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

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Short Title: A Low-Interventional Study of an Electronic Sickle Cell Disease Patient Reported Outcomes in Sickle Cell Participants

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment #2	25 August 2022	See table below.
Amendment #1	08 April 2022	See table below.
Original protocol	18 November 2021	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

Amendment 2 (25-Aug-2022)

Overall Rationale for the Amendment: The overall rationale is to allow for additional SCD-specific therapies beyond hydroxyurea in the Group 2 study cohort and to reduce washout time periods of SCD-specific therapy exclusion criteria in order to improve participant recruitment and retention without compromising study objectives and endpoints.

Section # and Name	**Description of Change**	**Brief Rationale**	**Substantial or not-substantial**
Study Title	Language throughout has been updated to reflect that Group 2 is now entitled the "SCD Disease Modifying Treatment Group", updated from the "Hydroxyurea Treatment Group".	The inclusion of additional SCD-specific therapies is for Group 2, now referred to as the "SCD Disease Modifying Treatment Group." Group 2 now allows for use of crizalizumab, which has demonstrated a comparable reduction in MU VOCs to that of hydroxyurea. In addition, treatment with hydroxyurea and/or crizanlizumab may be given in combination with voxelotor and/or L-glutamine as these therapies, while SCD	Substantial
Section 1 – Protocol Summary			
Section 2 - Introduction			
Section 3 – Research Questions, Objectives and Endpoints			
Section 4 – Study Design			
Section 5 – Study Population			

Section # and Name	Description of Change	Brief Rationale	Substantial or not-substantial
Section 8.1.1 – SCD ePRO Section 9 – Statistical Considerations		disease-modifying, have demonstrated a smaller impact in MU VOC reduction.	
Section 5 – Study Population	Updated exclusionary windows for history of chronic transfusion/exchange transfusion from within ≤16 weeks to within ≤12 weeks prior to Day 1.	Updated windows will improve participant recruitment and retention without compromising study objectives and endpoints.	Substantial
Section 1.3 – Schedule of Activities Section 8.8 - Biomarkers	Added flexibility in the collection of exploratory biomarker samples if the only feasible point of venous access is a port.	Flexibility will improve participant recruitment and retention without compromising study objectives and endpoints.	Substantial
Section 1 – Protocol Summary Section 10.5 – Appendix 5: Decentralized Clinical Trial User Guidance	Language modified to reflect the addition of in-person study sites in addition to decentralized site design.	Increasing the number/type of study sites to improve participant recruitment and retention without compromising study objectives and endpoints.	Not-substantial
Section 1.3 – Schedule of Activities	Included laboratory specifics of the hematology panel collected as part of the pre-specified SCD medical history.	Data to be collected for a more robust participant profile for future clinical program development.	Not-substantial
Section 3.1 – Variables	Included additional acceptable data sources	Inclusion of additional data sources will	Not-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial or not-substantial
Section 4.1 – Overall Design	if the medical record is not sufficient to determine participant eligibility and data collection, as applicable.	improve participant recruitment and retention without compromising study objectives and endpoints.	
Section 8.1.2 – SCD Events of Interest Section 8.3.7 – Disease-Related Events (DREs) and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs	Modified collection of "Hematuria" events to "Gross Hematuria" and combined with "Renal papillary necrosis."	Clarification will provide greater specificity of said events to participant's SCD-specific pathophysiology.	Not-substantial
Various sections of the protocol	Minor clarifications and editorial/typographical changes have been made throughout.	Provided text clarification and corrections.	Not-substantial

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title A Low-Interventional Study of an Electronic Sickle Cell Disease Patient Reported Outcomes in Sickle Cell Participants

Rationale

Pfizer is developing an ePRO that is completed on a daily basis using a diary to comprehensively self-report VOCs in participants with SCD and its impact on their lives. This is a prospective, low-intervention study to evaluate the responsiveness of the SCD ePRO in a therapeutic setting. Efficacy of drugs intended to reduce the frequency of VOC has historically been assessed based on frequency of VOC with an operational definition for VOC that requires MU, an endpoint approach that is limited in its utility for assessing benefit of therapeutic interventions across the totality of the disease experience. Thus, despite current available treatments, many patients with SCD still experience VOCs and there remains a significant unmet medical need and an opportunity to improve on existing endpoints. While previous studies have been conducted to consider this endpoint, they have not been conducted in a therapeutic setting and therefore unable to assess the responsiveness of the SCD ePRO.[1,2] This study aims to assess the responsiveness of the patient-reported endpoints in participants with SCD who are not on a disease modifying therapy versus those who are on SCD disease modifying therapy.

Objectives and Endpoints

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 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 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 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, 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).

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

- The analysis population is defined as all participants who were selected for analysis via matching procedure.
- 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 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 treatment group level mean estimates of rates (VOC Day rate, patient-reported VOC Event rate, and patient-reported MU VOC rate) and SCD ePRO scores (worst pain, worst tiredness, and ability to perform UPA), as well as the rate reduction in the SCD disease modifying treatment group compared to the control group.

Overall Design

This study consists of 2 concurrent enrolled groups of participants with SCD (HbS/S or HbS/β°-thalassemia), those who are either not on disease modifying treatment (control group) or on a stable dose of a SCD disease modifying treatment regimen (SCD disease modifying treatment group). Participants 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.

Number of Participants

Approximately 150 participants will be enrolled. A total of approximately 100 SCD participants will be enrolled in the control group (Group 1), where they are not on a SCD disease modifying therapy. A total of approximately 50 SCD participants will be in the SCD disease modifying treatment group (Group 2), participants who are on a stable dose of a SCD disease modifying treatment regimen prior to Day 1 enrollment. Based on ongoing assessment of data from enrolled participants, sample size may be increased up to a maximum overall study enrollment of 200 participants. A sample size reestimation may be performed when ≥20 participants have completed 180 days of observation in order to

confirm that sample size is sufficient to support study objectives. Sample size for Group 1 and/or Group 2 may be adjusted based on this analysis. Details regarding the sample size reestimation are specified in the SAP.

Study Cohorts and Duration of Study Participation

Screening assessments will be performed and completed 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 by study staff. A biomarker blood sample may also be collected on Day 1. Completion of the SCD ePRO will be reinforced via telehealth or in-person study site visits throughout the observation period.

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

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

The purpose of this study is to evaluate responsiveness of the SCD ePRO in SCD participants treated with SCD disease modifying therapy. The following analysis strategy was put forward.

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.

The primary objectives will be tested hierarchically as listed above. A detailed description of the testing procedures will be presented in the study SAP.

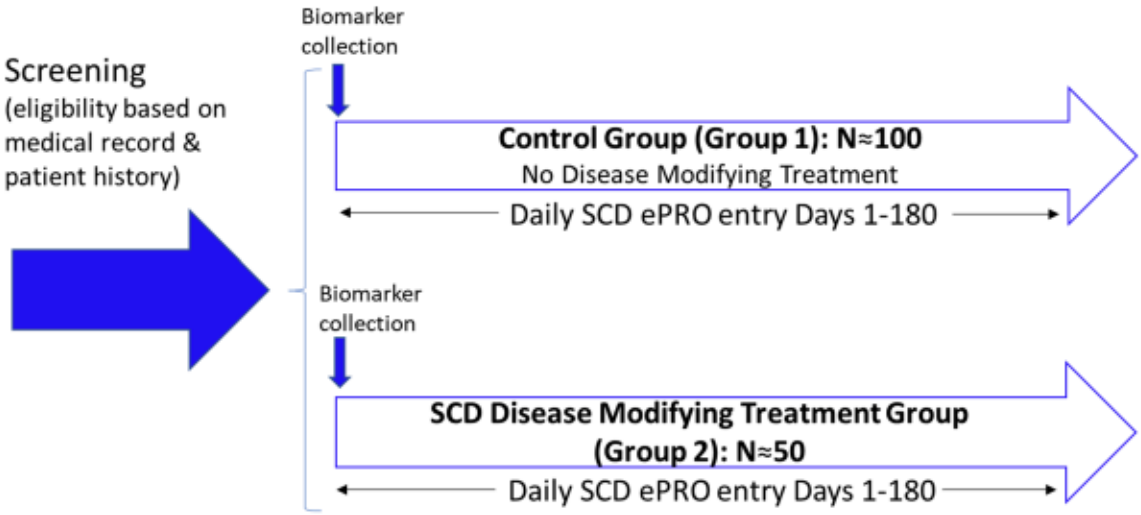
Additional analyses will be done to support exploratory objectives of the study.

