participant has been in another investigational trial within 30 days or 5 half-lives of the investigational agent (whichever is greater) prior to the Screening Visit.
13. Participant has had a major surgery within 8 weeks prior to the Screening Visit.
14. Participant is pregnant, breastfeeding, or planning to become pregnant during the 48-week treatment period.
15. Participant, parent, or legal guardian are unlikely to comply with the study procedures.

Participant has any other medical, psychological, or behavioral conditions that, in the opinion of the Investigator, would confound or interfere with evaluation of safety, efficacy, and/or PK of the investigational drug; prevent compliance with the study protocol; preclude informed consent; or render the participant, parent, or caretaker unable/unlikely to comply with the study procedures. (Note: blood samples for the determination of PK, PD, ADA, and biomarker endpoints will not be collected at sites located in Egypt.)

5. Study Assessments

The Schedule of Assessments (Appendix 1) summarizes the clinical procedures to be performed. Assessments and procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the Investigator or designee and/or the Sponsor for reasons related to participant safety.

5.3.4. Clinical Laboratory Tests

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

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

discretion of the Investigator.

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

Laboratory 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 and urine samples are provided in the Laboratory Manual.

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

A urine sample will be collected on Day 1 (pre-dose) and Week 48 for the assessment of biomarkers, including albumin, protein, creatinine, and hemoglobin.

Note: blood samples for the determination of PK, PD, ADA, and biomarker endpoints will not be collected at sites located in Egypt.

8.4.4. PK, PD, and ADA Analyses

Note: blood samples for the determination of PK, PD, ADA, and biomarker endpoints will not be collected at sites located in Egypt.

Appendix 1. Schedule of Assessments

Study Period	Screening	Treatment Period						Follow-up	Upon Presentation for VOC
Procedure	Day -28 to -1	Baseline Day 1 [a]	Week 6 Day 43 ±7 days	Week 12 Day 85 ±7 days	Week 24 Day 169 ±7 days	Week 36 Day 253 ±7 days	Week 48 Day 337 (EOS [c]/ET) ±7 days	Week 60 [b] Day 421 EOS [c] ±7 days	
Informed consent/assent	X								
Review of eligibility criteria	X	X							
Demographics	X								
Medical history	X								
VOC History	X	X							
Height (cm) & Weight (kg) [d]	X	X		X	X	X	X		
Vital Signs [e]	X	X		X	X	X	X	X	
Physical Examination	X	X		X	X	X	X	X	
Chest X-ray [f]		←	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - →	
CBC/diff [g] & Chemistry [h] (w FSH [i])	X	X	X	X	X	X	X	X	X
Hemoglobin Genotype [j]	X								
Fetal Hemoglobin		X							
Coagulation Assessments [k]	X	X	X	X	X		X		X
Urine spot test [l]	X						X		X
Pregnancy Test for WOCBP [i]	X	X	X	X	X	X	X	X	
Assessment of VOC & Other Pain Crises Events [m]		←	- - - - -	- - - - -	- - - - -	- - - - -	- - - - -	- - →	
Randomization		X							

Study Period	Screening	Treatment Period						Follow-up	Upon Presentation for VOC
Procedure	Day -28 to -1	Baseline Day 1 [a]	Week 6 Day 43 ±7 days	Week 12 Day 85 ±7 days	Week 24 Day 169 ±7 days	Week 36 Day 253 ±7 days	Week 48 Day 337 (EOS [c]/ET) ±7 days	Week 60 [b] Day 421 EOS [c] ±7 days	
CGI-C				X	X	X	X		
PGI-C				X	X	X	X		
ASCQ-Me weekly at home by participant [n]		X	X	X	X	X	X		
ASCQ-Me [n]		X	X	X	X	X	X		
Study Drug Infusion		X		X	X	X			
Adverse Events	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	

Abbreviations: ACS, acute chest syndrome; aPTT, activated partial thromboplastin time; ASCQ-Me, Adult Sickle Cell Quality of Life Measurement; CBC, complete blood count; CGI-C, clinician's global impression of change; EOS, end of study; ET, early termination; FSH, follicle-stimulating hormone; HDL, high-density lipoprotein, HIV, human immunodeficiency virus; LDL, low-density lipoprotein; OLE, open-label extension; PGI-C, patient's global impression of change; PLT, platelet; PT, prothrombin time; VOC, vaso-occlusive crisis; WOCBP, women of child-bearing potential.

