STATISTICAL ANALYSIS PLAN

Study Title:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF A SINGLE DOSE OF INCLACUMAB TO REDUCE RE-ADMISSION IN PARTICIPANTS WITH SICKLE CELL DISEASE AND RECURRENT VASO-OCCLUSIVE CRISES
Development Phase:	Phase 3
Protocol Number:	GBT2104-132 (C5361002)
Protocol Date and Version:	17 February 2022 (Amendment 2), Version 3.0
Investigational Product:	Inclacumab (GBT2104 / PF-07940370)
Sponsor:	Global Blood Therapeutics, Inc., a wholly owned subsidiary of Pfizer Inc. 181 Oyster Point Boulevard South San Francisco, CA 94080 United States of America
Analysis Plan Version:	Version 1.0
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STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

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1. GLOSSARY OF ABBREVIATIONS

ACS	acute chest syndrome
ADA	anti-drug antibodies
AESI	adverse event of special interest
ASCQ-Me	Adult Sickle Cell Quality of Life Measurement
CGI-C	Clinician's Global Impression of Change
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
EOS	end of study
HU	hydroxyurea
IRT	interactive response technology
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	nonsteroidal anti-inflammatory drug
OLE	open-label extension
PD	pharmacodynamics(s)
PGI-C	Patient's Global Impression of Change
PK	pharmacokinetic
CCI	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sickle cell disease
SOC	System Organ Class
TEAE	treatment-emergent adverse event
VOC	vaso-occlusive crisis
WHO	World Health Organization

2. INTRODUCTION

The primary objective of Study GBT2104-132 (C5361002) is to evaluate the safety and efficacy of a single dose of inclacumab compared with placebo to reduce the incidence of re-admission to a healthcare facility for a vaso-occlusive crisis (VOCs) after an admission for an index VOC in participants with sickle cell disease (SCD). However, as of June 2023, the Sponsor decided to discontinue Study GBT2104-132 early, prior to full enrollment. The decision is based on business considerations and not due to any specific safety reason or request from any regulatory authority.

This statistical analysis plan (SAP) provides details of the planned analyses and statistical methods for Study GBT2104-132. In many instances, analyses have been limited and/or are descriptive in nature, due to the early discontinuation of the study.

Where this document differs from the high-level analysis plan described in the study protocol, the methodology described in this SAP is considered the latest and supersedes the corresponding section(s) in the protocol.

Population pharmacokinetic (PK), exploratory pharmacodynamic (PD), and exploratory biomarker analyses will be described in a separate document.

2.1. Study Design

Study GBT2104-132 is a Phase 3, randomized, placebo-controlled, double-blind, multicenter, parallel-group study to assess the safety and efficacy of a single dose of inclacumab in reducing the incidence of re-admission to a healthcare facility for a VOC after an index VOC. As originally planned, the study was to include up to approximately 280 adult and adolescent participants (≥ 12 years of age) with SCD. However, as noted, the Sponsor has decided to discontinue the study prior to full enrollment (with approximately 26% of the total planned participants randomized). All randomized participants are to complete the study per the protocol Schedule of Assessments.

Initial enrollment was to 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 (up to approximately 140 participants per arm) as follows:

