Protocol C4071008

A LOW-INTERVENTIONAL LONGITUDINAL STUDY OF AN ELECTRONIC SICKLE CELL DISEASE PATIENT REPORTED OUTCOMES IN ADULT PARTICIPANTS AGED ⩾18 YEARS OF AGE

Statistical Analysis Plan (SAP)

[redacted]

Version: **2.1**

Date: 29 May 2024

[redacted]

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LIST OF APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1.0 1 Feb 2022	Original 1 Feb 2022	N/A	N/A
2.0 15 Aug 2023	Amendment 2 25 Aug 2022		• Updated study title • Section 2.1: Updated objectives and endpoints definitions • Section 2.1.1: Updated estimand definitions • Section 2.2: Updated study design • Appendix 1: Changed contrast direction to Active vs. Control and added propensity matching code • Throughout document: updated treatment group definition
2.1 15 May 2024	Amendment 2 25 Aug 2022		• Section 3.1: Description of the Non VOC Day endpoint • Section 4: Clarified definition of the Enrolled population • Section 5.2: Clarified analysis set for hypothesis testing • Section 5.2.1: Added Non VOC Day to analysis description • Section 6.1.2.2: Specified Non VOC Day reporting • Appendix 1: analysis of Non VOC days

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C4071008.

NOTE: Italicized text within this document has been taken verbatim from the Study Protocol Amendment 2, August 25, 2022.

2.1. Study Objectives, Endpoints, and Estimands

Following are the study objectives and endpoints of interest.

Objectives	Endpoints
Primary:	**Primary:**
Confirm that the population is suitable for assessing responsiveness of ePRO based upon a lower frequency of Physician-reported MU VOC in the SCD disease modifying treatment group.	Physician-reported MU VOC rate by Day 180.
To evaluate responsiveness of the SCD ePRO in participants treated with SCD disease modifying therapies.	Difference between the the SCD disease modifying treatment group and control group by Day 180 in the following: • VOC Day rate. • Patient-reported VOC Event rate. • Average SCD ePRO daily worst pain scores during VOC day and non-VOC day. • Average SCD ePRO daily worst tiredness scores during VOC day and non-VOC day. • Average SCD ePRO daily rating for ability to perform UPA during VOC day and non-VOC day.
Secondary:	**Secondary:**
To further characterize the quantitative relationship between the various SCD ePRO measures (including VOC Day and Patient-reported VOC Events) and Physician-reported MU VOC.	Within the SCD disease modifying treatment and control groups as well as difference between groups by Day 180 in the following: • VOC Day rate. • Patient-reported VOC Event rate. • Physician-reported MU VOC rate.
Tertiary/Exploratory:	**Tertiary/Exploratory:**
To characterize SCD participant's complications related to their SCD diagnosis.	SCD Events of Interest rate (as collected by the investigator) in the SCD disease modifying treatment group compared to the control group by Day 180.
Characterize the quantitative relationship between the secondary SCD ePRO measures and VOC Days, Patient-Reported VOC Events and Physician-reported MU VOC.	Difference between the SCD disease modifying treatment group and control group by Day 180 in the following: • Average SCD ePRO daily worst pain scores during VOC day and non-VOC day. • Average SCD ePRO daily worst tiredness scores during VOC day and non-VOC day. • Average SCD ePRO daily rating for ability to perform UPA during VOC day and non-VOC day.
Compare Patient-reported MU VOC Event rate versus Physician-reported MU VOC rate.	• Patient-reported MU VOC event rate by Day 180 • Physician-reported MU VOC rate by Day 180
To characterize the biomarker profile of: • SCD participants not receiving the SCD disease modifying treatment (control group). • SCD participants receiving disease modifying treatment (SCD disease modifying treatment group).	Quantitative difference between the SCD disease modifying treatment group and control group on Day 1 and Day 180, which may include: • Serum biomarkers (IL-6, IL-18, IP-10, IL-10, TNFα, soluble VCAM-1, soluble ICAM-1, soluble CCI, soluble CCI). • Plasma coagulation biomarkers (Tissue Factor, TAT, D-dimer).

2.1.1. Primary Estimand(s)

The "while-on treatment" [1] estimand strategy will be used for primary endpoints of this study. The estimands attributes are as follows.