The sample size for this study was calculated to have at least 80% power to detect 44% difference in median annualized MU VOC rates using Wilcoxon Rank Sum Test at 0.2 two-sided alpha level. This sample size would be sufficient to test the target effect on SCD ePRO measures.

The detailed description of the methods will be presented in the study SAP, that will be finalized before enrollment of the first study participant.

1.2. Schema

Figure 1. Study Schema



1.3. Schedule of Activities (SoA)

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Table 1. Schedule of Activities – All Groups

Visit Identifier[a]	Screening[b]	Observation Period								E/T
Study Day (relative to Day 1)	-56 to -1	1[c]	2 + 3	30 ± 7	60 ± 7	90 ± 7	120 ± 7	150 ± 7	180 + 7	
Informed consent	X									
Primary Diagnosis (SCD Phenotype or variant)	X									
SCD Details[d]	X									
Medical History and Demography	X									
Medication History	X									
Review of Eligibility Criteria	X									
Study Enrollment/Group Assignment[e]		X								
SCD ePRO[f]		X	→	→	→	→	→	→	X	X
Concomitant Treatments		X	→	→	→	→	→	→	X	X
Monitor serious/nonserious AEs[g]		X	X							
Monitor SCD Events of Interest[h]	X	→	→	→	→	→	→	→	X	X
Telehealth or In-Person Study Site Visit[i]			X	X	X	X	X	X	X	X
Blood Sampling:										
Serum exploratory biomarkers [j]		X								
Plasma exploratory biomarkers [j]		X								

a. The Day 1 visit may be conducted by a home health visit or by an in-person study site visit. All other visits may be conducted by an in-person study site visit or by telehealth visit.
b. Screening assessments may be completed up to Day 1 to confirm eligibility.
c. Day 1 activities may take place over more than 1 calendar day. However, participant enrollment should take place once eligibility has been confirmed.
d. Pre-specified significant medical history related to the diagnosis of SCD as well as genotype and hematology panel with HbF. Laboratory results within the hematology panel in the participant's medical record include absolute total cell number (WBC), erythrocytes, Hb, hematocrit, erythrocyte mean corpuscular volume, erythrocyte mean corpuscular hemoglobin, erythrocyte mean corpuscular hemoglobin concentration and platelets.
e. Participants will be enrolled in either the no disease modifying treatment/control group (Group 1) or the SCD disease modifying treatment group (Group 2).
f. SCD ePRO device and training will be provided on Day 1. Devices will be collected from participants following Day 180 or E/T.
g. Serious and nonserious AEs will be monitored for up to 24 hours following the blood sample collection on Day 1. Outside of this specified, limited active collection period, AEs and SAEs do not need to be actively solicited.
h. SCD events of interest will be reported as described in Section 8.1.2 and Section 8.3.7.
i. Telehealth or in-person study site visits may include compliance reinforcement of daily SCD ePRO entries, ensuring there are no emerging technical issues, confirming concomitant treatments including disease-modifying treatment and transfusion, and monitoring serious/nonserious AEs and SCD events of interest.
j. The biomarker sample may be collected on Day 1, however, if unable to obtain, the sample may be collected at any time during the observation period while the participant is in a non-VOC state. Should an issue occur with the sample collection (eg, preparation or shipment to the vendor) which renders the sample unusable, a repeat sample may be obtained at any time during the observation period as long as the participant is in a non-VOC state. If the only feasible point of venous access is a port (portacath, infusaport, etc.), then exploratory biomarker collection may be omitted. Placement of port should be documented in the medical history. See Section 8.8.

2. INTRODUCTION

Pfizer is developing drugs with various mechanisms of action as potential prophylactic treatment(s) to reduce the frequency of VOCs, a clinical hallmark of SCD and the most common reason for hospitalization among SCD patients. Historically, the efficacy of drugs intended to reduce the frequency of VOC has been evaluated by MU VOC, a definition that necessitates contact with a health-care provider (eg, emergency department visit, clinic/office visit or hospitalization). However, studies have shown that the majority of VOCs occur at home with no intervention provided by a healthcare provider.[2,3] Requiring MU to confirm a VOC event underestimates patient burden of VOC and limits the ability to fully evaluate the benefit of new treatments. Thus, there is a need for a PRO to accurately capture and record VOCs that may or may not culminate to MU.

On this basis, Pfizer is developing a SCD ePRO that is completed on a daily basis using a diary to comprehensively self-report VOC and its impact on SCD patient's lives. For approximately 6 months, participants who are or are not on a SCD disease modifying treatment will complete a daily SCD ePRO entry to report their experience.

2.1. Study Rationale

The purpose of the study is to evaluate the responsiveness of the SCD ePRO in participants in a therapeutic setting, which will support further validation of novel endpoints (eg, patient-reported VOC Event rate and VOC Day rate) and their relationship to the traditional endpoint utilized in drug development for SCD, MU VOC. Biomarkers may be evaluated to characterize hematologic parameters in SCD patient who are either being treated with disease modifying treatment or not on disease modifying treatment.

Evidence of responsiveness of the novel patient-reported endpoints in SCD will enable the use of these endpoints as primary measures for future investigational drug studies in SCD. Additionally, individual participant level data generated from this study may be utilized as external controls to supplement placebo data in future SCD studies.

2.2. Background

2.2.1. Background Information on Sickle Cell Disease

SCD is a multisystem disorder associated with episodes of acute illness and progressive organ damage and is one of the most common genetic disorders worldwide.[4] Approximately 250,000 new cases of SCD are diagnosed globally each year.[5] Within the United States, approximately 100,000 individuals are affected by SCD.[6] The frequency of SCD occurs in about 1/365 Black or African American births and in about 1/16,300 Hispanic-American births.

SCD is a result of a single point mutation in the β-globin chain. SCD comprises a number of serious and potentially disabling conditions that have similar symptoms but vary in underlying genotype and in clinical severity. Individuals homozygous for Hb S (SCD-S/S) have sickle cell anemia. Those who are compound (double) heterozygotes have 1 copy of

HbS and 1 copy of either HbC (SCD-S/C), Hb β^+-thalassemia (SCD-S/β^+-thal), or Hb β^0-thalassemia (SCD-S/β^0-thal).[7]

The pathophysiology of SCD is complex and heterogeneous. The primary indispensable event in the molecular pathogenesis of SCD is the tendency of HbS to polymerize under conditions of low oxygen tension causing RBCs to become rigid and sickle shaped.[8] This leads to anemia consequent upon a shortened RBC life span due to hemolysis and vascular occlusion that is precipitated by interactions between the vascular endothelium and sickled RBCs, leukocytes and platelets.[4]

VOCs are the most common clinical manifestation of SCD and are the result of microvascular occlusion.[9] VOCs are initiated by interaction between sickled RBCs and vascular endothelium in post-capillary venules, where oxygen tension is at its lowest.[10] This leads to endothelial damage that triggers an inflammatory response and causes leukocytes, platelets and additional RBCs to be recruited to the site of inflammation.[11]

Severe VOCs typically present as episodes of pain and inflammation at one or multiple sites, of varying degrees of severity, and occurring at varying intervals throughout life.[12] Based on a widely referenced study from 1991, approximately 60% of patients with homozygous SCD would be expected to have at least 1 severe VOC per year, but a proportion of patients would be expected to have many more episodes.[13] VOCs are responsible for >90% of hospitalizations, resulting in significant morbidity, mortality, and interruption of daily functioning such as individual's education, psychosocial development, and employment as well as causing severe pain, hospitalization, and premature death.[14]

With increasing age, chronic hemolytic anemia and recurrent episodes of vaso-occlusion and inflammation result in progressive damage to many organs, including the brain, kidneys, lungs, bones, and cardiovascular system.[4,8] This leads to markedly shortened life expectancy, with a median survival of approximately 56 years,[15] and overall, the lifespan for individuals with SCD remains approximately 3 decades less than for individuals without SCD.[16]

The management of SCD includes supportive care treatment of clinical manifestations and preventive measures including early education of patients and parents. Preventive measures include maintaining hydration and avoiding climate extremes, physical exhaustion, extremely high altitude and other unfavorable environmental factors. Other preventive measures include management of fevers, prophylactic antibiotics, immunizations, folic acid supplementation; and iron chelation therapy for those with iron overload.