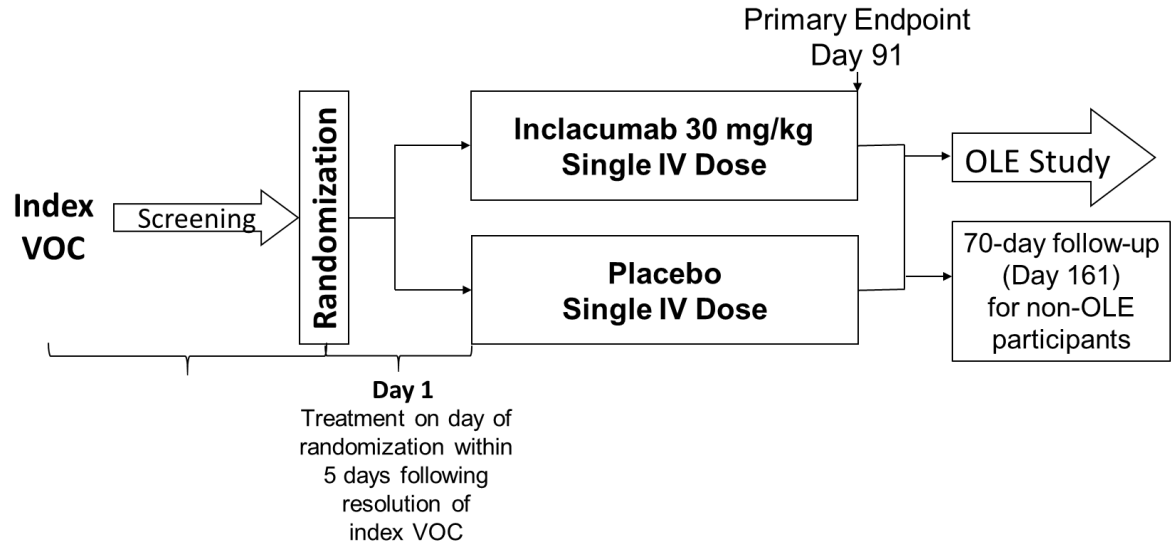
- Inclacumab 30 mg/kg administered IV; or
- Placebo administered IV.

All participants will undergo study assessments (safety, efficacy, PK, PD, and biomarkers, as applicable) at Screening, Baseline (Day 1), and through Day 91, as detailed in the Schedules of Assessments (see study protocol, Appendices 1 to 3).

Following completion of the Day 91 Visit, eligible participants will be given the option to enroll in an open-label extension (OLE) study under a separate protocol. For participants enrolling in the OLE study, the Day 91 Visit will be the end of study (EOS) visit. For participants not enrolling in the OLE study, an additional required Follow-up Visit at Day 161 will be the EOS visit.

A diagram of the study design is provided in Figure 1. Further study design details are provided in the study protocol.

Figure 1: GBT2104-132 Study Design



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

2.2. Study Endpoints

2.2.1. Primary Efficacy Endpoint

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

An admission for a VOC includes:

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

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

- Uncomplicated VOC, or
- Acute chest syndrome, or
- Hepatic sequestration, or
- Splenic sequestration. or
- Priapism.

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

To ensure consistency across study sites, all on-study VOCs reported by the study investigators will be adjudicated by an independent, blinded VOC Adjudication Committee comprised of experts in SCD. Unless otherwise noted, efficacy analyses will be performed on adjudicated data.

2.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints for the study are the following:

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

2.2.3. Exploratory Endpoints

The exploratory endpoints for the study are the following:

- Time to second VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days of randomization.
- Rate of complicated VOCs (i.e., acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism) during the 90 days following randomization.
- Rate of inpatient hospital admissions for any reason during the 90 days following randomization.
- Number of days of inpatient hospitalization for any reason during the 90 days following randomization.
- Proportion of participants rated as “very much improved” or “much improved” based on the Patient’s Global Impression of Change (PGI-C) at Day 46 and Day 91.
- Proportion of participants rated as “very much improved” or “much improved” based on the Clinician’s Global Impression of Change (CGI-C) at Day 46 and Day 91.
- Change from Baseline in the cumulative score for the Adult Sickle Cell Quality of Life Measurement (ASCQ-Me) Pain Impact – Short Form over time to Day 91.

2.2.4. Safety Endpoints

The safety endpoints for the study are the following:

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

2.2.5. Exploratory Pharmacology Endpoints

The exploratory pharmacology endpoints of the study are the following:

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

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

2.3. Determination of Sample Size

The original sample size determination was based on statistical power considerations for the primary efficacy endpoint, the proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days of randomization.

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

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

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

As of June 2023, the Sponsor has decided to discontinue the study prior to full enrollment, with approximately 26% of the total number of planned participants randomized. The ultimate study sample size is based on screening and enrollment at the time of the decision to discontinue, rather than any statistical considerations.

2.3.1. Basis for Original Sample Size Assumptions

Based on 2016 nationwide re-admission data, a 30-day all cause re-admission rate of 26.9% was reported among patients admitted with a principal diagnosis of sickle cell crisis (Kumar, 2020). The majority (86%) of such re-admissions were due to sickle cell crisis or related diagnosis. Similarly, an analysis of patient claims data (Source Healthcare Analytics Patient Transaction Dataset; August 2017 to July 2018 cohort) showed that among patients with a history of VOC, approximately 50% of patients hospitalized for an index VOC are expected to be re-hospitalized for a VOC within 90 days (data on file). However, overall hospital admissions have decreased with the COVID-19 pandemic (Birkmeyer, 2020) and patients with SCD may try to avoid hospitalizations (McFarling, 2020; Powell, 2020).

