CLINICAL STUDY PROTOCOL

Study Number	C5351005 (GBT021601-022)
Protocol Title	An Open-label Extension Study to Evaluate the Long-term Safety of Osivelotor Administered to Participants with Sickle Cell Disease Who Have Participated in an Osivelotor Clinical Trial
Investigational Product	Osivelotor (also known as PF-07940367 or GBT021601)
US IND Number	151677
EudraCT/EU CT Number	2023-508768-32-00
ClinicalTrials.gov ID	NCT05632354
Pediatric Investigational Plan Number:	EMEA-003241-PIP01-22 and PSP not available
Sponsor Legal Address	Global Blood Therapeutics, Inc., a wholly owned subsidiary of Pfizer 181 Oyster Point Blvd. South San Francisco, CA 94080 USA
Brief Title	An Open-label Extension Study of Osivelotor in Participants with Sickle Cell Disease
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Document History

Document	Version Date
Amendment 4	08 Feb 2024
Amendment 3	22 Jun 2023
Amendment 2	11 Oct 2022
Amendment 1	19 Jul 2022
Original protocol	09 May 2022

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table - Amendment 4 (08 Feb 2024)

Overall Rationale for the Amendment:

To optimize study design for optimal safety monitoring and to align with parent study design as well as Pfizer standards for interventional trials.

Description of Change	Brief Rationale	Section # & Name
Substantial Modification(s)		
Updated study design and modified SoA: added contraception check for reproductive age males or females of child-bearing age, added exploratory biomarkers, clarified participants should return to the study site for an EOS visit approximately 12 weeks after the last dose of study drug. Added PT, aPTT, INR to SoA and laboratory tests. Removed "other SCD-related biomarkers". Specifically for participants enrolling from C5351004 Part C: added visit at 2 weeks and removed flow adhesion, RBC deformability and RBC mitochondrial content.	Optimizing study design for optimal safety monitoring and to align with Pfizer standards for interventional trials	2.1 SoA; 5.1 Overall Design; 8.2 Discontinuation of Study Treatment; 9.2 Efficacy Assessments; 9.3.3 Clinical Laboratory Tests; 9.7 Pharmacodynamics/Biomarkers

Description of Change	Brief Rationale	Section # & Name
Included healthcare resource utilization assessments for participants enrolling from C5351004 Part B. Removed PRO from pediatric participants enrolling from C5351004 Part C. Provided clarification for HRQOL PRO assessments.	To align PROs with parent study C5351004.	2.1 SoA Table 2, Table 3 and Table 4; 7.7.1 Healthcare Resource Utilization for Participants Enrolling from C5351004 Part B; 9.8 Health-Related Quality of Life Assessments
Updated and identified objectives and endpoints as primary, secondary, or exploratory. Updated efficacy assessments.	To align with Pfizer standards for interventional trials	2 Synopsis; 2.1 SoA; 4 Objectives, Endpoints and Estimands; 9.2 Efficacy Assessments
Defined adult dose as 150 mg osivelotor. Adolescent and pediatric participants from C5351004 Parts B and C will be administered a dose that provides generally equivalent exposure to adult participants. Updated dose modification instructions.	Based on emerging data from C5351004 parent study	3.3 Study Rationale; 5.3 Justification for Dose: 7.5 Dose Modification; 11.3 Detailed Dosing Information for Osivelotor
Updated contraception/abstinence requirement to extend from study start to 84 days after the last dose of study drug for female participants of child-bearing potential and reproductive age males.	This time frame is sufficient coverage during osivelotor washout, considering the half-life in SCD patients.	2 Synopsis; 6.1 Inclusion Criteria; 9.3.5.1 Female Participants of Childbearing Potential; 9.3.5.2 Instructions for Male Participants Capable of Fathering a Child; 9.3.5.3 Acceptable Forms of Contraception for male Participants with Female partners Capable of Reproduction
Added males must refrain from donating sperm from study start through 84 days after the final dose to inclusion criteria.	To align with contraceptive/abstinence inclusion criteria.	2 Synopsis; 6.1 Inclusion Criteria
Updated exclusion criteria related to: marijuana use and clarified timing of use [redacted] Added	To align with Pfizer standards for interventional trials	6.2 Exclusion Criteria

Description of Change	Brief Rationale	Section # & Name
exclusion based on current or recent use of crizanlizumab.		
Provided updated blood volume collection limits. Provided guidance for minimizing fear/discomfort for pediatric participants. Provided a blood specimen assessment priority list.	To align with Pfizer safety guidance	9 Study Assessments and Procedures; 9.3.3 Clinical Laboratory Tests; 9.3.3.1 Total Blood Volume; 9.5 Pharmacokinetics
Revised recommended actions for drug-related adverse events due to dose modifications in Table 8. Provided updated guidance on Adverse Events that are VOC events. The time period for actively eliciting and collecting AEs and SAEs begins at informed consent, through 63 calendar days after the last administration of the study intervention. Added sections: 'Unexpected Adverse Reactions', 'Time Period and Frequency for Collecting AE and SAE Information', and 'Lack of Efficacy'. Added additional requirements for reporting EDPs.	To align with Pfizer safety guidance	9.4.5 Unexpected Adverse Reactions; 9.4.7 Time Period and Frequency for Collecting AE and SAE Information; 9.4.9 Drug-induced Liver Injury, 9.4.12.1 (and subsections) Adverse Events that are Vaso-Occlusive Crisis Events; 9.4.13.1 Exposure During Pregnancy; 9.4.14 Lack of Efficacy
Added estimands for primary endpoint. Updated Planned Statistical Analysis.	To align language with SAP	4 Objectives, Endpoints and Estimands; 10 Statistical Considerations (and subsections)
Non-Substantial Modification(s)		
Added Summary of Changes Table; Replaced Synopsis; Provided updated footnotes in SoA; Updated Introduction, Background, and Benefit/Risk Assessment sections; Updated study drug information; Added Protocol Amendment History	To align with Pfizer standards for interventional trials and provide up to date information	2 Synopsis; 2.1 SoA; 3 Introduction; 3.1 Background; 3.2 Benefit/Risk Assessment (and subsections); 7.1 Study Treatments Administered; 7.6 Treatment of Overdose; 11.7 Protocol Amendment History; 11.8 Abbreviations

Description of Change	Brief Rationale	Section # & Name
Appendix and moved list of abbreviations		
Removed reference to GBT021601-012 participants enrolling	GBT021601-012 study is complete, and participants will not be enrolling in C5351005	2.1 SoA; 3.2 Benefit/Risk Assessment; 5.1 Overall Design; 5.3 Justification for Dose; 9.2 Efficacy Assessments; 11.3 Detailed Dosing Information for Osivelotor
Updated visit window after 24 weeks from +/-4 weeks to +/- 14 days	To preserve drug supply	2.1 SoA Table 1, Table 2, Table 3, Table 4
Updated status of GBT021601-011 and GBT021601-012 to completed	To reflect completion of studies.	3.1 Background
Updated IB provided	Reflects 2023 approved version	3.1 Background; 12 References
Removed "at approximately 60 global clinical sites" and updated to "will have a global distribution".	To align with Pfizer standards for interventional trials	5.1 Overall Design
Replaced "male or female" in inclusion criteria.	More inclusivity	6.1 Inclusion Criteria
Combined overdose into single section and revised instructions for reporting overdose. Revised guidance for Concomitant Medications and Procedures and added appendix for Prohibited Concomitant Medications That May Result in DDI. Added new sections on Potential Cases of Acute Kidney Injury and Drug-induced Liver Injury. Updated guidance for calculating eCrCl or eGFR. Added appendix for Kidney Safety. Added clarifying text to Liver Safety appendix. Added serum cystatin C, haptoglobin, hemopexin, and	To align with Pfizer safety guidance for interventional trials	7.6. Treatment of Overdose; 7.7 Concomitant Medications and Procedures; 8.2.1 Potential Cases of Acute Kidney Injury; 9.3.3 Clinical Laboratory Tests; 9.4.9 Drug-induced Liver Injury; 11.4 Liver Safety: Suggested Actions and Follow-Up Assessments; 11.5 Kidney Safety Monitoring Guidelines; 11.6 Prohibited and Restricted Concomitant Medications That May Result in DDI

Description of Change	Brief Rationale	Section # & Name
soluble C3 collection to laboratory tests.		
Deleted redundant 'Reporting Pregnancy' section and updated 'Exposure During Pregnancy' section. Updated guidance for 'Exposure During Breastfeeding'.	To align with Pfizer standards for interventional trials	Deleted previous 8.4.7 Reporting Pregnancy; 9.4.13.1 Exposure During Pregnancy; 9.4.13.2 Exposure During Breastfeeding
Revised/refined pharmacodynamics/biomarkers	To reflect updated study design	9.7 Pharmacodynamics/Biomarkers
Specified SAEs, EDP and occupational exposure will be reported via PSSA. AE or SAE must be recorded on the CRF, the SAE reported using PSSA, and provided additional guidance for immediate reporting requirements. Medication errors will be reported via PSSA to Pfizer Safety (only if associated with an SAE) and clarified potential medication errors.	Incorporated PACL approved on 14 Jul 2023	9.4.6.1 General AE Reporting; 9.4.7 Time Period and Frequency for Collecting AE and SAE Information; 9.4.8 Serious Adverse Events, Serious Adverse Drug Reactions, and Requirements for Immediate Reporting; 9.4.13.1 Exposure During Pregnancy; 9.4.13.3 Occupational Exposure; 9.4.15 Medication Errors
For the assessment 'Dispense study drug: study drug should be dispensed from the IRT system at Baseline visit, Study Week 12, Week 24, and Every 12 weeks.	Incorporated PACL approved on 04 Oct 2023	2.1 SoA Table 1
The Emergency Contact Card is being replaced by a study information card and ECC will no longer be referenced.	The process for contacting a medically qualified individual has changed from a medical escalation process via a Pfizer Call Center to direct clinical team contact using a Study Team Contact List.	11.1.10 Sponsor's Medically Qualified Individual