Estimand 1:

- The analysis population is defined as all participants who were selected for analysis via matching procedure.
- Variables of interest are VOC Day rate, patient-reported VOC Event rate and physician-reported MU VOC rate calculated by day 180.
- All data from analysis population will be evaluated up to the occurrence of the intercurrent events or the end of the observation period. The intercurrent events include the following:
    - All study groups: study discontinuation, severely disabling event that precludes compliance with the completion of the SCD ePRO, or other major protocol violations.
    - SCD Disease Modifying Treatment group only: non-compliance with prescribed SCD disease modifying treatment regimen, and initiation of treatment with chronic transfusion, exchange transfusion, or other investigational drug.
    - Control group only: initiation of treatment with SCD disease modifying therapy (eg, HU, crizanlizumab, voxelotor, L-Glutamine or chronic transfusion, exchange transfusion, other investigational drug).
- The population-level summary parameters will include the study treatment group level mean estimates of rates (VOC Day rate, Patient-reported VOC Event rate and MU VOC rate), as well as the rate reduction in the SCD disease modifying treatment group compared to the control group.

Estimand 2:

- The analysis population is defined as all participants who were selected for analysis via matching procedure.
- Variables of interest are SCD ePRO daily worst pain scores, SCD ePRO daily worst tiredness scores and SCD ePRO daily rating for ability to perform UPA by day 180.
- All data from analysis population will be evaluated up to the occurrence of the intercurrent events or the end of the observation period. The intercurrent events include the following:
    - All study groups: study discontinuation, severely disabling event that precludes compliance with the completion of the SCD ePRO, or other major protocol violations.
    - SCD Disease Modifying Treatment group only: non-compliance with prescribed SCD disease modifying treatment regimen, and initiation of treatment with chronic transfusion, exchange transfusion, or other investigational drug.

  - Control group only: initiation of treatment with SCD disease modifying therapy (eg, HU, crizanlizumab, voxelotor, L-Glutamine or chronic transfusion, exchange transfusion, other investigational drug).
- The population-level summary parameters will include the study treatment group level mean estimates of SCD ePRO scores (worst pain, worst tiredness and ability to perform UPA), as well as the mean score reduction in the SCD disease modifying treatment group compared to the control group.

2.1.2. Secondary Estimand(s)

The "while-on treatment" estimand strategy will be used for secondary endpoints of this study. The estimands attributes are as follows.

Estimand 3:

- The analysis population is defined as all participants who were selected for analysis via matching procedure.
- Variables of interest are VOC Day rate, patient-reported VOC Event rate and a count of physician-reported MU VOCs calculated by day 180.
- All data from analysis population will be evaluated up to the occurrence of the intercurrent events or the end of the observation period. The intercurrent events include the following:
  - All study groups: study discontinuation, severely disabling event that precludes compliance with the completion of the SCD ePRO, or other major protocol violations.
  - SCD Disease Modifying Treatment group only: non-compliance with prescribed SCD disease modifying treatment regimen, and initiation of treatment with chronic transfusion, exchange transfusion, or other investigational drug.
  - Control group only: initiation of treatment with SCD disease modifying therapy (eg, HU, crizanlizumab, voxelotor, L-Glutamine or chronic transfusion, exchange transfusion, other investigational drug).
- The population-level summary parameters will include the beta coefficient from the Negative Bimomial models (for physician-reported MU VOC) reflecting association between physician-reported MU VOC rate and SCD ePRO rates (VOC Day rate and patient-reported VOC Event rate).

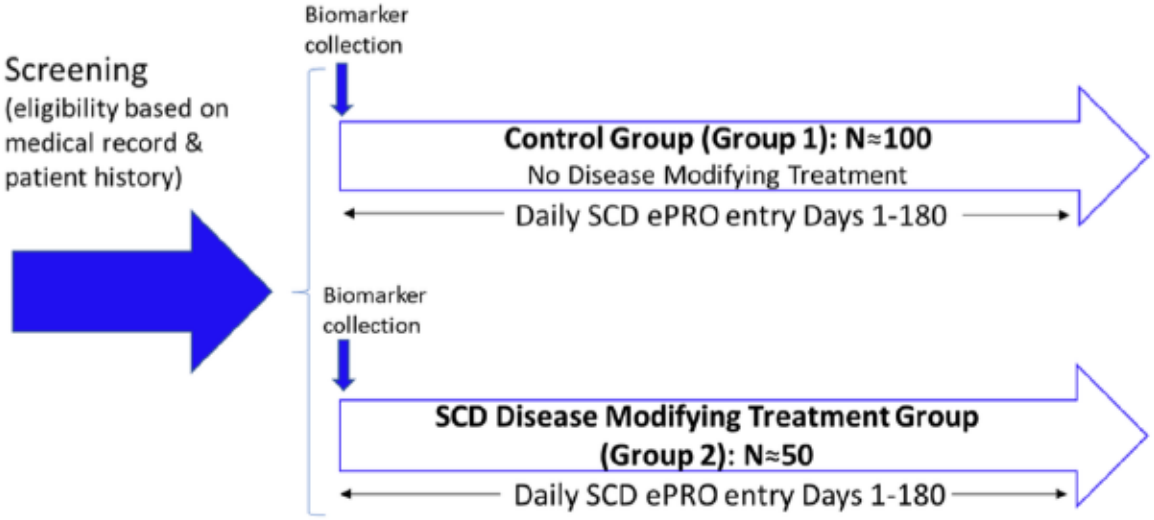
2.1.3. Additional Estimand(s)