2.2.2. Current Pharmacologic Treatments for SCD

Currently approved treatments for SCD aim at reducing incidence, duration, and severity of VOCs in patients with SCD and/or reduction in severity of the underlying hemolytic anemia, with potential longer-term benefits in terms of reducing the frequency of other disease-related morbidities.[17]

HU is an approved drug for long-term management and prevention of VOCs. In a Phase 3 clinical trial in adults with SCD (HbS/S or S/β^0-thal), treatment with HU reduced the median

frequency of VOCs, based on the study protocol definition, by approximately 40% (2.5 episodes/year versus [vs] 4.5).[18] HU treatment was also observed to reduce the incidence of acute chest syndrome.[19]

Adakveo® (crizanlizumab) has received approval in 36 countries including the United States and Europe.[20,21] It is indicated for the prevention of recurrent VOCs in SCD patients aged 16 years and older and can be administered in combination with HU/HC or as monotherapy in patients for whom HU/HC is inappropriate or inadequate. However, in the pivotal registration study, protection provided by crizanlizumab against VOCs was incomplete, ie, in the group treated with high dose (5 mg/kg) crizanlizumab the median annual rate of VOCs was 1.63 and 64% of individuals experienced at least one episode of VOC.[22,23]

Endari® (L-glutamine) is an approved drug in the US indicated to reduce the acute complications of SCD in adult and pediatric patients 5 years of age and older. In a Phase 3 safety and efficacy study to treat SCD (HbS/S or S/β^0-thal), treatment with L-glutamine reduced the average cumulative VOC count by 25%, as compared to placebo over a 48-month period.[24]

Oxbryta™ (voxelotor) recently received accelerated approval by the FDA for the treatment of SCD in adults and pediatric patients 12 years of age and older. In a clinical study, patients with SCD that received 1500 mg voxelotor daily had increased Hb levels and reduced incidence of worsening anemia as compared with placebo.[25] However, voxelotor did not achieve a significant reduction in frequency of VOCs.

Thus, despite current available treatments, many patients with SCD still experience VOCs and there remains a significant unmet medical need in this patient population for new therapeutic options to reduce incidence, duration, and severity of VOCs.

2.2.3. Currently Available Tools in Assessing Therapeutic Benefit and Clinical Drug Development, and Their Limitations

The efficacy of drugs intended to reduce the frequency of VOC has historically been assessed based on frequency of VOC with an operational definition for VOC that requires medical utilization (medical facility visit/medical facility utilization, MU VOC).[18, 22, 24]

However, the MU VOC endpoint has limitations in its utility for assessing benefit of therapeutic intervention(s) for patients and fails to include pain episodes that are treated at home and incompletely assesses the impact of a therapeutic intervention. Furthermore, data from the US NIH Cooperative Study of Sickle Cell Disease demonstrate that nearly 40% of SCD patients have zero MU VOC episodes per year[13] and the MU VOC endpoint has no utility in these patients.

In the longitudinal PiSCES of pain in SCD patients (≥16 years), patients recorded their maximum pain, whether they were in a pain crisis and required MU using a daily paper diary for up to 6 months.[1] In that study, the frequency of VOC episodes was higher than that captured by health care providers, and the crisis pain was largely managed at home.[1,3] More specifically, pain with or without crisis or utilization of medical care was reported on 54.5%

of 31,017 analyzed patient-days.[1] On 12.7% of patient-days, patients described their pain as a VOC but managed it at home as opposed to MU whereas patients reported an unplanned visit to their physician, emergency department or a hospitalization on only 3.5% of patient days.[3]

Results from ELIPSIS in a similar patient population support a similar conclusion based on an early iteration of an electronic PRO entitled the SCD ePRO (see Section 2.2.4). Patient reported information was collected on a daily basis, using an eDiary to identify the number of days on which a SCD patient experienced VOC pain (VOC Day). Using entries for VOC Day, the frequency of patient-reported VOC Events was derived. Self-treatment without MU (ie, hospitalization, direct healthcare utilization or indirect healthcare utilization) accounted for 78.3% of VOC Days whereas medical contact/medical facility utilization was reported for 8.7% of VOC Days and hospitalization was reported for 13.0% of VOC Days.[2]

Data from the ELIPSIS observational study demonstrated a quantitative relationship between VOC Day and MU VOC and between Patient reported VOC Event and MU VOC.

2.2.4. SCD ePRO

To capture the totality of the impact of VOC on patients with SCD, Pfizer is developing and validating a PRO entitled "SCD ePRO", which is planned for use in evaluating efficacy of drugs that are intended to reduce the frequency of VOCs. The original concept for a SCD ePRO was based on the paper-based diary approach used in the PiSCES study,[1] and has been iteratively refined based on feedback from regulatory agencies and interviews with SCD patients and their caregivers. In its current streamlined version, the SCD ePRO is collected on a daily basis via a handheld electronic device and is made up of up to six questions and should take approximately 3-5 minutes to complete.

The first question of the SCD ePRO asks participants about their "sickle cell pain crisis" in the past 24 hours. A sickle cell pain crisis day is defined as a day when pain is more severe than usual, participants can't do what they normally would do, they may be more tired and use extra pain medication to get by. During this crisis, participants may need to speak to a doctor or go to an emergency room or hospital or they may treat themselves at home. This item is also referred to as a "VOC Day". If they respond yes, they will be asked to provide the location of care for the pain crisis, eg, at home, contact with doctor or nurse, emergency room visit or overnight stay in a hospital. The next 3 questions are about participant's worst pain, worst fatigue, and their ability to perform physical activity during the same 24 hours. Finally, participants are asked about any pain medications they took during the same period to treat their sickle cell pain.

The data for VOC day is used to calculate a primary efficacy endpoint called the VOC Day rate. The other measures collected in the SCD ePRO (eg, pain, fatigue and physical activity) are supportive of this primary efficacy endpoint.

Data for VOC day entries is also used to derive the number/frequency of patient-reported VOC Events. A patient-reported VOC Event is defined as a sequence of patient-reported VOC Days that could also include single intervening days with no pain crisis. The

subsequent occurrence of two consecutive days with no pain crisis operationally defines the end of the respective patient-reported VOC Event.

Experience in the ELIPSIS observational study demonstrated that daily monitoring of the VOC status of patients can be facilitated in adolescents and adults using an ePRO diary which enables near real-time collection of the patient experience. Furthermore, reporting on pain, pain crisis status and other symptoms via a daily diary on an electronic device was well received by the adolescent and adult participants. In order to further development of the SCD ePRO and its associated efficacy endpoints, it will be necessary to characterize the responsiveness of this patient reported outcome in the context of a therapeutic setting. This information will contribute to the validation of the SCD ePRO as an efficacy endpoint. This study is being conducted in patients with SCD who are on a background of disease modifying therapy (SCD disease modifying treatment group) and those who are not (control group). In addition, to the primary measure of VOC Day, this study will incorporate the secondary efficacy measures of "number of patient-reported VOC Events" as derived from data collected from the VOC Day item of the SCD ePRO. Other secondary or exploratory endpoints based on the SCD ePRO items of Worst Pain, Worst Tiredness, and UPA will also be evaluated. This study will characterize these quantitative relationships in the setting of a therapeutic intervention.

2.3. Benefit/Risk Assessment

2.3.1. Benefit Assessment

Participants in this study may experience the benefit of contributing to the development of the SCD ePRO. This novel endpoint may enable the development of new treatments for SCD.

2.3.2. Risk Assessment

The minimal risk that participants may experience in this study is related to the biomarker blood collection which may occur during this study. A blood draw may cause faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There may also be a chance of infection. Blood collection will be performed by a qualified individual to minimize these potential risks.

Considering the minimal risk to participants participating in this study, the potential risks identified in association with blood collection are justified by the anticipated benefits that may be afforded to participants with SCD.

3. RESEARCH QUESTIONS, OBJECTIVES AND ENDPOINTS

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 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 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 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, 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).

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

- The analysis population is defined as all participants who were selected for analysis via matching procedure.
- 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 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 treatment group level mean estimates of rates (VOC Day rate, patient-reported VOC Event rate and MU VOC rate) and SCD ePRO scores (worst pain, worst tiredness and ability to perform UPA), as well as the rate reduction in the SCD disease modifying treatment group compared to the control group.

3.1. Variables

The following variables will be considered for use for matching participants in the control group to participants in the SCD disease modifying treatment group. Any additional variables that may be considered will be available in the SAP.