In this study, the primary endpoint evaluates, following an index VOC, the occurrence of at least 1 VOC that required admission to a healthcare facility (hospital admission; 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) and treatment with parenteral pain medication within 90 days of randomization. For purposes of sample size calculation, it was assumed that approximately 35% of participants in the placebo group experience such a protocol-defined VOC within 90 days of randomization.

The assumption of 5% drop-out rate during the 90-day study period was based on data from the Phase 3 clinical trial of voxelotor, Study GBT440-031, in patients with SCD (data on file).

2.4. Randomization

Eligible participants will be randomized on Day 1 through a central interactive response technology (IRT) system. Randomization may occur up to 5 days following investigator-assessed resolution of index VOC (for example, hospital discharge, completion of parenteral analgesia, or transition to oral analgesics).

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 hydroxyurea (HU) use (yes; no), number of VOCs in the preceding 12 months (2 to 4 episodes; 5 to 10 episodes), and geographic region (North America; rest of world).

On the day of randomization (Day 1), participants will receive a single dose of study drug.

2.5. Analysis Timing

Due to the early termination of the study, the protocol-specified interim efficacy analysis will not occur.

Final study data will be used for all the analyses to be performed for the CSR after all randomized participants have completed the study or discontinued early (i.e., last participant's last visit has occurred), and all corresponding data have been entered into the database, reviewed, and verified and the database is locked.

3. GENERAL CONSIDERATIONS

3.1. Definitions and Terminology

Study Drug

The term study drug refers to either inclacumab or placebo.

Baseline Value

Baseline is defined as the last available pre-treatment value taken on or before the day of randomization, and will be used for summary of baseline characteristics and change-from-baseline analyses, as appropriate. For ASCQ-Me, baseline is defined as the assessment taken on the day of randomization.

Day 1

Day 1 is the date of randomization.

Study Day

Study Day is defined relative to the date of randomization.

For study assessments or events that occur on or after the date of randomization, study day is calculated as:

Study Day = Event Date – Randomization Date + 1.

For study assessments or events that occur before the date of randomization, study day is calculated as:

Study Day = Event Date – Randomization Date.

Study Visit

Study Visit is the protocol visit as shown in Table 1.

Treatment Day

Treatment Day is defined relative to the date of first dose of study drug.

For study assessments or events that occur on or after the date of first dose, treatment day is calculated as:

Treatment Day = Event Date – First Dose Date + 1.

For study assessments or events that occur before the date of first dose, treatment day is calculated as:

Treatment Day = Event Date – First Dose Date.

Treatment-Emergent Adverse Event

Treatment-emergent adverse events (TEAEs) are defined as adverse 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. Note: Given the long half-life of inclacumab, events occurring through end of study will be considered treatment emergent.

Study Completion

Completion of study is specified on the End of Study (EOS) CRF. Participants are considered to have completed the study if (1) the subject completed the study through the Day 91 visit and elected to enroll in the open-label extension study, or (2) the subject did not enroll in the open-label extension study and completed the study through the Day 161 visit.

Treatment Completion

Completion of treatment is specified on the End of Treatment (EOT) CRF and includes all participants who did not permanently discontinue study drug early.

3.2. Visit Windows

For summaries by timepoint (e.g., CGI-C, PGI-C, vital signs, laboratory values), analysis visit windows will be used to classify assessments based on the actual study day of the measurement regardless of the original nominal visit label. This includes assessments collected at Unscheduled, Early Termination, or EOS visits. Target study days, the protocol-specified study day windows, and the analysis visit windows are shown in Table 1.

