STATISTICAL ANALYSIS PLAN

Study Title:	AN OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY OF INCLACUMAB ADMINISTERED TO PARTICIPANTS WITH SICKLE CELL DISEASE WHO HAVE PARTICIPATED IN AN INCLACUMAB CLINICAL TRIAL
Development Phase:	Open-Label Extension
Protocol Number:	GBT2104-133 (C5361003)
Protocol Date and Version:	13 July 2023 (Amendment 3), Version 4.0
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
Analysis Plan Date:	16 July 2024

CONFIDENTIAL AND PROPRIETARY INFORMATION

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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
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
EOS	end of study
EQ-5D-5L	EuroQol Health Questionnaire
GBT	Global Blood Therapeutics, Inc
HC	hydrocarbamide
HRQoL	health-related quality of life
HU	hydroxyurea
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibody
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
OLE	open-label extension
PD	pharmacodynamics
PGI-C	Patient's Global Impression of Change
PK	pharmacokinetics
CCI	[redacted]
Q12W	every 12 weeks
QoL	quality of life
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sickle cell disease

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SOC	System Organ Class
CCI	[redacted]
TEAE	treatment-emergent adverse event
CCI	[redacted]
VOC	vaso-occlusive crisis
WHO	World Health Organization

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2. INTRODUCTION

The primary objective of Study GBT2104-133 (C5361003) is to evaluate the long-term safety of every 12-week (Q12W) dosing of inclacumab in participants with sickle cell disease (SCD) who have completed a prior inclacumab clinical trial.

This statistical analysis plan (SAP) provides details of the planned analyses and statistical methods for Study GBT2104-133. 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) analyses will be described in a separate document.

2.1. Study Design

Study GBT2104-133 is a multicenter, global, open-label extension study to assess the safety of long-term use of inclacumab in participants with SCD. The study is conducted globally and available to eligible participants enrolled in a prior GBT-Sponsored inclacumab clinical study (originating study). Participants must have completed participation in their originating clinical study and must meet the entry criteria for this study to be eligible for enrollment.

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

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

Further study design details are provided in the study protocol.

2.2. Study Outcome Measures

2.2.1. Safety Outcome Measures

Safety outcome measures for the study include:

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

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2.2.2. Additional Outcome Measures

Additional outcome measures for the study are the following:

- Annualized rate of vaso-occlusive crises (VOCs). 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 (requiring a visit to a medical facility), that meet the requirements listed above are included.
- Annualized rate of VOCs that require admission to a healthcare facility and treatment with parenteral pain medication where an admission includes:
  - A hospital admission, or
  - An admission to an emergency room, observation unit, or infusion center for $\geq$ 12 hours, or
  - 2 visits to an emergency room, observation unit, or infusion center over a 72-hour period.
- Annualized number of days of inpatient hospitalization for a VOC.
- Annualized rate of all SCD-related urgent are visits to the clinic, emergency room, and hospital.
- Proportion of total days missed from school/work due to SCD pain symptoms for the first 48 weeks.
- Annualized rate of complicated VOCs.
- Annualized rate of red blood cell (RBC) transfusions.
- Annualized rate of inpatient hospital admissions for any reason.
- Annualized number of days of inpatient hospitalization for any reason.
- Proportion of participants rated as "very much improved" or "much improved" based on the Patient's Global Impression of Change (PGI-C) Q12W through Week 96.

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- Proportion of participants rated as "very much improved" or "much improved" based on the Clinician's Global Impression of Change (CGI-C) Q12W through Week 96.
- Cumulative score for the Adult Sickle Cell Quality of Life Measurement (ASCQ-Me) Pain Impact – Short Form over time through the first 48 weeks.
- Health-related quality of life (HRQoL) as assessed by the EuroQol Health Questionnare (EQ-5D-5L) Q12W through Week 96.