Description of Change	Brief Rationale	Section # & Name
PF-07940367 updated to generic name, osivelotor. GBT021601-021 updated to C5351004; GBT021601-022 updated to C5351005	To align with Pfizer standards for interventional trials	Throughout protocol
Minor editorial changes and clarifications	To provide clarity	Throughout Protocol

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2. SYNOPSIS

Protocol Title:

An Open-label Extension Study to Evaluate the Long-term Safety of Osivelotor Administered to Participants with Sickle Cell Disease Who Have Participated in an Osivelotor Clinical Trial

Brief Title:

An Open-label Extension Study of Osivelotor in Participants with Sickle Cell Disease

Regulatory Agency Identification Number(s):

US IND Number:	151677
EudraCT/EU CT Number:	2023-508768-32-00
ClinicalTrials.gov ID:	NCT05632354
Pediatric Investigational Plan Number:	EMEA-003241-PIP01-22 and PSP not available
Protocol Number:	C5351005 (GBT021601-022)
Phase:	2/3

Rationale:

This is a multicenter, global, open-label extension study to evaluate the long-term safety, tolerability, and sickle cell disease (SCD) related complications of participants who have been treated with osivelotor.

Objectives and Endpoints:

Objectives	Endpoint
Primary:	**Primary:**
To evaluate the long-term safety of osivelotor in participants with SCD.	• Incidence of treatment-emergent adverse events (TEAEs), changes in laboratory assessments, and changes in vital signs.
Secondary:	**Secondary:**
To evaluate frequency of SCD-related complications. To evaluate the effects of long-term use of osivelotor on hemolytic anemia.	• Annualized rate of vaso-occlusive crisis (VOC). • Incidence of SCD-related serious adverse events (SAEs). • Change from baseline in hematological laboratory parameters, including hemoglobin, reticulocytes, lactate dehydrogenase, and unconjugated bilirubin.

Overall Design:

This is a multicenter, global, open-label extension study in participants with SCD. The study will include participants 6 months of age and older with SCD who have participated and received study drug in an osivelotor clinical study and meet eligibility criteria.

All participants will receive daily osivelotor administered orally.

Eligible participants will receive open-label osivelotor on Day 1. It is intended that Day 1 coincides with the final visit from the originating osivelotor study. End of Treatment (EOT) assessments from the originating study will serve as Baseline assessments for this study. If Day 1 for this study is greater than 7 days from the completion of the originating study, new baseline assessments will be obtained. If during the period between Day 1 of this study and completion of the originating study no dose is received for greater than 3 consecutive days, an appropriate loading dose will be administered prior to continued maintenance dosing.

Study Population:

Inclusion Criteria Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

1. Aged 6 months or older with SCD who participated and received study drug in an osivelotor clinical study and completed the EOT visit.

   Note: Participants who discontinued study drug in the originating study due to an AE, but who remained on study, may be eligible for treatment in this study provided the AE does not pose a risk for treatment with osivelotor. Also, participants who completed treatment from the originating study but were not able to rollover into C5351005 due to delay in study site activation will be eligible provided other eligibility criteria are met.

2. Females of child-bearing potential are required to have a negative urine pregnancy test prior to dosing on Day 1.

   Note: Females who become of child-bearing potential during the study must be willing to have a negative urine pregnancy test to remain in the study.

3. If sexually active, females of child-bearing potential must consistently use highly effective methods of contraception consistently throughout the study and for at least 84 days after the last dose of study drug. Male participants are eligible to participate if they agree to the following requirements during the study intervention period and for 84 days after the last dose of study intervention:
   - Refrain from donating sperm

   PLUS either:
   - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

     OR
   - Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

Exclusion Criteria Participants with any of the following characteristics/conditions will be excluded:

1. Female who is breastfeeding or pregnant.
2. Withdrew consent or was noncompliant from the originating osivelotor clinical study.
3. Has any medical, psychological, safety, or behavioral conditions that, in the opinion of the Investigator, may confound safety interpretation, interfere with compliance, or preclude informed consent.

Study Arms:

Study Arms	
Arm Title	Osivelotor (PF-07940367 or GBT021601)
Adults	Adult participants enrolling from C5351004 Part A and Part B will receive 150 mg maintenance dose. Dose adjustment and or loading dose will be determined based on previous intervention/dose received in C5351004.
Adolescents and Pediatrics	Adolescent and pediatric participants from C5351004 Parts B and C will be administered a dose that provides generally equivalent exposure to adult participants.

Duration of Treatment: Participants may receive study drug for up to 252 days, as long as they continue to receive clinical benefit that outweighs risk as determined by the Investigator and/or until the participant has access to osivelotor from an alternative source (eg, through commercialization, a managed-access program, or a Sponsored initiative) or until the Sponsor decides to terminate the study.

Ethical Considerations:

The results of previous studies of osivelotor in healthy volunteers and SCD adult participants support the investigation of osivelotor for SCD. There is a favorable benefit-risk profile to support the rationale for this study. Taking into account the measures to minimize risk to participants, the potential risks associated with osivelotor are justified by the anticipated benefits that may be afforded to participants with SCD.

- SCD is a serious condition characterized by hemolytic anemia, chronic organ damage, and VOCs. Despite recent advances in therapy, there remain limited treatment options for patients with SCD; thus a high unmet medical need continues to exist. Osivelotor's potential to address this unmet medical need is supported by the nonclinical studies and preliminary clinical data which provide evidence for a treatment effect (gradual increase in hemoglobin (Hb) at both 100 mg and 150 mg daily maintenance dosing in C5351004). Given the mechanism of action (MOA), it is likely that higher Hb levels (and consequently a clinically significant reduction in the incidence of VOCs) will be achieved, which is supported by data for Hb and Hb occupancy from C5351002 and preliminary C5351004 data.
- Osivelotor has increased affinity for Hb and a longer half-life ($t_{1/2}$) compared to voxelotor. Osivelotor has the potential to achieve greater % Hb occupancy and attain desired hematological effects at lower doses than voxelotor, therefore reducing pill burden, increasing the durability of response, and improving clinical outcomes for individuals living with SCD.

- The current treatment options for pediatric participants with SCD, particularly in children less than 12 years of age, are limited. SCD requires life-long preventive maintenance and management of acute and chronic complications. Newborn screening, early immunization, and prophylactic penicillin treatment in infants and children as well as comprehensive management for pain and disease complications have improved outcomes in children with SCD in certain parts of the world. Despite these advances, the median life expectancy of affected individuals is only 43 years of age and treatment of SCD remains a serious unmet medical need (Brandow, AM and Liem, RI. Advances in the diagnosis and treatment of sickle cell disease. Journal of Hematology & Oncology 2022;15:20:1-13). C5351004 Part B will evaluate the efficacy and safety of the selected dose of osivelotor versus placebo in adult and pediatric participants (12 to <18 years of age) with SCD. Part C will evaluate the pharmacokinetics (PK) and safety of single and multiple doses of open-label osivelotor administered to pediatric participants 6 months to <18 years of age.
- For pediatric participants blood draws will be minimized, pain management encouraged, and techniques will be used to minimize fear and provide comfort. Additionally, effort will be made to engage caregivers to determine the most appropriate way to soothe participants.
- Based on the experience with osivelotor at the time of this Protocol Amendment, no participant has experienced any adverse reaction of clinical significance. The theoretical potential risk for osivelotor is decreased oxygen delivery, however there are no current adverse events attributed to the study drug that support this theoretical risk.
- Participant will be expected to commit time and may experience some discomfort while undergoing study assessments. In addition, female participants of childbearing potential must agree to use a highly effective method of contraception from study start to 84 days after the last dose of study drug. Males must either be abstinent or use a condom, in addition to their female partner of child-bearing potential using a highly effective method of contraception from study start to 84 days after the last dose of study drug.