Variable	Role	Data source(s)	Operational definition
%HbF	Baseline characteristic	Medical records, Information provided by participant's pediatric or current healthcare provider.	Data collected on SCD history. Data collected subsequent to 1 year of age, in the absence of recent transfusion and prior to initiation of any HU treatment.
MU VOC within 12 months prior to Screening (control group)	Baseline characteristic	Medical records, Participant self-reporting	Data collected on SCD history will reflect eligibility criteria for group.
MU VOC within 12 months prior to initiation of HU and/or	Baseline characteristic	Medical records, Participant self-reporting	Data collected on SCD history will reflect eligibility criteria for group.

Variable	Role	Data source(s)	Operational definition
crizanlizumab treatment (whichever was initiated earlier) (SCD disease modifying treatment group)			

4. STUDY DESIGN

4.1. Overall 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. Based on ongoing assessment of data from enrolled participants, sample size may be increased up to a maximum overall study enrollment of 200 participants. A sample size reestimation may be performed when ≥20 participants have completed 180 days of observation in order to confirm that sample size is sufficient to support study objectives. Sample size for Group 1 and/or Group 2 may be adjusted based on this analysis. Details regarding the sample size reestimation are specified in the SAP. 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. In order to assess the responsiveness of the SCD ePRO, it will be critical to first confirm that the SCD disease modifying treatment group has the expected treatment effect (lower rate of VOCs) on physician-reported MU VOCs as compared to the control group. Next the study will need to demonstrate a significant treatment effect on the SCD ePRO measures. Therefore, there are two primary objectives for this study.

Screening assessments will be performed and completed within 56 days prior to study enrollment (Day 1) to confirm eligibility per the SoA. On Day 1, the SCD ePRO device and training will be provided to study participants 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 may be collected on Day 1 to characterize hematologic parameters in SCD participants who are either being treated with disease modifying treatment or not on disease modifying treatment.

Participant's medical records will provide the source for primary SCD diagnosis, SCD details, demographics, medication history and other medical history as well as collection of

SCD events of interest. A medical record may include any trial data source document(s) for the participant. In the absence of available medical records and/or information provided by participant's pediatric or current healthcare provider, participant self-reported medical history may be appropriate. The study design purely contemplates capture of SCD ePRO entries by a study participant along with biomarker blood sampling. It does not involve in any respect the assessment, examination, diagnosis, prognostication or treatment of any study participant.

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.

Design overview of the study is shown in Section 1.2. Sample size for the respective study groups may be modified based on emerging data.

4.2. Scientific Rationale for Study Design

This is a prospective, low-intervention study to evaluate the responsiveness of the SCD ePRO in participants who are either not a disease modifying treatment or are on a stable dose of a SCD disease modifying treatment regimen. Pfizer is developing a daily SCD ePRO, stemming from previous clinical trial ePRO renditions, designed for SCD patients to comprehensively self-report their VOC experience(s) and its impact on their lives. This population is considered appropriate for evaluation of a daily SCD ePRO in participants with SCD.

The selection of the approximate 180-day (6 month) SCD ePRO entry time period and treatment with targeted SCD disease modifying therapies harmonizes with previous studies.

The selection of the biomarkers is based on potential pharmacology between participants on a stable dose of a SCD disease modifying treatment regimen and those not on a disease modifying treatment as well as various manifestations of SCD. Steady state SCD is characterized by elevated markers of hemolysis/anemia, coagulation, cell adhesion, endothelial activation, and inflammation. Individuals with sickle cell trait had significantly lower levels of these markers than patients with more severe forms of the disease who were in a non-VOC state.[2,26] This evidence suggests that therapeutic intervention(s) may favorably modulate disease-related biomarkers following treatment. Biomarkers analyzed in the study may include: 1) serum: soluble CCI, soluble CCI, soluble VCAM-1, soluble ICAM-1, IL-6, IL-18, IP-10, IL-10, and TNFα, and 2) plasma: Tissue Factor, TAT, and D-dimer.

4.2.1. Nomenclature Used Throughout This Protocol

The term **VOC Day** is used to define a day on which a SCD patient self-reports sickle cell pain crisis that was recorded in the SCD ePRO.

The term patient-reported **VOC Event** is used to define a sequence of VOC Days that could also include single intervening days with no pain crisis. The subsequent occurrence of two

consecutive days with no pain crisis operationally defines the end of the respective VOC Event.

MU VOC will be 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 non-steroidal anti-inflammatory drugs. MU VOCs will be reported from either patients (patient-reported MU VOC) or physicians (physician-reported MU VOC) as described below. Acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism (requiring a visit to a medical facility) will also be considered a MU VOC. The subsequent occurrence of two consecutive days with no pain crisis operationally defines the end of the respective MU VOC.

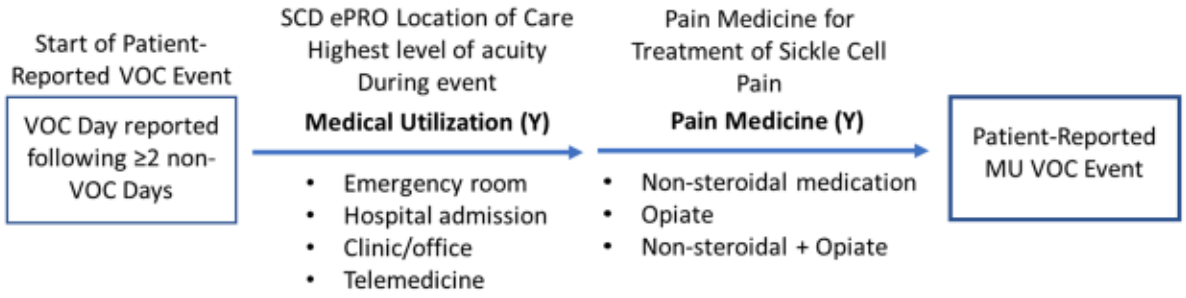
Contact with healthcare professionals will include:

- Called Health care 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.

Reports will be verified by participants medical records or participants recall when records are not available. The frequency of physician-reported MU VOC will be derived based on information provided by the respective investigator on the SCD Events of Interest form.

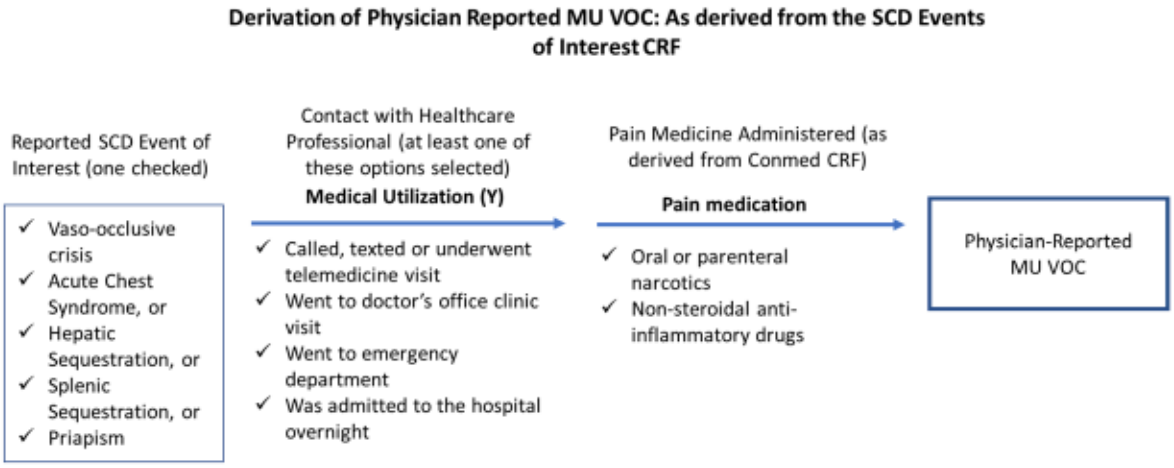
Patient-reported MU VOC Events will be derived from SCD ePRO entries using the process flow described in Figure 2 below:

Figure 2. Derivation of Patient-Reported MU VOC Events



Physician-reported MU VOC will be derived from the SCD Event of Interest entries using the process flow described in Figure 3 below:

Figure 3. Derivation of Physician-Reported MU VOC: As Derived from the SCD Events of Interest CRF



4.2.2. Conceptual Framework for VOC Experience

The ePRO, also referred to as the "SCD ePRO" is administered on a dedicated handheld device and is comprised of a primary item called the "VOC Day," and secondary items which capture information on "Worst Pain", "Worst Tiredness", and "Usual Physical Activity". The conceptual framework for capturing a VOC experience, using these respective measures, is shown below in Figure 4. The efficacy endpoint of VOC Day rate will be the primary SCD ePRO endpoint for evaluation of drugs that are intended to reduce the frequency of VOCs. The individual secondary efficacy endpoints derived from the individual secondary items in the SCD ePRO will be supportive of the primary efficacy endpoint. The frequency of Patient-reported VOC Events will also serve as a secondary efficacy endpoint.