Table 1: Analysis Windows for Assessments Other than ASCQ-Me

Study Visit	Target Study Day	Visit Window per Protocol (study days)	Window for Statistical Analysis (study days)
Screening	-	[-10, -1]	[-10, -1]
Day 1	1	1	1
Day 46	46	[39, 53]	[32, 60]
Day 91	91	[84, 98]	[77, 105]
Day 161	161	[147, 175]	[140, 182]

ASCQ-Me=Adult Sickle Cell Quality of Life Measurement,
Note: Baseline is defined as the last available pre-treatment value taken on or before the day of randomization.
Note: If multiple measurements fall within the statistical analysis window, the measurement closest to the target study day will be used. If two measurements are equally close, the earlier value will be used.

For the ASCQ-Me questionnaire (completed weekly at home), the analysis windows shown in Table 2 will apply for data summary.

Table 2: Analysis Windows for Assessment of ASCQ-Me

Analysis Timepoint	Target Study Day	Window for Statistical Analysis (study days)
Baseline	1	1
Week 1	8	[2, 11]
Week 2	15	[12, 18]
Week 3	22	[19, 25]
Week 4	29	[26, 32]
Week 5	36	[33, 39]
Week 6	43	[40, 46]
Week 7	50	[47, 53]
Week 8	57	[54, 60]
Week 9	64	[61, 67]
Week 10	71	[68, 74]
Week 11	78	[75, 81]
Week 12	85	[82, 88]
Week 13	92	[89, 95]

ASCQ-Me=Adult Sickle Cell Quality of Life Measurement
Note: Baseline is defined as the assessment taken on the day of randomization. If multiple measurements fall within the statistical analysis window, the measurement closest to the target study day will be used. If two measurements are equally close, the earlier value will be used.

4. ANALYSIS POPULATIONS

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

4.1. Intent-to-Treat 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.

4.2. Safety Population

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 study treatment received. Any participant who receives treatment with inclacumab will be classified in the inclacumab treatment arm. Participants who receive treatment with placebo only will be classified in the placebo treatment arm.

The safety population will be the primary analysis population for safety and exposure data.

5. STATISTICAL METHODS

5.1. Summaries of Study Conduct

The number of participants randomized will be tabulated by region, country, study site, and treatment group. Participant disposition (the number of participants randomized, treated, and completing the study) will be tabulated by treatment group. Reasons for study drug interruption and discontinuation, as well as study discontinuation, will be summarized.

Any eligibility criteria deviations, dosing errors, and other significant protocol deviations will also be tabulated by treatment group and evaluated for potential impact on the interpretation of study results.

5.2. Summaries of Demographic, Baseline Characteristics, and Concomitant Medications

Demographic and baseline characteristics (such as age, sex, race, body weight in kg, estimated glomerular filtration rate [eGFR], sickle cell genotype, number of VOCs in the 12 months prior to the screening visit, baseline HU use, baseline voxelotor use, prior crizanlizumab use, and geographic region) will be summarized for the ITT population by treatment group.

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA; the most current version at the time of the analysis will be used) and summarized for each treatment group. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized.

Time on study, defined as time from randomization (Day 1) to the participant's end of study date, will also be tabulated.

5.3. Efficacy Analyses

Efficacy analyses will be based on the ITT patient population (Section 4.1), with participants grouped according to the treatment assigned at randomization. Data from all randomized participants, regardless of treatment with study drug or adherence to the protocol will be included in the efficacy analyses.

Covariate Adjustment
Unless otherwise noted, analyses of primary and secondary efficacy endpoints will be adjusted for the following randomization stratification variables:

- Baseline HU use (yes; no)
- Number of VOCs in the 12 months prior to study entry (2 to 4 episodes; 5 to 10 episodes)

If convergence or model issues arise, then analyses will be simplified by excluding one of the above stratification variables.

Note: The additional randomization stratification variable of geographic region (North America; rest of world) will not be included in the analyses due to the early study discontinuation and the low number of subjects enrolled from North America.

For stratification variables, the value recorded in the clinical database (i.e., per case report form) will be compared to value captured in the IRT. If differences are observed, the values from the clinical database will be used in the analysis.

Statistical Tests
No adjustment for multiple comparisons will be performed.

5.3.1. Primary Efficacy Endpoint

For the primary efficacy endpoint, VOCs that meet the protocol-specified definition as assessed by the VOC Adjudication Committee with an onset date from randomization (Day 1) through the 90-day study period (Day 91), inclusive, will be used in the analysis.