2.1. Schedule(s) of Assessments and Procedures

Adult Participants with Delayed Start of Open Label Extension (OLE) Study (>42 days)

Table 1. Schedule of Assessments for Adult Participants with Delayed Start of OLE (>42 days)

			Treatment Period									
Study Week	**Baseline visit**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**Every 12 weeks**	**EOS[1]/ET**
Study Day	**1 (± 30)**	**7 (± 3)**	**14 (± 3)**	**28 (± 3)**	**42 (± 3)**	**56 (± 3)**	**84 (± 7)**	**112 (± 7)**	**140 (± 7)**	**168 (± 7)**	**252+ (± 14 Days)**	
Informed consent/assent	X											
Eligibility assessment	X											
Medical history	X											
Physical examination [a]	X						X			X	X	X
Height	X											
Weight	X						X			X	X	X
Vital signs [b]	X	X	X	X	X	X	X	X	X	X	X	X
Serology (hepatitis A, B, C, HIV) only if clinically indicated	X											
Hematology including reticulocyte count and serum chemistry	X		X	X	X	X	X	X	X	X	X	X
aPTT, INR, PT	X											
Serum erythropoietin	X						X			X	X	X
eGFR [c]	X									X	X	X
Urinalysis	X						X			X	X	X

Table 1. Schedule of Assessments for Adult Participants with Delayed Start of OLE (>42 days)

			Treatment Period									
Study Week	**Baseline visit**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**Every 12 weeks**	**EOS[1]/ET**
Study Day	**1 (± 30)**	**7 (± 3)**	**14 (± 3)**	**28 (± 3)**	**42 (± 3)**	**56 (± 3)**	**84 (± 7)**	**112 (± 7)**	**140 (± 7)**	**168 (± 7)**	**252+ (± 14 Days)**	
Pregnancy test (for females, post menarche) [d]	X			X		X	X	X	X	X	X	X
Contraception check [h]	X	X	X	X	X	X	X	X	X	X	X	X
PK samples (whole blood and plasma) [e]	X			X		X	X	X	X	X	X	X
RBC deformability and RBC mitochondrial content [f, i]	X						X			X	X	X
Flow adhesion [f, i]	X						X			X	X	X
Peripheral blood smear [f, i]	X						X			X	X	X
Exploratory Biomarkers [j]	X	X	X	X	X	X	X	X	X	X	X	X
PGI-C/CGI-C [f]	X						X			X	X	X
PGI-S/CGI-S [f]	X						X			X	X	X
PROMIS SF Fatigue 13a, SF Pain Interference 8a, and NRS Pain Intensity [f]	X						X			X	X	X
EQ-5D-5L [f]	X						X			X	X	X
WPAI+CIQ:SCD [f]	X						X			X	X	X
Qualitative interview [f,g]	X											
Study drug administration	←	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - - →	

Table 1. Schedule of Assessments for Adult Participants with Delayed Start of OLE (>42 days)

			Treatment Period									
Study Week	**Baseline visit**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**Every 12 weeks**	**EOS[1]/ET**
Study Day	**1 (± 30)**	**7 (± 3)**	**14 (± 3)**	**28 (± 3)**	**42 (± 3)**	**56 (± 3)**	**84 (± 7)**	**112 (± 7)**	**140 (± 7)**	**168 (± 7)**	**252+ (± 14 Days)**	
Dispense study drug	X						X			X	X	
Return unused study drug [k]		X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Serious and nonserious AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X

Table 1. Schedule of Assessments for Adult Participants with Delayed Start of OLE (>42 days)

			Treatment Period									
Study Week	**Baseline visit**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**Every 12 weeks**	**EOS[1]/ET**
Study Day	**1 (± 30)**	**7 (± 3)**	**14 (± 3)**	**28 (± 3)**	**42 (± 3)**	**56 (± 3)**	**84 (± 7)**	**112 (± 7)**	**140 (± 7)**	**168 (± 7)**	**252+ (± 14 Days)**	

Abbreviations: CGI-C, Clinician's Global Impression of Change; CGI-S, Clinician's Global Impression of Severity; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; EOS, end of study; EOT, end of treatment; ET, early termination; HIV, human immunodeficiency virus; NRS, numeric rating scale; PGI-C, Patient's Global Impression of Change; PGI-S, Patient's Global Impression of Severity; PK, pharmacokinetic; PROMIS, Patient-Reported Outcome Measurement Information System; RBC, red blood cell; SF, short form; WPAI+CIQ:SCD, Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire: Sickle Cell Disease.

a A full physical examination should be conducted at Baseline. All subsequent physical examinations can be brief. See Section 9.3.1 for details.

b Vital Signs include blood pressure, heart rate, respiration rate, body temperature will be obtained after the participant has been in a supine or recumbent position for at least 5 minutes.

c At Screening, eGFR will be calculated using 2021 CKD-EPI equations (for adults 18 years and above).

d Pregnancy tests will be performed on female participants who are post menarche and of child-bearing potential. A serum pregnancy test will be conducted at Baseline only if there is a delay of >7 days in start of OLE from the originating study, otherwise a urine pregnancy test will be administered and urine pregnancy test at all other visits. A serum pregnancy test will also be conducted when a positive urinary pregnancy test occurs for confirmation.

e At the Baseline Visit (Day 1), samples will be obtained at predose and between 1 to 2 hours postdose. Trough (predose) samples are to be obtained on Weeks 4, 8, 12, 16, 20 and 24, then at 12-week intervals thereafter. For the trough (predose) collections the time window is 24±3 hours since the most recent dose, but the sample must be collected before the dose given at the clinic visit. The date and time of collection for all PK samples must be recorded in the eCRF. The time of study drug administration prior to PK collection must also be recorded.

f Assessments will be conducted only at sites in regions where available.

g In selected regions, qualitative interviews with English speaking participants will be conducted during the Screening period and may include multiple interviews.

h Contraception check for reproductive age males or females of child-bearing age.

i Samples to be obtained predose for all visits.

j Exploratory biomarkers may include markers of hemolysis such as levels of haptoglobin, hemopexin, and soluble C3.

k Drug accountability to be completed if baseline visit is on the same day as EOT assessments from the originating study.

l Participants should return to the study site for an EOS visit approximately 12 weeks after the last dose of study drug.

Note: Eligible participants will receive open-label osivelotor on Day 1 (Baseline Visit). It is intended that Day 1 coincides with the final visit from the originating osivelotor study. EOT assessments from the originating study will serve as Baseline assessments for this study. If Day 1 for this study is greater than 7 days from the completion of the originating study, new Baseline assessments will be obtained. Additional assessments that may not have been included in the prior EOT assessments will need to be completed at the Day 1 visit prior to study drug administration.

Adult Participants from Part A of C5351004 and Other Applicable Osivelotor Open Label Studies with no Delay of Start

Table 2. Schedule of Assessments for Adult Participants from Part A of C5351004 and Other Applicable Osivelotor Open Label Studies with no Delay of Start

	Treatment Period				
Study Week	**Baseline visit**	**12**	**24**	**Every 12 weeks**	**EOS[k]/ET**
Study Day	**1 (± 30)**	**84 (± 7)**	**168 (± 7)**	**252+ (± 14 Days)**	
Informed consent/assent	X				
Eligibility assessment	X				
Medical history	X				
Physical examination [a]	X	X	X	X	X
Height	X				
Weight	X	X	X	X	X
Vital signs [b]	X	X	X	X	X
Serology (hepatitis A, B, C, HIV) only if clinically indicated	X				
Hematology including reticulocyte count and serum chemistry		X	X	X	X
aPTT, INR, PT	X				
Serum erythropoietin	X	X	X	X	X
eGFR (for adults, children or infants) or eCrCl (adolescents) [c]	X		X	X	X
Urinalysis	X	X	X	X	X
Pregnancy test (for females, post menarche) [d]	X	X	X	X	X
Contraception check [i]	X	X	X	X	X

Table 2. Schedule of Assessments for Adult Participants from Part A of C5351004 and Other Applicable Osivelotor Open Label Studies with no Delay of Start

	Treatment Period				
Study Week	**Baseline visit**	**12**	**24**	**Every 12 weeks**	**EOS[k]/ET**
Study Day	**1** (± 30)	**84** (± 7)	**168** (± 7)	**252+** (± 14 Days)	
PK samples (whole blood and plasma)[e]	X	X	X	X	X
RBC deformability and RBC mitochondrial content (at sites where available)[f,j]	X	X	X	X	X
Flow adhesion[f,j]	X	X	X	X	X
Peripheral blood smear[f,j]	X	X	X	X	X
Exploratory Biomarkers[l]	X	X	X	X	X
PGI-C/CGI-C[f]	X	X	X	X	X
PGI-S/CGI-S[f]	X	X	X	X	X
PROMIS SF Fatigue 13a, SF Pain Interference 8a, and NRS Pain Intensity[f]	X	X	X	X	X
EQ-5D-5L[f]	X	X	X	X	X
WPAI+CIQ:SCD[f]	X	X	X	X	X
Qualitative interview[f,g]	X				
Study drug administration	←--→				
Dispense study drug	X	X	X	X	
Return unused study drug[h]		X	X	X	X
Concomitant medication	X	X	X	X	X
Serious and nonserious AE monitoring	X	X	X	X	X

Table 2. Schedule of Assessments for Adult Participants from Part A of C5351004 and Other Applicable Osivelotor Open Label Studies with no Delay of Start

	Treatment Period				
Study Week	**Baseline visit**	**12**	**24**	**Every 12 weeks**	**EOS[k]/ET**
Study Day	**1 (± 30)**	**84 (± 7)**	**168 (± 7)**	**252+ (± 14 Days)**	

Abbreviations: CGI-C, Clinician's Global Impression of Change; CGI-S, Clinician's Global Impression of Severity; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eCrCl, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; EOS, end of study; EOT, End of Treatment; ET, early termination; HIV, human immunodeficiency virus; NRS, numeric rating scale; PGI-C, Patient's Global Impression of Change; PGI-S, Patient's Global Impression of Severity; PK, pharmacokinetic; PROMIS, Patient-Reported Outcome Measurement Information System; RBC, red blood cell; SF, short form; WPAI+CIQ:SCD, Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire: Sickle Cell Disease.