Figure 4. Conceptual Framework for VOC Experience

4.2.3. Intended Application(s) in Clinical Drug Development

Pfizer proposes to develop a VOC Day-based endpoint, the VOC Day rate, that would be suitable for use as a primary efficacy endpoint in the context of prospective randomized controlled studies of drugs to reduce the frequency of VOCs. These studies may include Phase 2 proof-of-concept studies to provide initial evidence of efficacy for the respective drug(s) and/or subsequent pivotal Phase 3 studies. In addition, Pfizer plans to incorporate the secondary efficacy endpoint of "number/frequency of patient-reported VOC Events" as derived from data collected from the VOC Day item of the SCD ePRO. Other secondary or exploratory endpoints based on the SCD ePRO items of Worst Pain, Worst Tiredness, and UPA may be considered as well.

4.2.4. Limitations of the Study Design and Methods

- The SCD ePRO addresses only VOCs, the clinical hallmark of SCD, but not other comorbidities associated with SCD (eg, end organ damage, hemolytic anemia, etc). Further, it should be noted that the validation conducted to date of the SCD ePRO has been done in the setting of prophylaxis and there are no data in the setting of acute VOCs.

- Participants who are on SCD-specific background treatment may have experienced more severe symptoms than participants who are not on any disease modifying treatment. Consequently, there may be a bias toward more severely affected patients being treated with SCD disease modifying therapy. To help control for this

possibility, availability of data for the rate of MU VOCs prior to start of treatment with HU and/or crizanlizumab, whichever comes first (as applicable), is an eligibility criterion for the SCD disease modifying treatment group.

- In this study, participants will be assigned to either one of two groups, but not both, based on their eligibility criteria. There is no randomization based on the two groups for which they are enrolled. All participants will undergo the same assessments after they are enrolled into the study.

4.2.5. Participant Input into Design

The study is designed with the focus of optimizing evaluation of SCD ePRO whilst minimizing burden of study participants. This study is designed with consultation from subject-matter clinical experts who actively treat SCD patients and have a history of involvement in SCD-related clinical studies. Interviews with SCD patients and caregivers before and during the ELIPSIS study as well as cognitive debriefing interviews informed the design of the original and streamlined versions of the SCD ePRO.

4.3. Justification for Dose

Not applicable.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit (follow-up contact) of the last participant in the study.

A participant is considered to have completed the study if he/she has completed all phases of the study as shown in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria (All Groups)

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants ages ≥18, inclusive, at Screening.

Type of Participant and Disease Characteristics:

2. Confirmed diagnosis of stable SCD (HbS/S or HbS/β^0-thalassemia).

   - Stable diagnosis is defined as no significant SCD-related complications for at least one week prior to Day 1 enrollment, such as a VOC requiring in-patient hospitalization, acute chest syndrome or any complication requiring in-patient hospitalization.

   - Diagnosis should be confirmed by Hb electrophoresis, HPLC or molecular based diagnostic methods.

3. Participants who are willing and able to comply with all scheduled visits, laboratory tests, and study procedures including daily eDiary entries using the dedicated SCD ePRO device.

Informed Consent:

4. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.1.1. Additional Inclusion Criteria – Control Group

1. Have experienced ≥1 episode(s) of MU VOC (see Section 4.2.1) within 12 months prior to Screening.

2. Data available for number of MU VOC(s) during the 12-month interval prior to Screening and a value for %HbF collected subsequent to 1 year of age in the absence of recent transfusion[27].

5.1.2. Additional Inclusion Criteria – SCD Disease Modifying Treatment Group

1. Have experienced ≥1 episode(s) of MU VOC (see Section 4.2.1) within 12 months prior to initiation of HU and/or crizanlizumab (whichever was initiated earlier).

2. Must be on a stable dose of their SCD treatment regimen ≥8 weeks prior to Day 1 with the intent of remaining on the same dose throughout the study, unless adjustments are medically necessary due to bone marrow suppression, in accordance with published guidelines[28], and/or product specific guidance (eg, package label). Accepted SCD disease modifying treatment regimens include:

   - HU alone and/or in combination with crizanlizumab, L-glutamine and/or voxelotor;

     or

- Crizanlizumab alone and/or in combination with HU, L-glutamine and/or voxelotor.

3. Data available for number of MU VOC(s) during the 12-month interval prior to initiation of any SCD disease modifying treatment, as described above, and a value for %HbF collected subsequent to 1 year of age, prior to initiation of any HU treatment, and in the absence of recent transfusion[27].

5.2. Exclusion Criteria (All Groups)

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Evidence or history of ongoing (condition or sequelae) clinically significant hematological (non-SCD), renal, endocrine, pulmonary, gastrointestinal, cardiovascular (including overt stroke but excluding silent cerebral infarct), hepatic (excluding cholelithiasis), psychiatric or neurological disease as assessed from medical records.

2. Participants with any of the following acute or chronic infections or infection history as self-reported and/or assessed from medical records prior to Day 1 enrollment:

   - Fever within ≤7 days;
   - Any infection requiring treatment with anti-infective drug(s) within ≤2 weeks;
   - COVID-19 infection unless 10 days have elapsed since symptoms first appeared, participant is without symptoms for ≥24 hours and is not experiencing post-COVID-19 symptoms.

3. Marked ongoing bone marrow suppression as evidenced by any of the following as per medical record: severe anemia, ANC <1000 mm^3 WBC, thrombocytopenia (platelet count <100,000 mm^3) within ≤8 weeks prior to Day 1 enrollment.

4. Major surgery <3 months prior to Day 1 as self-reported and/or assessed from medical records or planned significant medical procedures during the study.

5. Females who are pregnant or plan to become pregnant during the study.

6. Other medical or psychiatric condition including cognitive impairment that prevents accurate reporting of pain and/or assessment of SCD symptoms, recent (within the past year) or active suicidal ideation/behavior, or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

7. History of hematopoietic stem cell transplant or treatment with gene therapy as assessed from medical records.

8. History of simple transfusion within ≤4 weeks prior to Day 1 enrollment as assessed from medical records or participant self-report.

9. History of chronic transfusion/exchange transfusion within ≤12 weeks prior to Day 1 enrollment as assessed from medical records or participant self-report and/or plan to initiate such treatment during the 6-month observation period.

Prior/Concurrent Clinical Study Experience:

10. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding Day 1 (whichever is longer).

Other Exclusions:

11. Active use of illicit drug as determined by the investigator.

    - A history or use of opioids will not be considered an exclusion if participant takes prescribed opioids for pain related to the underlying SCD.

    - A history or use of cannabinoids is not exclusionary.

12. History of alcohol abuse, dependence, or binge drinking within 6 months of Screening as determined by the investigator.

    - Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit or 3 ounces (90 mL) of wine).

13. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section (Section 5.2.1) of this protocol.

14. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

5.2.1. Additional Exclusion Criteria – Control Criteria

1. Participant received HU and/or crizanlizumab at any time within ≤18 months of Day 1 enrollment and treatment(s) was discontinued due to lack of efficacy (no reduction in the frequency of VOCs, documented or perceived) and/or plan to initiate said treatment(s) during the 6-month observation period.

2. Participant received voxelotor or L-glutamine within ≤4 weeks of Day 1 enrollment and/or plan to initiate said treatment(s) during the 6-month observation period.

5.3. Lifestyle Considerations

Investigational drugs are not permitted during the study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study because they did not meet the eligibility criteria.

Minimal screen failure information including demography, screen failure details, and eligibility criteria will be collected.

Screen failures may be rescreened. Participants who are rescreened are required to reconsent.

6. STUDY INTERVENTIONS

In this study, there are no therapeutic study interventions, however the study does involve protocol-required diagnostic or monitoring procedures (study interventions) that are considered to be low risk or burden to the study participant; specifically:

- Biomarker blood (serum and plasma) sampling on Day 1.

6.1. Study Intervention(s)

6.1.1. Administration of Diagnostic or Monitoring Study Interventions

Biomarker blood sampling may be performed as per SoA. See additional details in Section 8.8

7. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM STUDY

7.1. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor.

At the time of discontinuing from the study, if possible, an E/T visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The E/T visit applies only to participants who are enrolled and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent for disclosure of future information (see Section 7.1.1), no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the protocol-required E/T procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.1.1. Withdrawal of Consent

Participants should notify the investigator in writing of the decision to withdraw consent for future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal was from study procedures and/or study follow-up, and this information should be entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only in a manner that is in accordance with local law.