The proportion of participants with at least 1 VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days (primary endpoint) from randomization will be compared between treatment groups using the exact Cochran-Mantel-Haenszel (CMH) general association test, stratified by the randomization stratification factors (baseline HU use [yes; no] and number of VOCs in the 12 months prior to study entry [2 to 4 episodes; 5 to 10 episodes]).

Every effort will be made to obtain the 90-day re-admission status for a VOC for each participant. For purposes of the primary analysis, participants with an unknown 90-day re-admission status (e.g., participants who discontinue the study prior to 90 days and without a re-admission for a VOC) will be classified as having experienced at least 1 protocol-defined VOC within 90 days (i.e., counted as "failure"). A sensitivity analyses based on observed data (i.e., without imputation of re-admission for early study discontinuation) will be performed to assess the robustness of the primary analysis results to assumptions regarding drop-outs.

SAS code for the exact CMH test similar to the following will be used for the primary analysis (where trtgrp is the randomized treatment group and response is an indicator variable for occurrence of at least one protocol-defined VOCs during the 90 days post randomization):

```
PROC LOGISTIC;
 CLASS trtgrp /PARAM=REF;
 MODEL response (event='Yes') = trtgrp;
 STRATA = <categorical variables>;
 EXACT trtgrp;
RUN;
```

Similarly, the proportion for each treatment group and the difference in proportions between treatment groups (inclacumab versus placebo) will be estimated by the weighted average of the observed proportions and the differences in observed proportions over the strata using the CMH weights and 95% confidence intervals (CIs) provided (Mehrotra and Railkar 2000).

5.3.2. Secondary Efficacy Endpoints

5.3.2.1. Time to First VOC

Time to first VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days will be measured from randomization (Day 1) to onset date of the first protocol-defined VOC event. For participants who do not experience a protocol-defined VOC within 90 days of randomization, time to first VOC will be censored at the end of their time at risk (participant's end of study date or Study Day 91, whichever is earlier).

Summary statistics will include number of subjects with event, number of subjects censored, median time to event along with 95% CI for the median and quartiles. The CIs for the median will be calculated according to Brookmeyer and Crowley (1982) and the CIs for the survival function estimates at fixed time points will be derived using the log-log transformation according to Kalbfleisch and Prentice (2002) (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.

Treatment comparison between inclacumab and placebo will be performed based on log-rank test stratified by the randomization factors of baseline HU use and number of VOCs in the 12 months prior to study entry. Kaplan-Meier plots will be generated. A Cox regression model will be used to estimate the hazard ratio between the inclacumab and placebo groups, as appropriate.

5.3.2.2. Participant Status with at Least 1 VOC Requiring Re-Admission with 30 Days

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

5.3.2.3. Rate of VOCs Leading to Healthcare Visit and Requiring Parenteral Pain Medication

For the rate of VOCs leading to a healthcare visit within 90 days, the total number of VOCs in the 90-day period will be compared between the treatment groups using a negative binomial regression model stratified by the randomization factors of baseline HU use and number of VOCs in the 12 months prior to study entry. For each participant, the time period at risk for evaluation of VOCs is from date of randomization (Day 1) to the participant's end of study date or Study Day 91, whichever is earlier.

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 to account for different lengths of follow-up across participants. 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.

A plot of the mean cumulative function of VOC episodes will be presented using recurrent events analysis methods.

5.3.3. Exploratory Efficacy Endpoints

Exploratory endpoints will be summarized by descriptive statistics. For comparison between inclacumab and placebo groups, point estimates, CIs, and p-values may be presented as appropriate, without adjustment for multiplicity.

Time to second VOC that required admission to a healthcare facility and treatment with parenteral pain medication within 90 days will be measured from randomization (Day 1) to onset date of the second protocol-defined VOC event and summarized using the same methodology as for time to first VOC (secondary endpoint).

The rate of complicated VOCs, rate of inpatient hospital admissions, and number of days of inpatient hospitalization for any reason during the 90 days following randomization will be summarized descriptively, using similar patient-time methodology as the rate of VOCs leading to a healthcare visit (secondary endpoint).

The proportion of participants rated as "very much improved" or "much improved" based on the PGI-C at Day 46 and Day 91 will be summarized descriptively by timepoint and treatment group. A similar analysis will be performed for the proportion of participants rated as "very much improved" or "much improved" based on the CGI-C.