a A full physical examination should be conducted at Baseline. All subsequent physical examinations can be brief. See Section 9.3.1 for details.

b Vital Signs include blood pressure, heart rate, respiration rate, body temperature will be obtained after the participant has been in a supine or recumbent position for at least 5 minutes.

c At Screening, eGFR will be calculated using 2021 CKD-EPI equations (for adults 18 years and above) or eCrCl will be calculated using Cockcroft-Gault formula (for adolescents 12 to <18 years) or eGFR will be calculated using Modified Schwartz Equation (for children 2 to <12 years), or Bedside Schwartz equation (for infants 6 months to <2 years), see Section 11.5.2.

d Pregnancy tests will be performed on female participants who are post menarche and of child-bearing potential. A urine pregnancy test will be conducted at Baseline and at all other visits as noted in the SoA. A serum pregnancy test will also be conducted when a positive urinary pregnancy test occurs for confirmation.

e At the Baseline Visit (Day 1), samples will be obtained at predose and between 1 to 2 hours postdose. Trough (predose) samples are to be obtained on Weeks 12 and 24, and then at 12-week intervals thereafter. For the trough (predose) collections the time window is 24±3 hours since the most recent dose, but the sample must be collected before the dose given at the clinic visit. The date and time of collection for all PK samples must be recorded in the eCRF. The time of study drug administration prior to PK collection must also be recorded.

f Assessments will be conducted only at sites in regions where available.

g In selected regions, qualitative interviews with English speaking participants will be conducted during the Screening period and may include multiple interviews.

h Drug accountability to be completed if baseline visit is on the same day as EOT assessments from the originating study.

i Contraception check for reproductive age males or females of child-bearing age.

j Samples to be obtained predose for all visits.

k Participants should return to the study site for an EOS visit approximately 12 weeks after the last dose of study drug.

l Exploratory biomarkers may include markers of hemolysis such as levels of haptoglobin, hemopexin, and soluble C3.

Note: Eligible participants will receive open-label osivelotor on Day 1 (Baseline Visit). It is intended that Day 1 coincides with the final visit from the originating osivelotor study. EOT assessments from the originating study will serve as Baseline assessments for this study. If Day 1 for this study is greater than 7 days from the completion of the originating study, new Baseline assessments will be obtained. Additional assessments that may not have been included in the prior EOT assessments will need to be completed at the Day 1 visit prior to study drug administration.

Participants from Part B of C5351004 and Other Osivelotor Randomized, Blinded, Placebo Controlled Studies

Table 3. Schedule of Assessments for Participants from Part B of C5351004 and Other Osivelotor Randomized, Blinded, Placebo Controlled Studies

	Treatment Period					
Study Week	**Baseline Visit**	**8**	**16**	**24**	**Every 12 weeks**	
Study Day	**1 (± 30)**	**56 (± 3)**	**112 (± 7)**	**168 (± 7)**	**252+ (± 14 Days)**	**EOS[k]/ET**
Informed consent/assent	X					
Eligibility assessment	X					
Medical history	X					
Physical examination [a]	X	X	X	X	X	X
Height	X					
Weight	X			X	X	X
Vital signs [b]	X	X	X	X	X	X
Healthcare resource utilization	X	X	X	X	X	X
Serology (hepatitis A, B, C, HIV) only if clinically indicated	X					
Hematology including reticulocyte counts and serum chemistry		X	X	X	X	X
aPTT, INR, PT	X					
Serum erythropoietin	X	X	X	X	X	X
eGFR (for adults, children or infants) or eCrCl (adolescents) [c]	X			X	X	X
Urinalysis	X	X	X	X	X	X
Pregnancy test (for females, post menarche) [d]	X	X	X	X	X	X
Contraception check [l]	X	X	X	X	X	X

Table 3. Schedule of Assessments for Participants from Part B of C5351004 and Other Osivelotor Randomized, Blinded, Placebo Controlled Studies

	Treatment Period					
Study Week	**Baseline Visit**	**8**	**16**	**24**	**Every 12 weeks**	
Study Day	**1 (± 30)**	**56 (± 3)**	**112 (± 7)**	**168 (± 7)**	**252+ (± 14 Days)**	**EOS[k]/ET**
PK samples (whole blood and plasma) [e]	X	X	X	X	X	X
RBC deformability and RBC mitochondrial content [f,j]	X	X	X	X	X	X
Flow adhesion [f,j]	X	X	X	X	X	X
Peripheral blood smear [f,j]	X	X	X	X	X	X
Exploratory Biomarkers [i]	X	X	X	X	X	X
PGI-C/CGI-C [f]	X	X	X	X	X	X
PGI-S/CGI-S [f]	X	X	X	X	X	X
PROMIS SF Fatigue 13a, SF Pain Interference 8a, and NRS Pain Intensity [f]	X	X	X	X	X	X
EQ-5D-5L[f]	X	X	X	X	X	X
WPAI+CIQ:SCD [f]	X	X	X	X	X	X
Qualitative interview [f,g]	X					
Study drug administration	←	- - - - -	- - - - -	- - - - -	→	
Dispense study drug	X	X	X	X	X	
Return unused study drug [h]		X	X	X	X	X
Concomitant medication	X	X	X	X	X	X
Serious and nonserious AE monitoring	X	X	X	X	X	X

Table 3. Schedule of Assessments for Participants from Part B of C5351004 and Other Osivelotor Randomized, Blinded, Placebo Controlled Studies

	Treatment Period					
Study Week	**Baseline Visit**	**8**	**16**	**24**	**Every 12 weeks**	
Study Day	**1 (± 30)**	**56 (± 3)**	**112 (± 7)**	**168 (± 7)**	**252+ (± 14 Days)**	**EOS[k]/ET**

Abbreviations: CGI-C, Clinician's Global Impression of Change; CGI-S, Clinician's Global Impression of Severity; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eCrCl, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; EOS, end of study; EOT, end of treatment; ET, early termination; HIV, human immunodeficiency virus; NRS, numeric rating scale; PGI-C, Patient's Global Impression of Change; PGI-S, Patient's Global Impression of Severity; PK, pharmacokinetic; PROMIS, Patient-Reported Outcome Measurement Information System; RBC, red blood cell; SF, short form; WPAI+CIQ:SCD, Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Sickle Cell Disease.

a A full physical examination should be conducted at Baseline. All subsequent physical examinations can be brief. See Section 9.3.1 for detail.

b Vital Signs include blood pressure, heart rate, respiration rate, body temperature will be obtained after the participant has been in a supine position for at least 5 minutes.

c At Screening, eGFR will be calculated using 2021 CKD-EPI equations (for adults 18 years and above) or eCrCl will be calculated using Cockcroft-Gault formula (for adolescents 12 to <18 years) or eGFR will be calculated using Modified Schwartz Equation (for children 2 to <12 years), or Bedside Schwartz equation (for infants 6 months to <2 years), see Section 11.5.2.

d Pregnancy tests will be performed on female participants who are post menarche and of child-bearing potential. A urine pregnancy test will be conducted at Baseline and at all other visits as noted in the SoA. A serum pregnancy test will also be conducted when a positive urinary pregnancy test occurs for confirmation.

e At the Baseline Visit (Day 1), samples will be obtained at predose and between 1 to 2 hours postdose. Trough (predose) samples are to be obtained on Weeks 8, 16, and 24, and then at 12-week intervals thereafter. For the trough (predose) collections the time window is 24±3 hours since the most recent dose, but the sample must be collected before the dose given at the clinic visit. The date and time of collection for all PK samples must be recorded in the eCRF. The time of study drug administration prior to PK collection must also be recorded.

f Assessments will be conducted only at sites in regions where available.

g In selected regions, qualitative interviews with English speaking participants will be conducted during the Screening period and may include multiple interviews.

h Drug accountability to be completed if baseline visit is on the same day as EOT assessments from the originating study.

i Exploratory biomarkers may include markers of hemolysis such as levels of haptoglobin, hemopexin, and soluble C3.

j Samples to be obtained predose for all visits.

k Participants should return to the study site for an EOS visit approximately 12 weeks after the last dose of study drug.

l Contraception check for reproductive age males or females of child-bearing potential.

Note: Eligible participants will receive open-label osivelotor on Day 1 (Baseline Visit). It is intended that Day 1 coincides with the final visit from the originating osivelotor study. EOT assessments from the originating study will serve as Baseline assessments for this study. If Day 1 for this study is greater than 7 days from the completion of the originating study, new Baseline assessments will be obtained. Additional assessments that may not have been included in the prior EOT assessments will need to be completed at the Day 1 visit prior to study drug administration.