Not applicable.

2.2. Study Design

This is a prospective, low-intervention study to evaluate the responsiveness of the SCD ePRO in a therapeutic setting. Approximately 150 participants with SCD (HbS/S or HbS/β°-thal) will be enrolled into two concurrent groups, those who are either not on disease modifying treatment (control group [Group 1], approximately 100 participants) or on a stable dose of a SCD treatment regimen (SCD disease modifying treatment group [Group 2], approximately 50 participants), will be enrolled in this study. There is no randomization, treatment during the study observation period is based on the SOC treatment being administered to individuals in two respective groups at the time they are enrolled. For a period of approximately 180 days (6 months), they will be asked to complete a daily SCD ePRO entry to report on their experience in the past 24 hours with sickle cell pain crisis (if they sought treatment and what medications they took), worst pain, worst tiredness and their ability to perform UPA.

Figure 1. Study Design



Screening assessments will be performed within 56 days prior to study enrollment (Day 1) to confirm eligibility. On Day 1, the SCD ePRO device and training will be provided to study participants during a home health visit arranged by study staff. Daily completion will be reinforced via telehealth or in-person study site visits throughout the observation period.

Telehealth or in-person study site visits are scheduled for Day 2 (+3 days), Day 30 (±7 days), Day 60 (±7 days), Day 90 (±7 days), Day 120 (±7 days), Day 150 (±7 days), and Day 180 (±7 days).

Blood samples to evaluate biomarkers will be collected on Day 1 to characterize hematologic parameters in SCD patients who are either being treated with disease modifying treatment or not on disease modifying treatment.

The total planned duration of participation, from screening through the end of follow-up, is approximately 32 weeks.

Participants who discontinue prior to completion of the study may be replaced at the discretion of the investigator and sponsor.

3. ENDPOINTS AND BASELINE VARIABLES

3.1. Primary Endpoint(s)

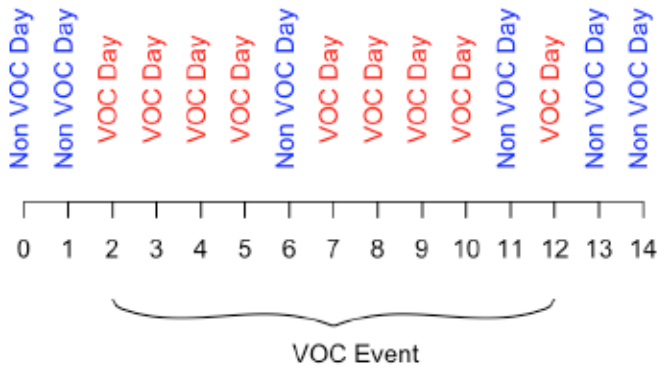
The VOC Day is a self-report by the subject of a VOC during the prior 24 hours. It is a response to dichotomous (YES/NO) item: "Did you have a pain crisis in the past 24 hours?" of SCD ePRO. A response of YES to this item will be counted as 1 VOC day.

Reciprocally, **the Non VOC Day** is a self-report by the subject of a VOC during the prior 24 hours. It is a response to dichotomous (YES/NO) item: "Did you have a pain crisis in the past 24 hours?" of SCD ePRO. A response of NO to this item will be counted as 1 Non VOC day. Non VOC Day rate analysis will be onducted as a supplementary evaluation for the primary endpoint of the VOC Day rate.

Note: Missed reporting (i.e. YES/NO response missing) will not be counted for both VOC Day and Non VOC Day endpoints.

The patient reported VOC Event begins with a VOC Day and it can last from one to many days. The event is a sequence of VOC Days that can also include intermittent single days with no pain crisis. The VOC Event resolves when there are no VOC Days for two consecutive study days. An example of VOC event is presented in Figure 2.