7.2. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a protocol-required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

- The SCD ePRO should be retrieved from the participant as soon as possible after Day 180.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any protocol-required) procedure.

Protocol-required study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues related to protocol-required procedures should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue from the study.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, lab test results) and recorded in the medical record prior to the participant signing of the ICD may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Every effort should be made to ensure that protocol-required tests and procedures (study interventions) are completed as described. However, it is anticipated that there may be circumstances outside the control of the investigator that may make it infeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately 8 mL. The actual collection times of blood sampling may change.

8.1. Efficacy Assessments

8.1.1. SCD ePRO

In order to consider the responsiveness of the patient-reported VOC Day as collected on the SCD ePRO, it is necessary to establish that a treatment effect can be measured in the SCD disease modifying treatment group versus the control (no treatment) groups. The treatment effect, physician-reported MU VOC will be derived from entries on the SCD Events of Interest eCRF.

The SCD ePRO is collected on a daily basis using a dedicated handheld device, is made up of up to six questions and should take approximately 1-2 minutes to complete. The first question will ask participants about their "sickle cell pain crisis" in the past 24 hours. A sickle cell pain crisis day is defined as a day when pain is more severe than usual, participants cannot do what they normally would do, they may be more tired and use extra pain medication to get by. During this crisis, participants may need to speak to a doctor or go to an emergency room or hospital or they may treat themselves at home. This item is also referred to as a "VOC Day". If they respond yes, participants will be asked to provide the manner in which they treated the crisis (eg, at home, contact with doctor or nurse, emergency room visit or overnight stay in a hospital). The next 3 questions will be about their worst pain, worst fatigue and their ability to perform physical activity during the same 24 hours. Finally, participants will be asked about any pain medications they took during the same period to treat their sickle cell pain.

The terms patient-reported VOC Day and patient-reported VOC Event are defined as seen in Section 4.2.1.

Guidance on the use of the device will also be provided within the device and the associated quick reference guide. Details regarding SCD ePRO reminders and alerts can be found in the appropriate manual. Following screening, participants will be asked to complete the SCD ePRO daily starting from Day 1 through Day 180. If there is evidence of noncompletion during the study, the site will contact the participant to help them work through any challenges with the completion. In addition, other incentives such as visual reports of completion may be provided to participants to incentivize them to keep up with the daily entries.

8.1.2. SCD Events of Interest

Starting at the time of the Screening visit and through the study duration as described in the SoA, the investigator or delegated and qualified personnel will be responsible for recording medical events (or diagnosis) that are directly related to the participant's SCD and treatment(s) they received for the event. These events will include:

- Vaso-occlusive crisis;
- Acute chest syndrome;
- Hepatic sequestration;

- Splenic sequestration;
- Priapism;
- Stroke – ischemic;
- Stroke – hemorrhagic;
- Stroke – type unknown;
- S/P stroke, infarct;
- Gross hematuria and renal papillary necrosis;
- Avascular necrosis of proximal humerus;
- Avascular necrosis of femur;
- Leg ulcer.

8.2. Safety Assessments

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

8.2.1. Protocol-Required Clinical Safety Laboratory Assessments

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

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE, SAE and RRI can be found in Appendix 2. The investigator is required to assess whether any AE may be related to participation in the study. All AEs (ie, serious and non-serious, including those attributed to a protocol-required procedure identified as RRI) are collected in the clinical study database. Should a participant, in the investigator's opinion, suffer a medically important research related injury caused by their participation in the study, the designated Pfizer clinician or medical monitor must be notified immediately by telephone or email.

AEs may arise from symptoms or other complaints reported to the investigator by the participants (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) or they may arise from clinical findings of the investigator or other HCPs (clinical signs, test results, etc.).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 6.1).

During the active collection period for safety events (see Section 8.3.1), each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

Procedure-Observation Timetable:

Procedure	Minimum Observation Time for Section 8.3.1
Biomarker blood sample collection	Up-to 24 hours following sampling

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 at Day 1 and ends 24 hours after that procedure/intervention has completed.

The investigator is required to perform appropriate follow-up of each adverse event throughout and after the active collection period and until the AE/SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the NIS AE Report form.

Since there is no product under study, there is no post-study active reporting period for the SAEs to be communicated to Pfizer Safety.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period (see Section 8.3.1) are reported to Pfizer Safety on the NIS AE Report form immediately upon awareness, as indicated in Appendix 2; under no circumstance should the time between awareness and reporting of the SAE exceed 24 hours. The investigator will also submit any updated SAE data to the sponsor within 24 hours of it being available.

Reportable SAEs include events related to an approved, Pfizer product taken by the participant under routine care, during the time they are participating in the study, should such events come to the attention of the Investigator (including an overdose or a medication error that led to the SAE). Refer to Appendix 2 for the definition of an overdose or medication error.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All applicable SAEs and nonserious AEs, as described in Appendix 2, that are directly observed and/or spontaneously reported by the participant during the active collection period (described in Section 8.3.1) will be recorded on the AE page of the CRF.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.2).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 2.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Environmental Exposure

The requirements for reporting pregnancy or breastfeeding and environmental exposure apply throughout the entire active collection period and are outlined below; when such reports are required per protocol, the report must be transmitted to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy (EDP)

An EDP occurs if:

- A female participant is found to be pregnant while taking any Pfizer product under routine care, at any time during the study period (eg, a concomitant medication that is not required by the study protocol); or,
- A male participant uses any Pfizer product under routine care during the study period (ie, a concomitant medication that is not required by the study protocol) and his partner subsequently becomes pregnant.

The investigator must report the EDP to Pfizer Safety within 24 hours of the investigator's awareness, whether or not an SAE has occurred.

- The initial information submitted should include the anticipated delivery date of the baby (see below for information related to termination of pregnancy).
- An EDP report is not required if the Pfizer product taken under routine care is specifically approved for use in pregnant women (eg, vitamins) and is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE must be reported along with the EDP.

The Investigator must report the EDP to Pfizer Safety on the NIS AE Report Form and the EDP Supplemental Form. Relevant details of the exposure and the pregnancy will be collected from the time informed consent was provided until final study follow-up. If there is an SAE associated with the EDP, then the SAE is reported to Pfizer Safety using the NIS AE Report Form.

Follow-up must be conducted to obtain general information on the pregnancy and its outcome for all EDP reports. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. For a live birth, information regarding the structural integrity of the neonate at the time of birth should be provided. In the event of a termination, the reason(s) for termination should be provided and information regarding the structural integrity of the terminated fetus should be included in the report (if available; not required if pre-procedure test findings were conclusive for a congenital anomaly and those findings are provided in the report).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), then the investigator should follow the procedures for reporting SAEs.

Additional pregnancy outcomes that must be reported to Pfizer Safety as SAEs include:

- Spontaneous abortion including miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death may be related to exposure to the Pfizer product used under routine care during the study.

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

8.3.5.2. Exposure During Breastfeeding (EDB)

- An EDB occurs if female participant is found to be breastfeeding while taking any Pfizer product under routine care, at any time during the study period (eg, a concomitant medication that is not required by the study protocol).

- An EDB report is not required when a Pfizer product specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE must be reported along with the EDB.

The investigator must report an EDB to Pfizer Safety within 24 hours of the investigator's awareness, whether or not an SAE has occurred.

- The investigator must report EDB to Pfizer Safety using the NIS AE Report form.

- If the EDB is associated with a SAE, then the SAE must be reported using the same NIS AE Report form.

8.3.5.3. Environmental Exposure

Not Applicable. Environmental or occupational exposure is not reportable in this study since there is no Pfizer product under study.

8.3.6. Cardiovascular and Death Events

Not Applicable.

8.3.7. Disease-Related Events (DREs) and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following DREs are common in participants with SCD and can be serious/life threatening:

- Vaso-occlusive crisis;

- Acute chest syndrome;

- Hepatic sequestration;
- Splenic sequestration;
- Priapism;
- Stroke – ischemic;
- Stroke – hemorrhagic;
- Stroke – type unknown;
- S/P stroke, infarct;
- Gross hematuria and renal papillary necrosis;
- Avascular necrosis of proximal humerus;
- Avascular necrosis of femur;
- Leg ulcer.