Pediatric Participants from Part C of C5351004

Table 4. Schedule of Assessments for Pediatric Participants from Part C of C5351004

		Treatment Period							
Study Week	**Baseline Visit**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**Every 12 weeks**
Study Day	**1 (± 30)**	**14 (± 3)**	**28 (± 3)**	**56 (± 3)**	**84 (± 3)**	**112 (± 7)**	**140 (± 7)**	**168 (± 7)**	**252+ (± 14 Days) & EOS[h]/ET**
Informed consent/assent	X								
Eligibility assessment	X								
Medical history	X								
Physical examination [a]	X	X	X	X	X	X	X	X	X
Height	X				X			X	X
Weight	X				X			X	X
Vital signs [b]	X	X	X	X	X	X	X	X	X
Serology (hepatitis A, B, C, HIV) only if clinically indicated	X								
Hematology including reticulocyte count and serum chemistry		X	X	X	X	X	X	X	X
Serum erythropoietin	X	X	X	X	X	X	X	X	X
eCrCl or eGFR [c]	X							X	X
Urinalysis	X	X	X	X	X	X	X	X	X
Pregnancy test (for females, post menarche) [d]	X		X	X	X	X	X	X	X
Contraception check [k]	X	X	X	X	X	X	X	X	X
PK samples (whole blood and plasma) [e]	X	X	X	X		X		X	X
Peripheral blood smear [f,j]	X			X		X		X	X

Table 4. Schedule of Assessments for Pediatric Participants from Part C of C5351004

		Treatment Period							
Study Week	**Baseline Visit**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**Every 12 weeks**
Study Day	**1 (± 30)**	**14 (± 3)**	**28 (± 3)**	**56 (± 3)**	**84 (± 3)**	**112 (± 7)**	**140 (± 7)**	**168 (± 7)**	**252+ (± 14 Days) & EOS[h]/ET**
Exploratory Biomarkers [i]	X				X			X	X
Study drug administration	◄----	----	----	----	----	----	----	----	----►
Dispense new study drug	X	X	X	X	X	X	X	X	X
Return unused study drug [g]		X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X
Serious and nonserious AE monitoring	X	X	X	X	X	X	X	X	X

Table 4. Schedule of Assessments for Pediatric Participants from Part C of C5351004

		Treatment Period							
Study Week	**Baseline Visit**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**Every 12 weeks**
Study Day	**1 (± 30)**	**14 (± 3)**	**28 (± 3)**	**56 (± 3)**	**84 (± 3)**	**112 (± 7)**	**140 (± 7)**	**168 (± 7)**	**252+ (± 14 Days) & EOS[h]/ET**

Abbreviations: CGI-C, Clinician's Global Impression of Change; CGI-S, Clinician's Global Impression of Severity; eCrCl, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; EOS, end of study; EOT, end of treatment; ET, early termination; HIV, human immunodeficiency virus; RBC, red blood cell.

a A full physical examination should be conducted at Baseline. All subsequent physical examinations can be brief. See Section 9.3.1 for detail.

b Vital Signs include blood pressure, heart rate, respiration rate, body temperature will be obtained after the participant has been in a supine position for at least 5 minutes.

c At screening, eCrCl will be calculated using the Cockcroft-Gault formula (for adolescents 12 to <18 years), or eGFR will be calculated using Modified Schwartz Equation (for children 2 to <12 years), or Bedside Schwartz equation (for infants 6 months to <2 years). See Section 11.5.2.

d Pregnancy tests will be performed on female participants who are post menarche and of child-bearing potential. A serum pregnancy test will be conducted at Baseline and urine pregnancy test at all other visits. A serum pregnancy test will also be conducted when a positive urinary pregnancy test occurs for confirmation.

e At the Baseline Visit (Day 1), samples will be obtained at predose and between 1 to 2 hours postdose. Trough (predose) samples are to be obtained on Weeks 2, 4, 8, 16, and 24, and then at 12-week intervals thereafter. For the trough (predose) collections the time window is 24±3 hours since the most recent dose, but the sample must be collected before the dose given at the clinic visit. The date and time of collection for all PK samples must be recorded in the eCRF. The time of study drug administration prior to PK collection must also be recorded.

f Assessments will only be conducted at sites in regions where available. If participant body weight is <15 kg, do not collect at any Visit.

g Drug accountability to be completed if baseline visit is on the same day as EOT assessments from the originating study.

h Participants should return to the study site for an EOS visit approximately 12 weeks after the last dose of study drug.

i Exploratory biomarkers may include markers of hemolysis such as levels of haptoglobin, hemopexin, and soluble C3.

j Samples to be collected predose for all visits.

k Contraception check for reproductive age males or females of child-bearing potential.

Note: Eligible participants will receive open-label osivelotor on Day 1 (Baseline Visit). It is intended that Day 1 coincides with the final visit from the originating osivelotor study. EOT assessments from the originating study will serve as Baseline assessments for this study. If Day 1 for this study is greater than 7 days from the completion of the originating study, new Baseline assessments will be obtained. Additional assessments that may not have been included in the prior EOT assessments will need to be completed at the Day 1 visit prior to study drug administration.

3. INTRODUCTION

Global Blood Therapeutics, Inc., a wholly owned subsidiary of Pfizer Inc. (GBT; the Sponsor) intends to develop osivelotor (also known as PF-07940367 or GBT021601), an oral sickle hemoglobin (HbS) polymerization inhibitor, for the treatment of sickle cell disease (SCD).

3.1. Background

Sickle Cell Disease

Sickle cell disease is an inherited disorder caused by a point mutation in the β-globin gene leading to formation of HbS. A primary and obligatory event in the molecular pathogenesis of SCD is the polymerization of intracellular HbS following deoxygenation in the microvasculature. HbS polymerization leads to decreased red blood cell (RBC) deformability, morphologic sickling of RBCs, decreased RBC survival, and microvascular obstruction (Bunn 1997). Clinically, SCD is a devastating and debilitating disease marked by the pathophysiologic features of hemolytic anemia, vaso-occlusion, and progressive end organ damage. Despite current standards of care, including hydroxyurea (HU), blood transfusion, and supportive care with analgesia, patients with SCD continue to suffer serious morbidity and premature mortality.

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

Osivelotor

Osivelotor shares the same mechanism of action as Oxbryta® (voxelotor) which is an orally administered drug indicated for treatment of SCD in adults and pediatric patients 12 years of age and older. Osivelotor is designed to optimize the potential for clinical benefit derived from stabilizing oxy-Hb as demonstrated by a comparison to voxelotor in a murine model of SCD where osivelotor was observed to be more potent, have a longer half-life, and achieve greater exposure per dose (Dufu, Alt et al. 2020). Thus, osivelotor has the potential to achieve a targeted Hb occupancy and attain desired hematological effects at lower doses than voxelotor, therefore reducing pill burden and improving clinical outcomes for individuals living with SCD. A more potent drug that inhibits HbS polymerization in all RBCs in a broader percentage of patients has the capability to provide superior efficacy to available treatments. By addressing this underlying mechanism of SCD, osivelotor has the potential to be a disease-modifying therapy, leading to improved anemia, reduced hemolysis, and the possibility of reducing the end-organ damage resulting from chronic hemolytic anemia. Based on the clinical and nonclinical experience with osivelotor, pharmacology-based hematological effects are expected to occur with osivelotor treatment and may include increased RBCs, Hb, hematocrit, and decreased number of reticulocytes.

Nonclinical Experience

Nonclinical studies have been conducted to characterize osivelotor, including primary and secondary pharmacodynamics (PD), safety, pharmacology, pharmacokinetics (PK), and toxicology. In SCD mice treated with osivelotor, a Hb occupancy of ~6% resulted in a >1 g/dL increase in Hb concentration in all animals. Moreover, at an osivelotor Hb occupancy of ~29% (similar to the mean achieved by the 1500 mg dose of voxelotor in SCD participants), osivelotor caused a sustained and almost complete elimination of circulating sickled RBCs, reduced reticulocyte counts by >50%, increased RBC half-life by 6.1 days, and normalized Hb with a 6.7 g/dL increase from baseline in SCD mice. Additional information on nonclinical experience may be found in the Investigator Brochure for osivelotor.

Clinical Experience

Two Phase 1 clinical studies have been completed.

A first-in-human single ascending and multiple ascending dose (SAD/MAD) study in healthy participants (GBT021601-011) has been completed. Safety and PK data on single doses up to 3000 mg in healthy participants demonstrated that osivelotor was well tolerated with a linear dose-dependent increase in percent Hb occupancy. Absorption following a single oral dose was relatively quick in plasma, with T_{max} generally ranging 0.5-3 h. Peak concentration in whole blood was achieved slower with T_{max} generally ranging 8-48 h. The terminal elimination half-life of approximately 25 to 28 days in plasma and blood was observed in healthy volunteers; however, approximately 3-fold lower terminal half-life (approximately 10 days) in plasma and whole blood was observed in SCD patients. PK exposure is generally dose-proportional and displays a high partitioning to whole blood (blood/plasma ratios of ~213 and ~68 for healthy volunteers and SCD patients, respectively, following a single 100 mg dose).

In addition, a Phase 1b Study GBT021601-012 in adult participants with SCD was conducted to evaluate the PK, safety, tolerability, and PD of single dose and MAD of osivelotor. In this open label study, a within participant dose escalation was explored. Safety, tolerability, and available PK data after each dose level were reviewed by the Safety Review Committee before escalation to the next dose level. Six adults with SCD received a single 100 mg dose of osivelotor. After an 8-week washout, participants received osivelotor loading doses of 300 mg on Day 1 and 200 mg on Day 2, followed by a maintenance dose of 50 mg/day for 5 weeks. Dose escalation occurred at Week 13 with participants receiving a 500 mg dose on Day 91, 400 mg dose on Day 92, followed by a maintenance dose of 100 mg/day for approximately 3 weeks. The study was amended to evaluate an additional maintenance dose of 150 mg/day over 6 weeks.