Figure 2. Patient reported VOC Event.



Physician-reported medical utilization (MU) VOC is defined as an acute episode of pain with no other cause other than a VOC event that required a medical facility visit or contact with a health care professional and treatment with oral or parenteral narcotics, or parenteral non-steroidal anti-inflammatory drugs. Acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism (requiring a visit to a medical facility) will also be considered a MU VOC.

Contact with healthcare professional will include:

- Called Healthcare provider (or telemedicine visit) and received treatment.

- Went to clinic and received treatment.

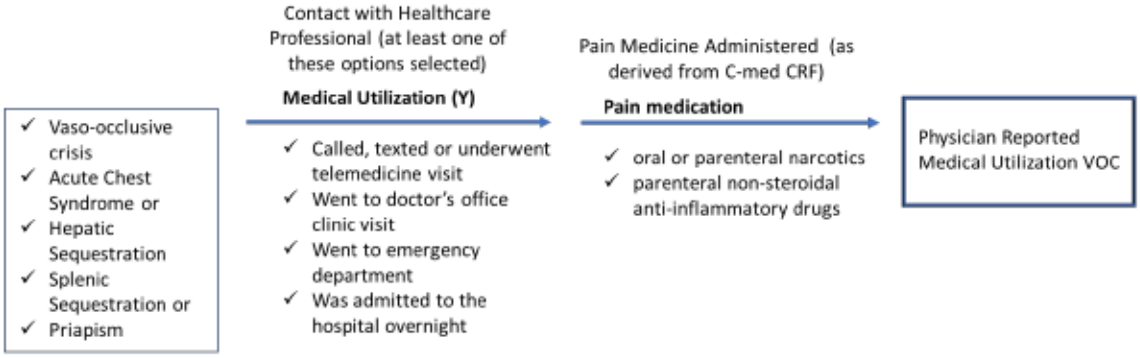
- Went to emergency department and received treatment.

- Was admitted to the hospital and received treatment.

The physician reported MU VOC programatically derived from the data reported on the Sickle Cell Disease of Interest CRF and the Concomitant Medication CRF.

Annualized rates of VOC Day, patient-reported VOC Event and physician-reported MU VOC Event will be computed for each participant as the number of VOC days/events divided by the follow-up time with non-missing ePRO recordings expressed as proportion of 1 calendar year.

Figure 3. Physician-reported MU VOC Event.



Patient-reported daily worst pain (0-10 scale), **worst tiredness** (0-10 scale) and **ability to perform usual physical activities or UPA** (1-4 scale) will be collected daily via SCD ePRO.

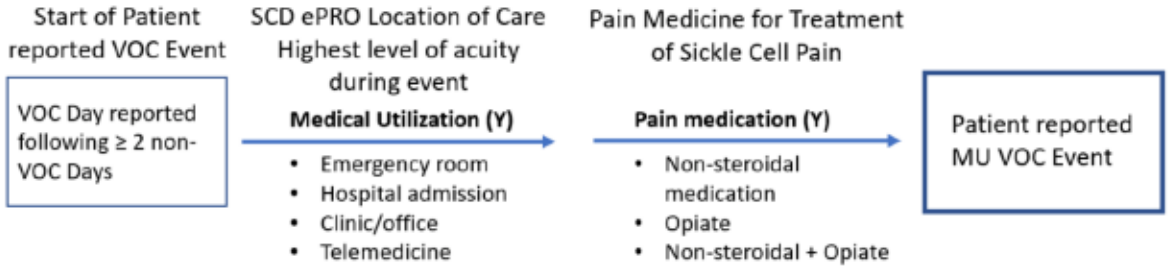
3.2. Secondary Endpoint(s)

Secondary endpoints will describe the relationships between primary endpoints based on statistical model.

3.3. Other Endpoint(s)

Patient-reported MU VOC is defined as a patient-reported VOC Event during which patient reported a contact with health care proffesional as defined in Figure 4 below and use of pain medication.

Figure 4. Patient-reported MU VOC Event.



The patient-reported MU VOC is programmatically derived based on SCD ePRO data, using the highest level of medical utilization indicated by patient during the patient-reported VOC Event. The pain medicine use will be limited to the medication type used during the event, since information about route of administration is not collected by SCD ePRO.