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE. These events will be recorded on the SCD Events of Interest page in the participant's CRF within 24 hours of awareness. These DREs will be monitored by a safety review team on a routine basis.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a DRE):

- The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

  OR

- The investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.3.8. Adverse Events of Special Interest

Not Applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy is the failure of expected pharmacologic action or therapeutic benefit. In this study, lack of efficacy is reportable to Pfizer Safety for an approved Pfizer product used by the participant under routine care, if the Investigator is made aware.

Lack of efficacy should be reported as an SAE to Pfizer Safety if the lack of efficacy involves a vaccine, a contraceptive or a product that is used in the treatment of life-threatening diseases or conditions (eg, anti-infectives) (excluding HIV and cancer).

For Pfizer products that are not covered in paragraph above, lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not Applicable.

8.4. Treatment of Overdose

Not Applicable.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Not Applicable.

8.8. Biomarkers

The following samples for biomarker research may be collected from participants in this study as specified in the SoA. No biomarker specimens collected in this study will be used for genetic testing.

If the only feasible point of venous access is a port (portacath, infusaport, etc.), then biomarker collection may be omitted. Placement of port should be documented in the medical history.

8.8.1. Serum Exploratory Biomarkers

Blood samples of approximately 5 mL, to provide approximately 2 mL serum, may be collected for potential measurement of soluble [CCI redacted], soluble [CCI redacted], soluble VCAM-1, soluble ICAM-1, IL-6, IL-18, IP-10, IL-10, and TNFα as specified in the SoA.

8.8.2. Plasma Exploratory Biomarkers

Blood samples of approximately 2.5 mL, to provide approximately 1.0 mL plasma, may be collected for potential measurement of Tissue Factor, TAT, and D-dimer as specified in the SoA.

8.9. Immunogenicity Assessments

Immunogenicity assessments will not be performed in this study.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

The purpose of this study is to evaluate responsiveness of the SCD ePRO in SCD participants treated with SCD disease modifying therapy. The following analysis strategy was put forward to attain this goal.

First (study primary objective #1), the study sample needs to demonstrate the expected treatment effect of HU and/or crizanlizumab on physician-reported MU VOC. That expected effect is 44% to 45% reduction in median physician-reported MU VOC rate .[18 22] Because the planned study is observational in nature and lacks randomization, we will use matching to create comparable SCD disease modifying treatment and control groups. The matching algorithm will use historical information (eg, event rates, biomarkers, etc.) and will be fully described in SAP.

Second (study primary objective #2), the study needs to demonstrate a significant treatment effect on SCD ePRO measures.

Third (study secondary objective), the study needs to demonstrate presence of a quantifiable relationship between physician-reported MU VOC rate and VOC Day rate and patient-reported VOC Event, respectively.

Additional analyses (study tertiary/exploratory objectives) will be done to support the study goal.

The detailed description of the methods will be presented in the study SAP, that will be finalized before enrollment of the first study participant.

9.1. Statistical Hypotheses

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.

The primary objectives will be tested hierarchically as listed above. A detailed description of the testing procedures will be presented in the study SAP.

9.2. Sample Size Determination

The sample size for this study was calculated to have at least 80% power to detect 44% difference in median annualized MU VOC rates using Wilcoxon Rank Sum Test at 0.2 two-sided alpha level. Based on ongoing assessment of data from enrolled participants, sample size may be increased up to a maximum overall study enrollment of 200 participants. A sample size reestimation may be performed when ≥20 participants have completed 180 days of observation in order to confirm that sample size is sufficient to support study objectives. Sample size for Group 1 and/or Group 2 may be adjusted based on this analysis.

The pre-specified sample size is considered sufficient to test the target effect on SCD ePRO measures.

A detailed description of the sample size calculation will be presented in the study SAP.

9.3. Data Management

A Pfizer database will be used, and Pfizer will be responsible for the data management of this study, including quality checking of the data. Details are included in the Data Management Plan.

9.4. Case Report Forms (CRF)/Data Collection Tools (DCT)/Electronic Data Record (EDR)

As used in this protocol, the term CRF[/DCT] should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF[/DCT] is required and should be completed for each included participant. The completed original CRFs[/DCTs] are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs[/DCTs] are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs[/DCTs] and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable,

complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs[/DCTs] must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs[/DCTs] are true. Any corrections to entries made in the CRFs[/DCTs] or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs[/DCTs] must match those charts.

In some cases, the CRF[/DCT] may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF[/DCT], and for which the CRF[/DCT] will stand as the source document.

9.5. Data Analysis

The groups will be compared considering the comparability of participants assessed based on propensity scores. The propensity score model and related methodology will be fully described in the SAP.

The first primary objective - the verification of detectable treatment effect - will be evaluated using Wilcoxon Rank Sum Test. The second primary objective - the quantification of treatment effect using novel endpoints - will be evaluated using Negative Binomial regression.

The estimand strategy for the primary and secondary endpoints is described in Section 3.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in an SAP, which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.6. Interim Analyses

A sample size reestimation may be performed in order to confirm that sample size is sufficient to support study objectives. Details regarding the sample size reestimation are specified in the SAP.

9.7. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a Data Monitoring Committee.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

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

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

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

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

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

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

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

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant.

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

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional

research. Participants who decline to participate in this optional additional research will not provide this separate signature.

10.1.3. Data Protection

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

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

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

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

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

www.clinicaltrials.gov

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

EudraCT

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

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient -level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient -level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

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

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic form and are password protected to prevent access by unauthorized third parties.

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

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

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

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

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

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's study records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, the participant's current medical record must be available.

Definition of what constitutes source data can be found in clinical monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study site start date is the date on which the clinical study will be open for recruitment of participants study site.

The first act of recruitment is the date of the first study participant's first visit and will be the study start date.

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

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

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

10.1.8. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with a study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with a study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:

  - Is associated with accompanying symptoms.

  - Requires additional diagnostic testing or medical/surgical intervention.

  - Leads to a change in the study intervention schedule (outside of any protocol-specified adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.

  - Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Research Related Injury

Should a participant, in the investigator's opinion, suffer a medically important research related injury caused by their participation in the study, the designated Pfizer clinician or medical monitor must be notified immediately by telephone or email.

A medically important research related injury is any untoward medical occurrence that:

- Results in death;
- Is lifethreatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an injury is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as a research related injury.

- An investigator may be requested by the designated Pfizer clinician or medical monitor to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the injury in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant treatments, vaccines, and/or illnesses must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Definition of Medication Error:

A medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the healthcare professional, patient, or consumer. Such events may be related to:

- Professional practice,
- Procedures,
- Systems, including:
  - Prescribing;
  - Order communication;
  - Product labeling, packaging, and nomenclature;
  - Dispensing;
  - Distribution;
  - Administration;
  - Education;
  - Monitoring;
  - Use.

Medication errors include near-misses involving or not involving a patient directly or confusion regarding invented names (eg, trade name, brand name).

Definition of Overdose

An overdose is an administration of a quantity of a medicinal product given per administration or cumulatively that is above the maximum recommended dose according to the authorized product information.

10.2.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting During the Active Collection Period

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the NIS AE Report form to Pfizer Safety throughout the active collection period(s). These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to a Pfizer product used under routine care during pregnancy or breastfeeding.

It should be noted that the NIS AE Report form for reporting of SAE information is not the same as the AE page of the CRF. Wherever the same data or information are to be collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and, when referring to a specific event, the same AE term should be used on both the CRF and the NIS AE Report form.

Safety Event	Record on the CRF	Report on the NIS AE Report Form to Pfizer Safety within 24 hours of awareness
SAE	Any SAE that occurs during the active collection period(s). Any SAE that occurs outside the active collection period(s) that the investigator suspects may be related to the protocol-required procedure/intervention.	Any SAE that the investigator suspects may be related to any Pfizer product used by the participant under routine care during and outside any active collection period.
Non-serious AEs	Any non-serious AE that occurs during the active collection period(s). Any AE that occurs outside the active collection period(s) that the investigator suspects may be related to the protocol-required procedure/intervention.	None
Scenarios involving exposure during pregnancy (EDP) and exposure during breast feeding (EDB).	Instances of EDP or EDB are not captured in the CRF.	All instances of EDP (whether or not there is an associated SAE). * All instances of EDB are reported (whether or not there is an associated AE/SAE). **

*__EDP__ (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the NIS AE Report Form and the EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the NIS AE Report Form.

**__EDB__ is reported to Pfizer Safety using the NIS AE Report Form, which would also include details of any SAE that might be associated with the EDB.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the NIS AE Report form or the Adverse Event CRF page.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between any study intervention (or Pfizer product used under routine care) and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- In making his/her assessment, the investigator will also consult the product information for a marketed Pfizer product used under routine care.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change his/her opinion of causality in light of followup information and send an SAE followup report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedure/intervention, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the NIS AE Report form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.

- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.2.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.

- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.

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

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

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

SAE Reporting to Pfizer Safety via NIS AE Report Form

- Facsimile transmission of the NIS AE Report form is the preferred method to transmit this information to Pfizer Safety.

- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the NIS AE Report form sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the NIS AE Report form pages within the designated reporting time frames.

10.3. Appendix 3: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms that the investigator suspects may be due to a Pfizer product used under routine care, then, such LFT results should be managed and followed as described below.

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

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

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

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

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

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

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

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

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

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

10.4. Appendix 4: Medical Device Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not Applicable.

10.5. Appendix 5: Decentralized Clinical Trial User Guidance

10.5.1. Telehealth Visits

Telehealth visits will be performed by a qualified individual and may be used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely. The following assessments must be performed during a telehealth visit in the observation period:

- Study participants to review and sign ICD.
- Review participant eligibility criteria.
- Review compliance on daily SCD ePRO entries and ensure there are no emerging technical issues.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record any AEs and SAEs approximately 24 hours after Day 1 visit occurs. Refer to Section 8.3.
- Monitor SCD Events of Interest.
- Study participants must be reminded to promptly notify site staff about any change in their health status.

10.5.2. Alterative Facilities for Assessments

10.5.2.1. Exploratory Biomarkers

If sample collection were to occur at home through home health, follow home health procedures.

- Collect blood samples for:
  - Serum exploratory biomarkers.
  - Plasma exploratory biomarkers.

10.5.3. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the SoA. Home health visits include a qualified individual (eg, healthcare provider) conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- Provide study participants with SCD ePRO device and assist with set-up and training.

- Review compliance on daily SCD ePRO entries and ensure there are no emerging technical issues.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Monitor SCD Events of Interest.
- Review and record any AEs and SAEs approximately 24 hours after Day 1 visit occurs. Refer to Section 8.3.
- Collect blood samples for:
  - Serum exploratory biomarkers.
  - Plasma exploratory biomarkers.

10.6. Appendix 6: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Amendment 1 (08-Apr-2022)

Section # and Name	Description of Change	Brief Rationale
Section 1 – Protocol Summary	Updated number of participants from approximately 200 to approximately 150 (100 in the no disease modifying treatment [control] group and 50 in the HU treatment group) and included conditional language for additional participants up to a maximum overall study enrollment of 200.	Modifications to reduce scope/scale of study assessments.
Section 4.1 – Overall Design		
Section 9.2 – Sample Size Determination		
Section 9.6 – Interim Analyses		
Section 1 – Protocol Summary	Removed Day 180 serum and plasma exploratory biomarker collection.	
Section 3 – Research Questions, Objectives and Endpoints		
Section 1.3 – Schedule of Activities	Modified the Day 180 and/or Early Termination (E/T) home health visits to a telehealth visit. Removed collection of serum and plasma exploratory biomarkers from Day 180 or E/T visit.	
Section 4.1 – Overall Design		
Section 6 – Study Interventions		
Section 7.2 – Lost to Follow-up		

Section # and Name	Description of Change	Brief Rationale
Section 8 – Study Assessments and Procedures	Modified blood sampling volume for individual participants from approximately 15 mL to 8 mL.	
Section 1.3 – Schedule of Activities Section 8.3.1 – Time Period and Frequency for Collecting AE and SAE information Section 10.5 – Appendix 5: Decentralized Clinical Trial User Guidance	Removed Day 188 'Final Contact' procedures/assessments and language of AE monitoring for up to 24 hours following the blood sample collection at Day 180.	Removal of Day 180 exploratory biomarker collection no longer necessitates AE monitoring within 24 hours post-collection.
Section 5 – Study Population	Modified inclusion/exclusion criteria.	Refined language will improve participant recruitment and retention without compromising study objectives and endpoints.
	IC: Modified language for eligibility in both the control and HU treatment criteria.	IC: Modifications ensure consistency with definitions presented in Section 4.2.1. Also, to include participants who have previously been on but no longer are on a hydroxyurea regimen for treatment of condition as long as the reason for discontinuation was not lack of efficacy. Under such circumstances, there is no likelihood that study result could be confounded and the population eligible for study participation is expanded.
	EC #1:Updated language to "Evidence or history of	EC #1: To not exclude participants who have previously experienced such a

Section # and Name	Description of Change	Brief Rationale
	ongoing (condition or sequelae) clinically…"	complication/condition but no longer have evidence or sequelae from such an episode. Under such circumstances, there is no likelihood that study result could be confounded and there are no incremental risks for adverse outcome to the participant.
	EC #3: Updated language to "Marked ongoing bone marrow…" and "ANC <1000 mm^3 WBC".	EC #3: To elaborate that participants should not be excluded if they experienced marked bone marrow suppression in the past as there is no potential to confound study results unless the bone marrow suppression is ongoing. Absolute Neutrophil Count (ANC) exclusionary cutoff criteria is reduced from 1500 to 1000 mm^3 as there is no additional increased risk of infection if ANC is >1000 mm^3 and there is no risk for confounding study results. As well, benign ethnic neutropenia is a condition commonly observed in the demographic commonly affected by Sickle Cell Disease.
Section 3.1 - Variables	Removed "…(HU treatment group)" as HbF% variable is now applicable for both groups.	Ensure consistency with modifications to inclusion/exclusion criteria.
Section 4.2.1 – Nomenclature Used Throughout This Protocol	Updated MU VOC Nomenclature.	Clarify definition and ensure consistency throughout protocol.
Section 1 – Protocol Summary	Updated screening period window from 28 days	Increase flexibility of screening period to ensure ample time to

Section # and Name	Description of Change	Brief Rationale
Section 4.1 – Overall Design	(4 weeks) to 56 days (8 weeks).	obtain verifiable source documents for eligibility.
Section 5.4 – Screen Failures	Included "Participants who are rescreened are required to reconsent."	Clarification of rescreening procedures.
Section 1.3 – Schedule of Activities	Clarified specifics of SCD details to be obtained during the Screening Visit, "Pre-specified significant medical history to the diagnosis of SCD as well as genotype and hematology panel with HbF."	Clarification of SCD details
		Minor editorial/typographical changes have been made throughout.

10.7. Appendix 7: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
→	ongoing/continuous event
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DCT	data collection tool
DILI	drug-induced liver injury
DRE	disease-related event
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EDB	exposure during breastfeeding
EDP	exposure during pregnancy
ELIPSIS	Evaluation of Longitudinal Pain in Sickle Cell Disease Study
EMA	European Medicines Agency
ePRO	electronic patient reported outcome
E/T	early termination
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
Hb	hemoglobin
HbC	hemoglobin c
HbF	fetal hemoglobin
HbS	hemoglobin S
HbS/S	hemoglobin S inherited from both parents
HbS/β^0thalassemia	hemoglobin S inherited from one parent and hemoglobin beta thalassemia inherited from the other parent
HC	hydroxycarbamide
HCP	health-care provider
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus

Abbreviation	Term
HPLC	high-performance liquid chromatography
HU	hydroxyurea
ICAM	intracellular adhesion molecule
ICD	informed consent document
ICH	International Council for Harmonisation
ID	identification
IL	interleukin
IND	investigational new drug
INR	international normalized ratio
IP	interferon γ-induced protein
IRB	institutional review board
IV	intravenous
LFT	liver function test
MU	medical utilization
N	total number of individuals or observations
N/A	not applicable
NIH	National Institutes of Health
NIS	non-interventional study
PiSCES	Pain in Sickle Cell Epidemiology Study
PRO	patient-reported outcome
PT	prothrombin time
RBC	red blood cell
RRI	research related injury
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sickle cell disease
SCD-S/C	have 1 copy of HbS and 1 copy of either HbC (heterozygous)
SCD-S/S	have 1 copy of HbS inherited from both parents (homozygous)
SCD-S/β^+-thal	hemoglobin- S/β^+- thalassemia
SCD-S/β^0-thal	hemoglobin-S/β^0-thalassemia
SoA	schedule of activities
SOC	standard of care
SOP	standard operating procedure
SRSD	single reference safety document
TAT	thrombin-antithrombin
TBili	total bilirubin
TNF	tumor necrosis factor
ULN	upper limit of normal
UPA	usual physical activity
US	United States
VCAM-1	vascular cell adhesion molecule-1
VOC	vaso-occlusive crisis
WBC	white blood cell

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