Preliminary data from these studies demonstrates that osivelotor has an acceptable safety and tolerability profile in healthy volunteers and participants with SCD as further described in Section 3.2. After single doses of osivelotor, blood and plasma PK and the mean % Hb occupancy of osivelotor increased in a linear manner following a single oral dose in healthy volunteers (Study GBT021601-011). In the initial part of the GBT021601-012 study of six SCD participants, after treatment at two dose levels, 50 mg for 5 weeks and 100 mg for 3

weeks, the % Hb occupancy averaged 32.6% (range 19.7% to 41.8%) and Hb levels increased by up to 3.1 g/dL (mean increase of 2.3 g/dL). Within the same timeframe, all participants demonstrated improvements in hematologic parameters, including reticulocytes and absolute reticulocytes, lactate dehydrogenase (LDH), and indirect bilirubin (Brown, Redfern et al. 2021).

GBT021601-013 is an ongoing Phase 1, single-center, open-label study to assess the mass balance, excretion, and PK of a single oral dose of [^{14}C]-osivelotor in healthy participants.

GBT021601-014 is an ongoing Phase 1, open-label, single-dose, non-randomized, parallel group study to evaluate the PK, safety, and tolerability of osivelotor in adult participants with renal impairment.

C5351004 is a three-part, multicenter, Phase 2/3 study of orally administered osivelotor in participants with SCD. Part A will evaluate the safety, tolerability, and efficacy of 12 weeks of osivelotor in adult participants with SCD, and determined the optimal dose of 150 mg for Part B. Part B will evaluate the efficacy of 150 mg osivelotor versus placebo in adult and adolescent participants with SCD for 48 weeks. Part C is a single-arm study which will evaluate the PK and safety of single and multiple doses of open-label osivelotor administered to pediatric participants. The study is ongoing.

Participants with SCD who participated in an osivelotor clinical study may be eligible to enroll in this open-label extension study (C5351005).

A detailed description of the chemistry, pharmacology, efficacy, and safety of osivelotor is provided in the PF-07940367 Investigator's Brochure (IB) (Pfizer, 2023), which is the Single Reference Safety Document (SRSD) for this study.

3.2. Benefit/Risk Assessment

3.2.1. Risk Assessment

Based on the experience with osivelotor at the time of this Protocol Amendment, no participant has experienced any adverse reaction of clinical significance. The theoretical potential risk for osivelotor is decreased oxygen delivery, however there are no current adverse events attributed to the study drug that support this theoretical risk.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention Osivelotor (PF-07940367 or GBT021601)		
Decreased oxygen delivery	Increased oxygen affinity associated with the osivelotor mechanism has a theoretical potential to result in decreased oxygen delivery	Close monitoring of AEs through TME monitoring, vital signs, EPO levels, and hemoximetry Planned near infrared spectroscopy (NIRS) study to assess evidence of organ preservation designed to address this risk.
Study Procedures		

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Worsening anemia in participant with underlying sickle cell anemia.	Frequent blood samples will be collected from anemic participants during the study which may result in potential loss of blood volume in already anemic participants	A reduced PK sampling scheme is incorporated for pediatric participants so as not to exceed blood draw limits (0.8 mL/kg in a given 24-hour period; 2.4 mL/kg in a given 4-week period). Collection kits that limit blood volume draws are being used for pediatric participants. Investigators are allowed to limit blood sample collection in consideration of patient condition, with the guidance of a sample priority list (Table 10). Blood volume limits are following guidelines included in EU guidance for ethical considerations for clinical trials conducted with minors. Best practices for pediatric blood collection are provided in Section 9.3.3.1.
Potential DDI	Based on preliminary in vitro data, osivelotor has the potential to interact with CCI [redacted]	Close monitoring of the Prohibited/Restricted medication list

Adult participants in this study who have completed Part A of C5351004 (with open label osivelotor treatment), or any other open label osivelotor study, will be assessed every 12 weeks for safety and response to treatment.

Participants from Part B of C5351004, or any other randomized, blinded, placebo controlled osivelotor study, will be assessed every 8 weeks, for safety and response for the initial 24 weeks and then every 12 weeks thereafter.

Pediatric participants from Part C of C5351004 will be assessed at Week 2 and Week 4, then every 4 weeks for the initial 24 weeks, and then every 12 weeks thereafter.

For participants who have been off study drug treatment prior to enrolling into this study, an appropriate loading dose regimen will be initiated (Table 14), and participants will be assessed every 2 weeks up to Week 8, then every 4 weeks up to Week 24, and every 12 weeks thereafter.

3.2.2. Benefit Assessment

Osivelotor increases hemoglobin (Hb) oxygen affinity and stabilizes Hb in the oxy-hemoglobin state thereby inhibiting polymerization of HbS in RBCs and increasing RBC deformability and reducing morphologic sickling of RBCs (Dufu, Alt et al. 2020). In preclinical animal studies, osivelotor partitioned preferentially to the RBC compartment with a mean blood/plasma ratio of 48–122:1. Thus, similar to voxelotor, osivelotor is expected to

partition preferentially into RBCs in humans, where it specifically binds to Hb, thereby minimizing plasma exposures.

- SCD is a serious condition characterized by hemolytic anemia, chronic organ damage, and VOCs. Despite recent advances in therapy, there remain limited treatment options for patients with SCD; thus a high unmet medical need continues to exist. Osivelotor's potential to address this unmet medical need is supported by the nonclinical studies and preliminary clinical data which provide evidence for a treatment effect (gradual increase in Hb at both 100 mg and 150 mg daily maintenance dosing in C5351004). Given the MOA, it is likely that higher Hb levels (and consequently a clinically significant reduction in the incidence of VOCs) will be achieved, which is supported by data for Hb and Hb occupancy from C5351002 and preliminary data for C5351004.
- Osivelotor has increased affinity for Hb and a longer $t_{1/2}$ compared to voxelotor. Osivelotor has the potential to achieve greater % Hb occupancy and attain desired hematological effects at lower doses than voxelotor, therefore reducing pill burden, increasing the durability of response, and improving clinical outcomes for individuals living with SCD.
- The current treatment options for pediatric participants with SCD, particularly in children less than 12 years of age, are limited. SCD requires life-long preventive maintenance and management of acute and chronic complications. Newborn screening, early immunization, and prophylactic penicillin treatment in infants and children as well as comprehensive management for pain and disease complications have improved outcomes in children with SCD. Despite these advances, the median life expectancy of affected individuals is only 43 years of age and treatment of SCD remains a serious unmet medical need (Brandow, 2022). C5351004 Part B will evaluate the efficacy and safety of the selected dose of osivelotor versus placebo in adult and pediatric participants (12 to <18 years of age) with SCD. Part C will evaluate the PK and safety of single and multiple doses of open-label osivelotor administered to pediatric participants 6 months to <18 years of age.

3.2.3. Overall Benefit/Risk Conclusion

The results of previous studies of osivelotor in healthy volunteers and SCD adult participants support the investigation of osivelotor for SCD. There is a favorable benefit-risk profile to support the rationale for this study. Taking into account the measures to minimize risk to participants, the potential risks associated with osivelotor are justified by the anticipated benefits that may be afforded to participants with SCD.

3.3. Study Rationale

This is a multicenter, global, open-label extension study to evaluate the long-term safety, tolerability and SCD related complications of participants who have been treated with osivelotor. Gathering more patient-years of exposure to osivelotor will allow the Sponsor to further understand and characterize the safety profile of osivelotor.

All participants in this study are participants with SCD who have previously participated in an osivelotor clinical study. Participation in this study will provide continued access to

treatment until the participant has access to osivelotor from an alternative source (eg, through commercialization, a managed-access program, or a Sponsored initiative) or until the Sponsor decides to terminate the Study. Some participants in this study will have received osivelotor or placebo in a prior study in a blinded fashion and therefore this study will evaluate the first exposure to osivelotor in some participants. As such, the safety of initial exposure to osivelotor will also be evaluated in this study.

The daily maintenance dose for adult participants entering the study will be 150 mg osivelotor, which is the optimal dose selected from Part A of C5351004. The daily maintenance dose for all adult participants who have already enrolled into C5351005 prior to this amendment may be adjusted to the selected dose of 150 mg. Adolescent and pediatric participants from C5351004 Parts B and C will be administered a dose that provides generally equivalent exposure to adult participants.

4. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

The objectives of the study will be assessed by the endpoints and estimands as shown in Table 5.