Disease-Related Events include acute chest syndrome, hepatic sequestration, splenic sequestration, priapism, stroke – ischemic, stroke – hemorrhagic, stroke – type unknown, S/P

stroke – cerebral infarct, hematuria, renal papillary necrosis, avascular necrosis of proximal humerus, avascular necrosis of femur, and leg ulcer.

Serum biomarkers: potential measurement of soluble [redacted], soluble [redacted], soluble VCAM-1, soluble ICAM-1, IL-6, IL-18, IP-10, IL-10, and TNFα.

Plasma biomarkers: potential measurement of Tissue Factor, TAT, and D-dimer.

3.4. Baseline Variables

This study will be using the propensity score matching to select patients from Control group comparable to patients in the SCD disease modifying treatment group for all analyses. A large simulation study using MSH patient-level data was conducted to understand optimal characteristics of the matching. Based on results of the simulation, the following baseline variables were selected for matching participants in the Control group to participants in the SCD disease modifying treatment group.

1. %HbF collected subsequent to 1 year of age in the absence of recent transfusion and prior to initiation of SCD disease modifying treatment (for the SCD disease modifying treatment group).

2. Number of MU VOC(s) during the 12-month interval prior to Screening (Control group) and prior to initiation of SCD disease modifying treatment (for the SCD disease modifying treatment group).

The values of these variables will be extracted from medical records and reported on a CRF.

3.5. Safety Endpoints

Unscheduled clinical laboratory measurements or other safety assessments may be obtained at any time during the study to assess any perceived safety issues.

3.5.1. Adverse Events

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins at the time that the biomarker blood sampling is performed and ends 24 hours after that procedure/intervention has completed.

3.5.2. Laboratory Data

Protocol-required clinical safety laboratory assessments will not be performed in this study.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per standard operating procedures.

Population	Description
Enrolled	All participants who sign the informed consent document and met eligibility criteria.
Evaluable for efficacy	All enrolled participants who had at least one SCD ePRO recording.
Matched for efficacy	All enrolled participants who had at least one SCD ePRO recording and was selected for analysis via matching procedure. The data will be analyzed up to intercurrent event as described Section 2.1.
Evaluable Safety/Biomarkers	All enrolled participants who underwent a phlebotomy procedure.

5. GENERAL METHODOLOGY AND CONVENTIONS

Selection of participants from control group for analyses will be done using 1:1 propensity score matching. The propensity model (logistic regression) will include two variables – the MU VOC rate during the year before study and the fetal hemoglobin (HbF) value. Caliper for matching will be set initially to 0.2 standard deviations, and it may be increased if necessary to match at least 45 participants.

All analyses will be performed in the Matched population. Descriptive summaries will be presented in both Evaluable and Matched populations.

5.1. Hypotheses and Decision Rules

Primary objective #1: To assess whether the effect of SCD disease modifying therapy on frequency of physician-reported MU VOC is observed in the study population, the annualized rate reduction in those on SCD disease modifying therapy as compared to matched participants in control group will be evaluated. The null hypothesis is that the annualized physician-reported MU VOC rate in SCD disease modifying treatment group is not different from one in control group.

Primary objective #2: To assess whether the effect of SCD disease modifying therapy on frequency of patient-reported crisis rates (VOC Day rate and patient-reported VOC Event rate) calculated using SCD ePRO is observed in the study population, the annualized rates

reduction in SCD disease modifying treatment group as compared to matched participants in control group will be evaluated. The corresponding null hypotheses are that the annualized patient reported crisis rates in SCD disease modifying treatment group are not different from ones in control group.

Secondary objective: To assess whether the patient-reported crisis rates (VOC Day rate and patient-reported VOC Event rate) calculated using the SCD ePRO are associated with physician-reported MU VOC rate. The assessment will be done in the matched sample, as well as in those in SCD disease modifying treatment group and in matched control group participants. The corresponding null hypotheses are that the annualized patient-reported crisis rates are not associated with physician-reported MU VOC.

These objectives will be tested hierarchically as listed above.

5.2. General Methods

Reporting of descriptive statistics will be done using four groups: all Enrolled Control group participants, all Enrolled SCD disease modifying treatment group participants, matched for efficacy Conrol group participants and matched for efficacy SCD disease modifying treatment group participants.

Reporting of hypotheses testing will be done by the study treatment group of matched for efficacy set (see section 4 of this SAP).

All ePRO data collected after final study visit will not be used in the analysis.