2.2.3. Pharmacology Outcome Measures

Pharmacology outcome measures through Week 48 in a planned [redacted] include:

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

2.3. Determination of Sample Size

The protocol sample size of [redacted] was based on the combined planned sample sizes from the originating studies.

However, the sample size of this open-label extension study is not expected to exceed 312 participants (up to 240 participants as planned from the originating study GBT2104-131 [C5361001] and up to 72 of the planned 280 participants from the originating study GBT2104-132 [C5361002] which was discontinued prior to full enrollment).

2.4. Analysis Timing

The final study analysis will be based on complete data from the study and performed after all enrolled 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.

Prior to the final study analysis, interim data from this open-label extension study may be summarized as necessary (e.g., interim safety data summarized to support regulatory applications or health authority requests). The data included for the interim analyses will depend on the purpose of the regulatory submission. If performed, the interim analysis will be descriptive and no formal hypothesis testing performed.

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3. GENERAL CONSIDERATIONS

3.1. Definitions and Terminology

Baseline Value

Baseline is defined as the last available value (including from the last study visit or End of Study [EOS] visit from the originating study) taken on or within 30 days before the day of first dose in GBT2104-133, and will be used for summary of baseline characteristics and change-from-baseline analyses, as appropriate.

Day 1

Day 1 is the date of first dose in Study GBT2104-133.

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.

Study Day

Study Day is defined relative to the date of first dose of study drug. In this study, study day is the same as treatment day.

Study Visit

Study Visit is the nominal visit as recorded as defined in Table 1.

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.

Prior Study Drug

Prior study drug (or prior study treatment) refers to the study drug (inclacumab or placebo) received during the originating study. All participants receive open-label inclacumab as study drug during GBT2104-133.

Time Period at Risk

For each participant, the time period at risk for evaluation of VOCs, hospitalizations, and transfusions is from date of first dose (Day 1) to the participant's EOS date (inclusive).

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3.2. Visit Windows

For summaries by timepoint (e.g., laboratory values, vital signs, height, weight, CGI-C, PGI-C, EQ-5D-5L), 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

Visit	Target Study Day	Visit Window per Protocol (study days)	Window for Statistical Analysis (study days)
Baseline	1	1	[-30,1]
Week 6	43	[36, 50]	[29, 57]
Week 12	85	[78, 92]	[64, 106]
Week 24	169	[162, 176]	[148, 190]
Week 36	253	[246, 260]	[232, 274]
Week 48	337	[330, 344]	[316, 358]
Week 60	421	[414, 428]	[400, 442]
Week 72	505	[498, 512]	[484, 526]
Week 84	589	[582, 596]	[568, 610]
Week 96	673	[666, 680]	[652, 694]
[Continue every 12 weeks]	…	…	…

Note: Baseline is defined as the last available value taken on or within 30 days before the day of first dose in Study GBT2104-133. If multiple measurements fall within a 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 through Week 48), 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]

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Analysis Timepoint	Target Study Day	Window for Statistical Analysis (study days)
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]
Week 14	99	[96, 102]
Week 15	106	[103, 109]
Week 16	113	[110, 116]
Week 17	120	[117, 123]
Week 18	127	[124, 130]
Week 19	134	[131, 137]
Week 20	141	[138, 144]
Week 21	148	[145, 151]
Week 22	155	[152, 158]
Week 23	162	[159, 165]
Week 24	169	[166, 172]
Week 25	176	[173, 179]
Week 26	183	[180, 186]
Week 27	190	[187, 193]
Week 28	197	[194, 200]
Week 29	204	[201, 207]
Week 30	211	[208, 214]
Week 31	218	[215, 221]
Week 32	225	[222, 228]
Week 33	232	[229, 235]
Week 34	239	[236, 242]
Week 35	246	[243, 249]

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Analysis Timepoint	Target Study Day	Window for Statistical Analysis (study days)
Week 36	253	[250, 256]
Week 37	260	[257, 263]
Week 38	267	[264, 270]
Week 39	274	[271, 277]
Week 40	282	[278, 284]
Week 41	288	[285, 291]
Week 42	295	[292, 298]
Week 43	302	[299, 305]
Week 44	309	[306, 312]
Week 45	316	[313, 319]
Week 46	323	[320, 326]
Week 47	330	[327, 333]
Week 48	337	[334, 340]

ASCQ-Me=Adult Sickle Cell Quality of Life Measurement.
Note: Baseline is defined as the assessment taken on the day of first dose in Study GBT2104-133. 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.