Table 5. Objectives, Endpoints and Estimands

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
To evaluate the long-term safety of osivelotor in participants with SCD.	• Incidence of TEAEs, changes in laboratory assessments, and changes in vital signs.	The safety estimand for the primary endpoints will consider all safety data collected. Specifically, all data collected on or after obtaining informed consent will be included in the analysis.
Secondary:	**Secondary:**	**Secondary:**
To evaluate frequency of SCD-related complications. To evaluate the effects of long-term use of osivelotor on hemolytic anemia.	• Annualized rate of VOC. • Incidence of SCD-related SAEs. • Change from baseline in hematological laboratory parameters, including hemoglobin, reticulocytes, lactate dehydrogenase, and unconjugated bilirubin.	Not Applicable
Exploratory:	**Exploratory:**	**Exploratory:**

Table 5. Objectives, Endpoints and Estimands

Objectives	Endpoints	Estimands
To evaluate the long-term effects of osivelotor treatment on inflammation, erythropoietin levels, SCD-specific biomarkers, and HRQOL assessments.	• Change from baseline in adhesion of whole blood to microfluidic channels. • Change from baseline in RBC sickling from peripheral blood smears. • Change from baseline in RBC deformability and RBC mitochondrial content. • Change from baseline in albumin-to-creatinine ratio and kidney injury molecule. • Change from baseline in erythropoietin levels. • Change from baseline in haptoglobin, hemopexin, and soluble C3. • Change from baseline in HRQOL assessments including PROMIS SF Fatigue 13a, PROMIS SF Pain Interference 8a, PROMIS NRS Pain intensity, PGI-C of fatigue and pain, CGI-C of SCD, PGI-S of fatigue and pain, and CGI-S of SCD, EuroQol EQ-5D-5L, and WPAI+CIQ:SCD.	Not Applicable
To evaluate the PK parameters of long-term exposure to osivelotor	• Blood and plasma concentrations of osivelotor.	Not Applicable

Abbreviations: CGI-C, Clinician's Global Impression of Change; CGI-S, Clinician's Global Impression of Severity; PGI-C, Patient's Global Impression of Change; PGI-S, Patient's Global Impression of Severity; PK, pharmacokinetic; PROMIS, Patient-Reported Outcome Measurement Information System; HRQOL, health-related quality of life; RBC, red blood cell; SCD, sickle cell disease; SF, short form, WPAI+CIQ:SCD, Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Sickle Cell Disease.

5. STUDY DESIGN

5.1. Overall Design

This multicenter, global, open-label extension study is designed to assess the safety of long-term treatment with osivelotor in participants with SCD. The study will be conducted globally and will be available to eligible participants enrolled in a prior Pfizer-sponsored osivelotor clinical study (originating study). Participants must meet the entry criteria for this

study to be eligible for enrollment (see Section 6.1). The study will have a global distribution, and up to approximately 500 participants will be enrolled.

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

Eligible participants will receive open-label osivelotor at Baseline (Day 1). It is intended that Day 1 coincides with the final visit from the originating osivelotor study. End of Treatment (EOT) assessments from the originating study will serve as Baseline assessments for this study. If Day 1 for this study is greater than 7 days from the completion of the originating study, new baseline assessments will be obtained. If during the period between Day 1 of this study and completion of the originating study no dose is received for greater than 3 consecutive days, an appropriate loading dose will be administered prior to continued maintenance dosing (see Section 11.3 for detail). Additional assessments that may not have been included in the prior EOT assessments are outlined in the Schedule of Assessments and will need to be completed prior to study drug administration.

Participants who participated in Part A of C5351004 or any other open label osivelotor study, will undergo safety and outcome assessments at Baseline (Day 1) and every 12 weeks thereafter (Table 2).

Participants from Part B of C5351004, or any other randomized, blinded, placebo controlled osivelotor study will undergo safety and outcome assessments at Baseline (Day 1), Week 8, Week 16, Week 24, and every 12 weeks thereafter (Table 3).

Pediatric participants from Part C of C5351004 will undergo safety and outcome assessments at Baseline (Day 1), Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, and every 12 weeks thereafter (Table 4).

Participants will be followed for approximately 12 weeks after completing dosing to further assess safety. Participants should return to the study site for an EOS visit approximately 12 weeks after the last dose of study drug.

5.2. Scientific Rationale for Study Design

This study is an open-label study to evaluate the safety of long-term administration of osivelotor without a comparator. Participants in this study will have participated in a controlled clinical trial of osivelotor (originating study) in which they will have received osivelotor or placebo. Given the long half-life of osivelotor at the dose to be evaluated in this study, most of the participants are expected to maintain target concentrations throughout the study.

5.3. Justification for Dose

The daily maintenance dose for adults in the open label extension study will be 150 mg, which was the optimal efficacious dose determined from Part A of C5351004. The daily maintenance dose for all adult participants who have already enrolled in C5351005 prior to this amendment may be adjusted to 150 mg.

Adolescent and pediatric participants from C5351004 Parts B and C will be administered a dose that provides generally equivalent exposure to adult participants.

Further modifications to the loading doses may be made based on cumulative data from a population PK (PPK) model. Additionally, if there are safety/tolerability issues or lack of biomarker response at higher doses in the originating study, a drug dose reduction may be instituted as noted in Section 11.3.

The methodology for loading dose selection used in this open label study will differ for participants completing Parts A, B, and C of C5351004 and are shown in Section 11.3 and Table 6. For participants from the parent study who have been off study drug treatment greater than 3 consecutive days prior to enrolling into this study, a new loading dose regimen will be initiated as shown in Section 11.3.

Table 6. Doses Planned Based on Participation from C5351004

Participants from Part	Planned Dose to Initiate Treatment in Open Label Extension	Dose Adjustment
A	150 mg osivelotor	If dose is increased, a loading dose may be required. Details on the loading doses are provided in Section 11.3. The maintenance dose for all participants who have already enrolled in C5351005 prior to this amendment may be modified to 150 mg.
B	Adults: Initiate or continue with QD osivelotor 150 mg dose from Part B of C5351004. Adolescents: Initiate or continue with QD dose of osivelotor from Part B of C5351004.	Adults: Not applicable Adolescents: Adolescent participants will be administered a dose that provides generally equivalent exposure to adult participants.
C	Continue with QD assigned dose of osivelotor from Part C of C5351004.	Treatment may be modified based on emerging data from C5351004. Adolescent and pediatric participants will be administered a dose that provides generally equivalent exposure to adult participants.

Abbreviations: QD, once daily.

Detailed information on loading dose and maintenance dose to be used based on prior participation in C5351004 can be found in Section 11.3.

5.4. End of Study Definition

The EOS is defined as the date when the last participant has completed all study procedures up to and including EOS or ET visits, as specified in the Schedules of Assessments and Procedures (Section 2.1).

6. STUDY POPULATION

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

6.1. Inclusion Criteria

Participants must meet all inclusion criteria to be eligible for study participation.

1. Aged 6 months or older with SCD who participated and received study drug in an osivelotor clinical study and completed the EOT visit.

   Note: Participants who discontinued study drug in the originating study due to an AE, but who remained on study, may be eligible for treatment in this study provided the AE does not pose a risk for treatment with osivelotor. Also, participants who completed treatment from the originating study but were not able to rollover into C5351005 due to delay in study site activation will be eligible provided other eligibility criteria are met.

2. Females of child-bearing potential are required to have a negative urine pregnancy test prior to dosing on Day 1.

   Note: Females who become of child-bearing potential during the study must be willing to have a negative urine pregnancy test to remain in the study.

3. If sexually active, females of child-bearing potential must consistently use highly effective methods of contraception consistently throughout the study and for at least 84 days after the last dose of study drug. Male participants are eligible to participate if they agree to the following requirements during the study intervention period and for 84 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention:

   - Refrain from donating sperm

   PLUS either:

   - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

     OR

   - Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

   A male participant should be advised of the benefit for a female of child-bearing potential partner using a highly effective method of contraception with a failure rate of <1% per year.

4. Has provided written informed consent/assent. For underage participants, both the consent of the participant's legal representative or legal guardian and the participant's assent (where applicable) must be obtained based on local requirements.

6.2. Exclusion Criteria

Participants meeting any of the following exclusion criteria will not be eligible for study enrollment:

1. Female who is breastfeeding or pregnant.

2. Withdrew consent or was noncompliant from the originating osivelotor clinical study.

3. Has any medical, psychological, safety, or behavioral conditions that, in the opinion of the Investigator, may confound safety interpretation, interfere with compliance, or preclude informed consent.

4. Use of prohibited prescription or nonprescription drugs and dietary supplements (including herbal and alternative medications).Marijuana and all forms of ingested or inhaled cannabidiol (CBD) and THC-containing products usage meeting DSM-V criteria for substance abuse disorder is prohibited. However, occasional marijuana use is allowed, except for 24 hours prior to neurocognitive assessment as outlined in the SoA.

5. Ongoing or recent use of CCI [redacted]. Recent is defined as within 5 elimination half-lives or 14 days, whichever is longer prior to Day 1.

6. Ongoing or recent use of CCI [redacted] Recent is defined as within 5 elimination half-lives or 14 days, whichever is longer, prior to Day 1.

7. Ongoing or recent use of the CCI [redacted] Recent is defined as within 5 elimination half-lives prior to Day 1.

8. Current or recent use of voxelotor. Recent use is defined as within 10 days prior to Day 1.

9. Consumption of grapefruit, grapefruit juice, and/or Seville oranges within 14 days prior to Day 1 and is unwilling to abstain from consumption of grapefruit, grapefruit juice, and/or Seville oranges until the EOS/ET.

10. Has received an investigational drug (including investigational vaccines) within 5 times the elimination half-life (if known) or within 30 days (if the elimination half-life- is unknown) prior to study drug administration or is concurrently enrolled in any research judged not to be scientifically or medically compatible with this study.

11. Current or recent use of crizanlizumab. Recent use is defined as within 90 days prior to Day 1.

7. STUDY TREATMENT AND CONCOMITANT THERAPY

7.1. Study Treatments Administered

Study drug information is presented below.