5.2.1. Analyses for Count Endpoints

For all count endpoints (number of VOC Days, patient-repoted VOC Events, physician-reported MU VOC Events, patient-reported MU VOC Events and Non VOC Days), the annualized rates will be derived. The annualized rates will be computed for each participant as number of days/events divided the follow-up time with non-missing ePRO recordings expressed as proportion of 1 calendar year. For example, the VOC Day rate for 10 VOC Days observed over 6-month period with 80% compliance (ePRO records available for 144 of 180 days) will be calculated as: 10*365.25/(0.8*180)=25.4. For Non VOC Days the annualized rate will be computed based on the target length of follow up (180 days) regardless of compliance, dropout or death, assuming no benefit during days with missing response, i.e. if for example there was 120 Non VOC days reported, the Non VOC Day rate will be calculated as 120*365.25/180=243.5.

To evaluate primary count endpoints (objective #1) the Wilcoxon Rank Sum Test at 0.2 two-sided alpha level will be conducted. Hodges-Lehmann estimator with corresponding 80% confidence intervals (CIs) will be calculated for difference between treatment groups (See Appendix 1).

To evaluate primary count endpoints (objective #2) and secondary count endpoints, negative binomial regression model will be fit to the data from Evaluable analysis set (See Appendix 1). The model-based annualized rate estimates for each study group in study evaluable analysis population and the rate reduction will be calculated by specifying the offset as natural logarithm of follow-up time expressed as proportion of 1 calendar year. For example, the offset for 6 months of fully compliant follow-up will be log(0.5). The study group will be the only variable included into the model. Percent rate reduction with corresponding 95% CIs will be calculated.

5.2.2. Analyses for Continuous Endpoints

To evaluate secondary continuous endpoints (patient-reported daily worst pain, worst tiredness and ability to perform UPA), mixed effects regression model will be fit to the daily data from the Evaluable analysis set (See Appendix 1). The model-based mean estimates for each study group and the mean difference will be calculated accounting for correlation of observations within participants. The estimates with corresponding 95% CIs will be calculated (See Appendix 1). The biomarkers data may be analyzed in a similar way.

5.2.3. Analyses for Categorical Endpoints

Not Applicable.

5.2.4. Analyses for Time-to-Event Endpoints

Not Applicable.

5.3. Methods to Manage Missing Data

For primary analyses missing data will be treated as missing completely at random (MCAR). Additional sensitivity analyses may be performed to assess sensitivity of the results to that assumption.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Physician reported MU VOC Event rate

6.1.1.1. Main Analysis

- Estimand strategy: "While-on treatment" (section 2.1.1).
- Analysis set: Matched for efficacy (section 4).
- Analysis methodology: Wilcoxon Rank Sum Test will be conducted to compare individual event rates between control and SCD disease modifying treatment groups (section 5.2.1).

- Intercurrent events and missing data: Data after intercurrent events (as described in Section 2.1.1) will be excluded; intermediate missing values will not be imputed.
- The sample size, mean, standard deviation, median, minimum, and maximum will be presented for each treatment arm.
- Hodges-Lehmann estimator with corresponding 80% confidence intervals (CIs) will be calculated for difference between treatment groups.

6.1.1.2. Sensitivity/Supplementary Analyses

Negative binomial regression model may be fit to the data from Evaluable analysis set. The model-based annualized rate estimates for each study group and the rate reduction may be calculated by specifying the offset as natural logarithm of follow-up time expressed as proportion of 1 calendar year. Percent rate reduction with corresponding 95% CIs may be calculated.

6.1.2. VOC Day rate

6.1.2.1. Main Analysis

- Estimand strategy: "While-on treatment" (section 2.1.1).
- Analysis set: Matched for efficacy (section 4).
- Analysis methodology: Negative binomial regression model will be fit to the data from Evaluable analysis set (section 5.2.1).
- Intercurrent events and missing data: Data after intercurrent events (as described in Section 2.1.1) will be excluded; intermediate missing values will not be imputed.
- The sample size, mean, standard deviation, median, minimum, and maximum will be presented for each treatment arm.
- The model-based annualized rate estimates for each study group and the rate reduction will be calculated by specifying the offset as natural logarithm of follow-up time expressed as proportion of 1 calendar year. Percent rate reduction with corresponding 95% CIs will be calculated.

6.1.2.2. Sensitivity/Supplementary Analysis

Wilcoxon Rank Sum Test may be conducted to compare individual event rates between control and SCD disease modifying treatment groups. Hodges-Lehmann estimator with corresponding 80%CIs may be calculated for difference between treatment groups.

Anualized Non VOC Day rates will be summarized and analyzed in the same way as annualized VOC Day rates.