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4. ANALYSIS POPULATIONS

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

Note: Participants with signed informed consent / assent form who subsequently do not meet study eligibility criteria (e.g., due to positive pregnancy test) and are not dosed will be classified as screen failures.

PK analysis population is defined as participants who receive inclacumab and have at least 1 measurable post-dose concentration.

Pharmacodynamic (PD) analysis population is defined as participants who receive inclacumab and have at least 1 PD measurement evaluable.

Immunogenicity analysis population is defined as participants who receive inclacumab and have at least 1 ADA measurement evaluable.

Analyses will be presented for the overall population, and by participants grouped based on originating study enrollment and/or treatment received in the originating study, as appropriate.

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5. STATISTICAL METHODS

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

5.1. Summaries of Study Conduct

Study enrollment (number screened and number treated) will be tabulated by originating study and prior treatment group, geographic region, country, and study site. Participant disposition (the number of participants screened, treated, and completing the study) will be tabulated. Reasons for early study drug discontinuation and early study discontinuation will be summarized.

Any eligibility criteria deviations and other protocol deviations (such as dosing errors) will be tabulated 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, sickle cell genotype, randomized treatment in prior study (inclacumab or placebo), concomitant hydroxyurea (HU)/hydrocarbamide (HC) use, and geographic region will be summarized for the safety population. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized. Adverse events continuing from the originating study (i.e., ongoing at GBT2104-133 baseline) will be summarized.

Time on study, defined as time from first dose to the participant's EOS date, will also be summarized.

5.3. Safety Analyses

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

5.3.1. Exposure to Study Drug and Compliance

Exposure to study drug (number of study drug treatments received and duration of treatment) will be summarized.

Duration of treatment will be defined based on the difference between the dates of the first and the earlier of last dose of study drug and participant's end of study date plus 12 weeks (inclusive), i.e.,

$$Duration\ (weeks) = \frac{\min(LastDosingDate + 84,\ EndofStudyDate) - FirstDosingDate + 1}{7}$$

For each dosing visit, the actual dose administered (in mg) and the difference between the planned dose ([CCI] mg/kg) and actual dose administered (in mg/kg) will be calculated.

For each participant, the overall percent compliance with study drug will be calculated based on the ratio of the average dose administered (mg/kg) during the participant's time on study to the planned dose (i.e., [CCI] mg/kg):

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$$\text{Compliance}(\%) = 100 \times \frac{(\sum_{j=1}^{J} \frac{\text{Actual Dose Administered at Visit j [mg]}}{\text{Body Weight at Visit j [kg]}})/J}{\text{CCI [mg/kg]}}$$

The overall percent compliance with study drug will be summarized descriptively.

In addition, the number and percentage of participants with at least one infusion interruption during the study will be summarized.

5.3.2. Adverse Events

Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (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 coved in the NCI CTCAE.

Summaries of 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 will be provided for the following categories:

- All TEAEs
- All TEAEs by severity
- TEAEs assessed as related to study drug by the investigator
- TEAEs leading to study drug interruption or 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 will be provided.

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

5.3.3. 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. 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.

For selected laboratory parameters, laboratory abnormalities will be graded via NCI CTCAE. A treatment-emergent laboratory abnormality is any post-baseline laboratory assessment that emerges on or after initiation of study drug which demonstrates an increase of 1 grade or more

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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 is deemed treatment emergent. The number and percentage of participants experiencing treatment-emergent laboratory abnormalities will be summarized. Laboratory abnormality shifts from baseline through each evaluation post baseline will be summarized.