Note: During the treatment period, study assessments are to be collected pre-dose unless otherwise specified.

a. All blood draws for Baseline assessments will be obtained prior to study drug administration.
b. Week 60 (Day 421) Visit will be for participants who choose not to enroll, or are ineligible for, the OLE study. At this visit, safety, and efficacy assessments will be collected.
c. For participants electing to enroll in the OLE study, the Day 337 (Week 48) Visit will be the EOS Visit. For participants not enrolling in the OLE study, an additional required visit will occur on Day 421 (Week 60) for safety follow-up.
d. Height and weight to be captured at Screening with only weight captured thereafter.
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. Vital signs will also be collected at the completion of infusion and at one hour after completion of infusion. Participants should be clinically well with stable vital signs and without signs or symptoms of an infusion-related reaction prior to release from observation. A 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.
f. Chest X-ray required for all suspected cases of ACS.
g. Hematology assessments include the following: hemoglobin, hematocrit, white blood cells with differential, red blood cells, % and absolute reticulocytes, and PLTs. An iron panel will also be performed (iron, ferritin, total iron binding capacity [TIBC]). **Collect at presentation for VOC, as feasible.**
h. Chemistry assessments include the following: blood urea nitrogen, bilirubin (total, direct and indirect), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, serum albumin, sodium, potassium, magnesium, calcium, chloride, glucose, bicarbonate, creatinine kinase, serum creatinine, total protein, total globulin, IgG. lactate dehydrogenase, cystatin-C, C-reactive protein (CRP), high sensitivity-reactive protein (hs-CRP), and lipid panel (total cholesterol, HDL, LDL, triglycerides). **Collect at presentation for VOC, as feasible.**
i. Pregnancy tests will be performed on WOCBP. A serum test will be conducted at screening and a urine test at subsequent visits. A positive urine pregnancy test at any time during the study requires confirmation via a serum pregnancy test. Female participants will not be considered of childbearing potential if they are pre-menarchal, surgically

Study Period	Screening	Treatment Period						Follow-up	Upon Presentation for VOC
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sterile (hysterectomy, bilateral salpingectomy, tubal ligation, or bilateral oophorectomy) or postmenopausal (no menses for 12 months without an alternative medical cause, confirmed by follicle-stimulating hormone test results).

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

k. Coagulation parameters are PT, aPTT, D-dimer, von Willebrand factor (vWF), and fibrinogen. Collect at presentation for VOC as feasible.

l. A urine sample will be collected on Day 1 (pre-dose) and Week 48 for the assessment of albumin, protein, creatinine, and hemoglobin.

m. The incidence of VOC events will be recorded weekly by the participant and collected every 4 weeks (±7 days). On non-visit days (Week 4 [Day 29], Week 8 [Day 57], Week 16 [Day 113], Week 20 [Day 141], Week 28 [Day 197], Week 32 [Day 225], Week 40 [Day 281], and Week 44 [Day 309], participants will be contacted by phone to determine if a VOC event or a pain crisis 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.

n. The participant will complete the ASCQ-Me questionnaire weekly, when available. Questionnaires will be distributed to sites once available in local language. The ASCQ-Me questionnaire completed by participants at home will be collected during the participant's visits to the clinical site at Weeks 6, 12, 24, 36, and 48. In addition, the ASCQ-Me questionnaire will be administered during the participant's visits to the clinical site at Weeks 6, 12, 24, 36, and 48.