6.1.3. Patient-reported VOC Event rate

6.1.3.1. Main Analysis

- Estimand strategy: "While-on treatment" (section 2.1.1).
- Analysis set: Matched for efficacy (section 4).
- Analysis methodology: Negative binomial regression model will be fit to the data from Evaluable analysis set (section 5.2.1).
- Intercurrent events and missing data: Data after intercurrent events (as described in Section 2.1.1) will be excluded; intermediate missing values will not be imputed.
- The sample size, mean, standard deviation, median, minimum, and maximum will be presented for each treatment arm.
- The model-based annualized rate estimates for each study group and the rate reduction will be calculated by specifying the offset as natural logarithm of follow-up time expressed as proportion of 1 calendar year. Percent rate reduction with corresponding 95% CIs will be calculated.

6.1.3.2. Sensitivity/Supplementary Analysis

Wilcoxon Rank Sum Test may be conducted to compare individual event rates between control and SCD disease modifying treatment groups. Hodges-Lehmann estimator with corresponding 80%CIs may be calculated for difference between treatment groups.

6.1.4. Patient-reported daily worst pain, worst tiredness and ability to perform UPA

6.1.4.1. Main Analysis

- Estimand strategy: "While-on treatment" (section 2.1.1).
- Analysis set: Matched for efficacy (section 4).
- Analysis methodology: Mixed effects regression model will be fit to the daily data from Evaluable analysis set (section 5.2.2).
- Intercurrent events and missing data: Data after intercurrent events (as described in Section 2.1.1) will be excluded; intermediate missing values will not be imputed.

- The sample size, mean, standard deviation, median, minimum, and maximum will be presented for each treatment arm and VOC vs. Non-VOC state.
- The model-based mean estimates for each study group (and VOC vs. Non-VOC state) and the mean difference will be calculated with corresponding 95% CIs.

6.1.4.2. Sensitivity/Supplementary Analysis

Similar models may be fit with VOC state based on patient-reported VOC Event.

6.2. Secondary Endpoint(s)

6.2.1. Physician reported MU VOC Event rate

6.2.1.1. Main Analysis

- Estimand strategy: "While-on treatment" (section 2.1.2).
- Analysis set: Matched for efficacy (section 4).
- Analysis methodology: Negative binomial regression model will be fit to the data from Evaluable analysis set (section 5.2.1).
- Intercurrent events and missing data: Data after intercurrent events (as described in Section 2.1.1) will be excluded; intermediate missing values will not be imputed.
- The parameter of interest is the beta coefficient from the Negative Bimomial models reflecting association between physician-reported MU VOC rate and SCD ePRO rates (VOC Day rate and patient-reported VOC Event rate). Percent rate reduction with corresponding 95% CIs will be calculated.

6.3. Subset Analyses

Not applicable.

6.4. Baseline and Other Summaries and Analyses

6.4.1. Baseline Summaries

Demographics and baseline characteristics will be summarized for Enrolled and Evaluable sets by treatment group and total according to Pfizer standards.

6.4.2. Study Conduct and Participant Disposition

Participants evaluation, disposition and discontinuation will be summarized according to Pfizer standards.

6.4.3. Study Treatment Exposure

Not Applicable.

6.4.4. Concomitant Medications and Nondrug Treatments

Prior drug and non-drug treatment, concomitant drug and non-drug treatment will be summarized according to Pfizer standards.

6.5. Safety Summaries and Analyses

6.5.1. Adverse Events

No formal analyses are planned for safety data. The safety endpoints (see Section 3.5) will be listed and summarized in accordance with sponsor reporting standards, where the resulting data presentations will consist of participants from the safety analysis set (as defined in Section 4).

6.5.2. Laboratory Data

Not Applicable.

6.5.3. Vital Signs

Not applicable.

6.5.4. Electrocardiograms

Not applicable.

6.5.5. Physical Examination

Not applicable.

7. INTERIM ANALYSES

7.1. Introduction

Not applicable.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

[1] FDA. E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials Guidance for Industry. January 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9r1-statistical-principles-clinical-trials-addendum-estimands-and-sensitivity-analysis-clinical

[2] Pittman DD, et al. Evaluation of Longitudinal Pain Study in Sickle Cell Disease (ELIPSIS) by patient-reported outcomes, actigraphy, and biomarkers. Blood 2021; 137(15):2010-2020

[3] Rosenbaum, P. R. and Rubin, D. B. The central role of the propensity score in observational studies for causal effects. Biometrika 1983; 70:41–55

[4] Brookhart MA, et al. Variable selection for propensity score models. Am J Epidemiol 2006; 163:1149-1156

9. APPENDICES

Appendix 1. SAS Code Examples

Count endpoints

Let trt be treatment (Active/Control), lntime be natural log of observation time (sum of non-missing ePRO days) expressed as proportion of 1 year (e.g. 90 days is 90/365.25=0.2464, and lntime=log(0.2464)) and &var be count of one of the two measures - VOC Days and patient-reported VOC Events. For Non VOC days lntime=log(180/365.25).