5.3.4. Vital Signs, Height, and Weight

Descriptive summaries of vital signs (eg, systolic and diastolic blood pressure, heart rate, and body temperature), height, and weight at baseline and each evaluation post baseline, as well as changes from baseline over time, will be generated.

5.3.5. ECG

Available ECG results, including overall interpretation (normal, abnormal clinically significant, abnormal not clinically significant) and applicable ECG intervals, will be listed by participant, visit, and assessment timepoint.

5.4. Analysis of Additional Outcome Measures

5.4.1. Annualized Rate of VOC

VOCs that meet the protocol-specified definition (per investigator report) with an onset date during the time period at risk (Section 3.1) will be included in the analysis. The number of VOCs per participant will be summarized descriptively. For the safety population, the annualized rate of VOCs will be estimated by dividing the total number of protocol-defined VOCs observed by the total patient-time and a 95% Poisson exact confidence interval (CI) [1] provided.

5.4.2. Annualized Rate of VOCs that Require Admission to a Healthcare Facility and Treatment with Parenteral Pain Medication

The annualized rate of VOCs that require admission to a healthcare facility and treatment with parenteral pain medication will be summarized descriptively and 95% CI provided, using methodology per Section 5.4.1.

5.4.3. Annualized Number of Days of Inpatient Hospitalization for a VOC

Inpatient hospitalizations for a VOC with an admission date during the time period at risk (Section 3.1) will be included in the analysis. For each VOC event requiring inpatient hospitalization (regardless of treatment received), the number of days hospitalized will be determined based on the hospital admission and discharge dates. The total number of inpatient hospitalization days for VOCs for each participant will be summarized descriptively. For the safety population, the annualized number of days of inpatient hospitalization for a VOC will be summarized descriptively using patient-time methodology and 95% CI provided.

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5.4.4. Annualized Rate of All SCD-Related Urgent Care Visits to the Clinic, Emergency Room and Hospital

The annualized rate of all SCD-related urgent care visits to the clinic, emergency room, and hospital will be summarized descriptively with 95% CI provided, using methodology per Section 5.4.1.

5.4.5. Proportion of Total Days Missed from School/Work due to SCD Pain Symptoms

For each participant working outside of the home or attending school, the proportion of total days missed from school or work due to SCD out of the total expected days will be calculated for the first 48 weeks of treatment and summarized descriptively. Only participants for whom the number of days of work and/or school that should have been attended is > 0 will be included in the analysis.

5.4.6. Annualized Rate of Complicated VOCs

The annualized rate of complicated VOCs will be summarized descriptively with 95% CI provided, using methodology per Section 5.4.1

5.4.7. Annualized Rate of RBC Transfusions

The annualized rate of RBC transfusions will be summarized descriptively with 95% CI provided, using methodology per Section 5.4.1.

5.4.8. Annualized Rate of Inpatient Hospital Admissions for Any Reason

The annualized rate of inpatient hospital admissions for any reason will be summarized descriptively with 95% CI provided, using methodology per Section 5.4.1.

5.4.9. Annualized Number of Days of Inpatient Hospitalization for Any Reason

The annualized number of days of inpatient hospitalization for any reason will be summarized descriptively using methodology per Section 5.4.3.

5.4.10. Proportion of Participants Rated as "very much improved" or "much improved" based on the PGI-C

The proportion of participants rated as "very much improved" or "much improved" based on the PGI-C at Weeks 12, 24, 36, 48, 60, 72, 84, and Week 96 will be summarized descriptively by study visit with 95% CIs provided.

5.4.11. Proportion of Participants Rated as "very much improved" or "much improved" based on the CGI-C

Proportion of participants rated as "very much improved" or "much improved" based on the CGI-C at Weeks 12, 24, 36, 48, 60, 72, 84, and Week 96 will be summarized descriptive by study visit with 95% CIs provided.