A cumulative score for the ASCQ-Me Pain Impact (Short Form) will be calculated for each participant and assessment timepoint. For each assessment a cumulative score will only be calculated if all five questions on the form were answered. The cumulative score is the sum of the individual raw scores according to the response mapping in Table 3.

Table 3: ASCQ-Me Pain Impact (Short Form) Response Mapping

Response to Each Question	Raw Score
Always	1
Often	2
Sometimes	3
Rarely	4
Never	5

Changes from baseline over time to Day 91 will be calculated and summarized descriptively by timepoint (weekly) and treatment group.

5.4. Safety Analyses

Safety analyses will be based on the safety patient population (Section 4.2), with participants grouped according to the actual study treatment received. Safety will be assessed through descriptive summaries of adverse events, clinical laboratory test results, and vital signs.

5.4.1. Exposure to Study Drug and Compliance

Exposure to study drug (amount of study drug administered) will be summarized by treatment group.

For Day 1, the actual dose administered (in mg) and the difference between the planned dose and actual dose administered (in mg/kg) will be summarized descriptively by treatment group. For each participant, the percent compliance with study drug will be calculated based on the ratio of the actual dose administered (mg/kg) and the planned dose (i.e., 30 mg/kg). The percent compliance will be summarized by treatment group.

In addition, the number and percentage of participants with an infusion interruption will be summarized by treatment group.

5.4.2. Adverse Events

Adverse events will be classified according to MedDRA; the most current version at the time of analysis will be used. Severity of adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0, when possible, or based on the protocol-specified grading for adverse events not covered in the NCI CTCAE.

Summaries of treatment emergent adverse events (TEAEs), defined as adverse 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 (SOC) and preferred term, as appropriate.

Summaries of TEAEs by treatment group will be provided for the following categories:

- All TEAEs
- All TEAEs by maximum severity
- TEAEs assessed as related to study drug by the investigator
- TEAEs leading to study drug interruption
- TEAEs leading to study drug discontinuation
- Adverse events of special interest (AESIs) (i.e., infusion-related reaction TEAEs)
- Treatment-emergent serious adverse events (SAEs)

Listings for all adverse events, TEAEs leading to study drug discontinuation, AESIs, SAEs, and deaths (if any) will be provided.

VOC events will be collected and summarized separately (uncomplicated VOC, acute chest syndrome [ACS], hepatic sequestration, splenic sequestration, and priapism).

5.4.3. Clinical Laboratory Assessments

Laboratory abnormalities assessed by the Investigator as clinically significant will be recorded as adverse events.

Descriptive summaries of laboratory parameters (hematology, serum chemistry, and coagulation) at baseline and each evaluation post baseline, as well as changes from baseline over time, will be provided by treatment group. If any of the results are below the limit of quantitation or above the limit of quantitation, then the numerical limit will be used in the descriptive summaries.

Laboratory abnormalities will be graded via the Common Terminology Criteria for Adverse Event (CTCAE). A treatment-emergent laboratory abnormality is any post-baseline laboratory assessment performed on or after initiation of study drug which demonstrates an increase of 1 grade or more from the baseline toxicity value. If the baseline value is missing, any graded abnormality (grade 1 or higher) that occurs following initiation of study drug will be deemed treatment emergent. The number and percentage of participants experiencing treatment-emergent laboratory abnormalities will be summarized by treatment group. Laboratory abnormality shifts from baseline through each evaluation post baseline will be summarized by treatment group.

5.4.4. Vital Signs and Weight

Descriptive summaries of vital signs (e.g., systolic and diastolic blood pressure, heart rate, and body temperature) at baseline and each evaluation post baseline, as well as changes from baseline over time, will be generated by treatment group. In addition, descriptive summaries of weight at baseline will be generated by treatment group.

5.5. Exploratory PK, ADA, and PD Analyses

5.5.1. Pharmacokinetic Analyses

CCI

[redacted]

5.5.2. Anti-drug Antibody Analyses

CCI

[redacted]

CCI

[redacted]

5.5.3. Pharmacodynamic Analyses

CCI

[redacted]

6. TABLES, LISTINGS, AND FIGURES

A separate document will provide mockups of the tables, listings, and figures that support the analyses proposed in this SAP.

7. REFERENCES

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