Then Model is as follows.

```
ods output estimates=est1;

proc genmod data=temp;

        class trt;

        model &var = trt / dist=negbin offset=lntime type3;

        estimate "Active" intercept 1 trt 1 0 / exp;

        estimate "Control" intercept 1 trt 0 1 / exp;

        estimate "Treatment effect" trt 1 -1 / exp;

run;
```

Continuous endpoints

Let trt be treatment (Active/Control), voc be a VOC Day indicator (No/Yes), subjectcode be participants' ID, studyday be day post randomization/study start and &var be one of the three measures - worst pain, worsttiredness and ability to perform UPA.

Then Model 1 is as follows.

```
ods output estimates=est1 lsmeans=lsm1;

proc mixed data=temp;

        class trt subjectcode studyday;

        model &var = trt / solution ddfm=kr;

        repeated studyday / type=cs subject=subjectcode;
```

```
        lsmeans trt / cl;
        estimate "Active vs. Control" trt 1 -1 / cl;
run;
```

And Model 2 is as follows.

```
ods output estimates=est2 lsmeans=lsm2;
proc mixed data=temp;
        class trt voc subjectcode studyday;
        model &var = trt voc trt*voc / solution ddfm=kr;
        repeated studyday / type=cs subject=subjectcode;
        lsmeans trt*voc / cl;
        estimate "Active vs. Control: VOC Day" trt 1 -1 trt*voc 0 1 0 -1 / cl;
        estimate "Active vs. Control: Non-VOC Day" trt 1 -1 trt*voc 1 0 -1 0 / cl;
run;
```

Propensity score matching will be conducted based on two variabes: Hb0 (baseline hemoglbin value) and MUVOC0 (baseline MUVOC rate). Where baseline is defined as a. year before enrollment for Control group and a year before beginning of the SCD disease modifying treatment for Active group. Propensity score matching code is as follows.

```
ods graphics on;
output out(obs=match)= Matchdata matchid=_MatchID;
proc psmatch data=temp region=cs;
        class trt;
        psmodel trt(Treated='Active') = Hb0 MUVOC0;
        match method=optimal(k=1) distance=lps caliper=0.2;
        assess lps var=( Hb0 MUVOC0) / plots=all;
run;
```

Appendix 2. List of abbreviations

Abbreviation	Term
Abs	absolute
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ATC	Anatomic Therapeutic Chemical
AUC	area under the curve
BA	bioavailability
BE	bioequivalence
BLQ	below the limit of quantitation
BOCF	baseline observation carried forward
BP	blood pressure
CDARS	Clinical Data Analysis and Reporting System (of US Food and Drug Administration)
CI	confidence interval
C_{max}	maximum observed concentration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
DMC	data monitoring committee
EAC	event adjudication committee
ECG	electrocardiogram
ePRO	electronic patient reported outcome
FAS	full analysis set
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GLIMMIX	generalized linear mixed-effects model with repeated measures
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
HbF	fetal hemoglobin
HU	Hydroxyurea
ICD	informed consent document
ICH	International Council for Harmonisation
IRC	internal review committee

Abbreviation	Term
IST	independent statistical team
ITT	intent-to-treat
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
LOD	limit of detection
LS	least-squares
LSM	least-squares mean
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed-effects model with repeated measures
MNAR	missing not at random
MU	medical utilization
NNB	number needed to benefit
NNH	number needed to harm
NNT	number needed to treat
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per-protocol
PPAS	per-protocol analysis set
PRO	patient-reported outcome
PT	preferred term
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
qual	qualitative
RCDC	reverse cumulative distribution curve
RR	relative risk
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sickle cell disease
SD	standard deviation
SGS	Statistical Guidance Standards
SUSAR	suspected unexpected serious adverse reaction
TA	therapeutic area
ULN	upper limit of normal
UPA	usual physical activity
VOC	vaso-occlusive crisis
WHODD	World Health Organization Drug Dictionary