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5.4.12. Cumulative Score for the ASCQ-Me Pain Impact – Short Form over Time

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 Week 48 will be calculated and summarized descriptively by timepoint (weekly).

5.4.13. HRQoL as Assessed by the EQ-5D-5L

5.4.13.1. EQ-5D-5L Index Scoring

The EQ-5D-5L will be scored according to guideline. The current version at the time of analysis, of US weights, will be used to construct the index values of the EQ-5D-5L. Missing item will be handled per scoring manuals.

5.4.13.2. EQ-5D Index and VAS

Summary of VAS score: Descriptive summary statistics at baseline and post-baseline visits through Week 96 for observed and change from baseline values will be presented.

Summary of EQ-5D-5L Index: Descriptive summary statistics at baseline and post baseline visits through Week 96 for observed and change from baseline values will be presented by treatment group.

5.4.13.3. EQ-5D-5L Health Status

Summary of the 5 dimensions: For each dimension, the number and percentage of participants in each of the 5 response levels ("none", "slight", "moderate", "severe", or "extreme/unable") will be presented by visit. A change from baseline score at each visit will also be calculated and the following categories will be summarized:

- Better by 4 points
- Better by 3 points

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- Better by 2 points
- Better by 1 point
- No change
- Worse by 1 point
- Worse by 2 points
- Worse by 3 points
- Worse by 4 points

5.5. Exploratory PK, ADA, and PD Analyses

5.5.1. Pharmacokinetic Analyses

In the participants that consent to participation in the pharmacology sub-study, plasma samples will be collected CCI [redacted] PK analysis population is defined as participants who receive inclacumab 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.

Presentations for inclacumab plasma concentration, will include:

- A listing of all concentrations sorted by participant ID, age group, visit time point, planned and actual time postdose (ie. relative to start of infusion) and date/times of sample collection.
- A summary of concentrations by nominal time, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.
- Mean concentration versus nominal time plots (on both linear and semi-log scales)

Population PK analysis using nonlinear mixed effects modeling will be performed, together with data from other studies, to characterize inclacumab PK in plasma. The influence of demographic covariates (such as body weight, sex, age, race, ethnicity, and renal function) on inclacumab PK parameters will be investigated, if data permits. Details of the population PK analyses will be reported separately.

5.5.2. Immunogenicity Analyses

In the participants that consent to participation in the pharmacology sub-study, CCI [redacted]

Analyses for ADAs will include data from all participants who receive inclacumab and have at least 1 assessment for ADA after the start of dosing. ADA characterization will include, but is not limited to, incidence, timing, and persistence of ADA. Descriptive summaries and listings of ADA and neutralizing antibodies (NAb) will be provided.

A multi-tiered ADA testing approach will be used for sample immunogenicity assessment. The screening assay will be performed on all collected samples to detect the presence of binding

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ADAs to inclacumab. Samples deemed positive in the screening assay will then be tested in the confirmatory assay to confirm specificity to the response. Participants with samples that are confirmed positive will be reported as positive for the presence of anti-inclacumab antibody and these samples will be titered to determine the relative level of ADA. The ADA confirmed positive samples will be run in a NAb assay to assess their ability to neutralize drug activity and results reported.

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 relationship of ADA with PK, safety, and efficacy observations will be explored, as appropriate, and may be reported separately.

5.5.3. Pharmacodynamic Analyses

In the participants that consent to participation in the pharmacology sub-study, CCI [redacted].

Exploratory pharmacodynamic analyses will be performed on data from all participants who have at least 1 measurable result. Descriptive summaries and listings of the PD markers will be provided. Analyses of CCI [redacted], as appropriate, and may be reported separately.

Pharmacodynamic markers include:

CCI [redacted]

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6. REFERENCES

1. Rothman KJ, Greenland S. Modern Epidemiology (2nd edition). Philadelphia: Lippincott-Raven 1998

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