Table 7. Study Drug Information

Study Intervention	
Intervention Name	Osivelotor (PF-07940367 or GBT021601)
Type	Drug
Use	Experimental
IMP or NIMP/AxMP	IMP
Dose Formulation	Tablet (or age appropriate oral formulation for pediatric participants <6 years of age)
Unit Dose Strength(s)	100 mg/tablet, 25 mg/tablet
Dosage Level(s)	100 mg, 150 mg, 200 mg
Route of Administration	oral
Sourcing	Provided centrally by the sponsor.
Packaging and Labeling	Study intervention will be provided in bottles, Each bottle will be labeled as required per country requirement. Provided blinded.
SRSD	PF-07940367 Investigator's Brochure
Study Arms	
Arm Title	Osivelotor (PF-07940367 or GBT021601)
Adults	Adult participants enrolling from C5351004 Part A and Part B will receive 150 mg maintenance dose. Dose adjustment and or loading dose will be determined based on previous intervention/dose received in C5351004. Details are provided in Appendix 1.
Adolescents and Pediatrics	Adolescent and pediatric participants from C5351004 Parts B and C will be administered a dose that provides generally equivalent exposure to adult participants.

See Appendix 1: Detailed Dosing Information For Osivelotor for dose information for participants rolling into this study.

Osivelotor will be administered orally. Study drug will be dispensed to the participant for completion of loading doses and initiation of maintenance dosing at home daily until the next clinical site visit.

Study drug should be taken two hours before a meal or one hour after a meal. Each dose will be administered orally with approximately 240 mL of water (additional water to complete dosing is allowed). Participants should swallow the tablets (≥6 years old) or age appropriate

pediatric formulation (<6 years old) within 5 minutes. If the participant vomits, the dose should not be repeated.

On the days that PK samples are to be taken, study drug is to be taken in the clinic and the participant must record the time and date of the last three doses of study drug taken at home. It is anticipated that these samples are to be taken 24 ± 3 hours after the last dose at home.

7.2. Preparation, Handling, Storage, and Accountability

Osivelotor will be provided in high density polyethylene bottles with child resistant caps with induction seal and labeled according to local regulations.

Study drug will be stored at controlled room temperature between 15ºC to 25ºC, either in the storage area of the investigational site pharmacy, which is a secure, temperature controlled, locked environment with restricted access, or in a secure location at the participants' home.

No special considerations for safe handling of osivelotor are required.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual or Pharmacy Manual.

7.3. Randomization and Blinding

This is an open-label study. Randomization and blinding are not applicable.

As this is an open-label, long-term extension study, the sponsor may conduct unblinded reviews and/or summaries of the data during the course of the study for the purpose of safety assessment, supporting clinical development, and/or supporting regulatory review.

7.4. Study Treatment Compliance

The first dose of the study drug will be administered by clinical staff at the study site. Details regarding dosing, including the dose administered and the date and time of dosing, will be recorded. The participant/parent/legal guardian/legally authorized representative will be required to bring the dispensed osivelotor bottle(s) to the study center at each visit and the Investigator or designee is to confirm the number of tablets or amount of age-appropriate formulationtaken and remaining before the next dispensation.

The participant/parent/legal guardian/legally authorized representative will also be supplied with a diary on which to record the date and time each dose of study drug is taken. Reasons for missed doses should be recorded. The diary will be dispensed at onsite visits and the participant will be required to bring the diary to each visit at the study center where the

Investigator or designee will review the records and enter the details into the electronic case report form (eCRF).

If a participant misses a dose, the participants should resume normal dosing the next day (ie, the dose on the day after a missed dose should not be increased or decreased).

7.5. Dose Modification

Guidelines for dose interruption or drug discontinuation are provided in Table 8. Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the study medical monitor as needed based on the clinical evaluation of the participant. The Medical Monitor should be notified of all dose modifications within 72 hours.

All instances of study drug modification (dose interruption or discontinuation) should be documented in the participants' medical record and recorded in the eCRF. If the condition/event leading to the dose modification has resolved, the original dose level should be resumed, unless in the judgment of the Investigator this cannot be done safely.

Table 8. Dose Modification Guidelines for Study Drug–Related Adverse Events

Dose Interruption	
Event	**Recommended Action**
Grade 3 or higher AE that is (1) study -drug related in the opinion of the Investigator AND (2) that precludes continued dosing at the current dose level due to safety concern or lack of tolerability (in the Investigator's judgment)	**Study Drug**: May be held for 10 days. If, in the opinion of the Investigator, a Grade 3 AE has resolved to ≤ Grade 1, participant may resume daily dosing of study drug at a lower dose (not lower than 100 mg) or continue with the original dose or a lower daily dose. Maximum dose hold is 28 continuous days. If, in the opinion of the Investigator, a longer dose hold is clinically needed, the Medical Monitor should be consulted.
ALT ≥3X ULN if ALT WNL at baseline OR >3X ULN AND a ≥2-fold increase above baseline values if elevated ALT values at baseline In the absence of additional signs of compromised liver function such as elevated PT, aPTT, INR, elevated conjugated bilirubin, jaundice, or hepatic pain.	**Study drug**: Confirm by repeat testing within 48 to 72 hours if possible and then repeat liver panel at least weekly until ALT levels improve. **Additional Actions**: If ALT levels continue to increase hold the study drug for 10 days and notify the Medical Monitor. Upon resolution of the elevated ALT, the participant may resume daily dosing of study drug at the original dose or a lower dose.
ALT ≥5X and <8X ULN (confirmed by repeat testing within 48 to 72 hours) In the absence of additional signs of compromised liver function such as elevated PT, aPTT, INR, elevated conjugated bilirubin, jaundice, or hepatic pain.	**Study drug**: Hold the study drug for 10 days.

Table 8. Dose Modification Guidelines for Study Drug–Related Adverse Events

	Additional actions: Repeat liver panel test within 48 to 72 hours if possible and then at least weekly until resolution to <5X ULN, with continued monitoring thereafter. If ALT continues to increase within 1 week after the medication is restarted, treatment should be interrupted, and the Medical Monitor should be notified. Upon resolution of the elevated ALT, the participant may resume daily dosing of study drug at the original dose or a lower dose.
Drug Discontinuation	
Event	**Recommended Action**
Grade 3 or Higher Study Drug-Related SAE	**Study Drug**: Discontinue study drug. If the Investigator considers that the participant would benefit from continuing treatment, the Medical Monitor should be contacted for discussion.
Consider treatment discontinuation if: • **ALT >8X × ULN** • **ALT >3X ULN with additional signs of compromised liver function** such as elevated PT, aPTT, INR, elevated conjugated bilirubin, jaundice, or hepatic pain, appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia	**Study drug**: Hold dose. **Additional actions**: Sponsor recommends confirmation by repeat testing within 48 to 72 hours and assess potential reversible causes of liver function test abnormalities. Contact the Medical Monitor for discussion of study drug discontinuation.

Abbreviations: AE, adverse event; ALT, Alanine aminotransferase; aPTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time; SAE, serious adverse event; ULN, upper limit of normal; WNL, within normal limits.

7.5.1. Individual Level Stopping Rules for Participants Enrolling in C5351005 from the 200 mg Treatment Arm from Part A of C5351004

Continued dosing of the respective individual at the 200 mg dose level may be paused for review if any of the following occurs:

- If a participant reaches the ULN for Hb or hematocrit (based on local laboratory reference ranges for gender) and a Grade 2 or higher severity TEAE that is related to osivelotor.
- If a participant has signs of impaired tissue offloading of oxygen (new or increased from baseline headache, dizziness, fatigue).

7.6. Treatment of Overdose

For this study, any dose of osivelotor greater than the protocol defined dose of study intervention within a 24-hour time period will be considered an overdose. Based on the mechanism of action of osivelotor, an extreme overdose might decrease oxygen delivery to tissues. Transfusion, exchange transfusion, and/or hyperbaric oxygen therapy may be considered in the event of a medical emergency due to a suspected osivelotor overdose.

The Investigator will discuss the risks and concerns of investigational agent exposure with the participant/parent/legal guardian/legally authorized representative. Participant/parent/legal guardian/legally authorized representative are to be instructed to contact their study site immediately if an overdose of study drug is suspected.

If a participant takes more than the protocol-defined dose of study drug in a day and experiences a drug related AE/SAE, this will be reported as an overdose (AEs/SAEs must be recorded on the AE eCRF and SAEs reported to Pfizer Safety) and a protocol deviation. However, if the participant did not experience any AEs/SAEs, this will only be reported as a protocol deviation. An overdose with AEs must be followed until any adverse effects are resolved or stabilized, or until reasonable attempts to determine resolution of the event are exhausted.

In the event of an overdose, the Investigator/treating physician should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE**.
5. Obtain a blood sample for PK analysis within 1 day from the date of the last dose of study drug intervention if requested by the medical monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the study medical monitor as needed based on the clinical evaluation of the participant.

7.7. Concomitant Medications and Procedures

Study participants will be allowed to take other medications as needed except for those described in Section 11.6. Vaccines are allowed during the study. All concomitant medications will be documented.

In the interests of participant safety and acceptable standards of medical care, the Investigator will be permitted to prescribe treatment(s) at their discretion. Treatment with stable doses of

HU, L-glutamine are allowed. However, initiation of new SOC agents (eg, crizanlizumab and voxelotor) during treatment is strongly discouraged. All other standard therapeutic interventions for SCD and its complications (eg, hydration, analgesia, acute transfusions) are allowed under this protocol.

All concomitant treatments and/or procedures must be recorded in the participants' eCRF (procedure, medication, dose, treatment duration and indication).

7.7.1. Healthcare Resource Utilization for Participants Enrolling from C5351004 Part B

Healthcare resource utilization data (eg, hospitalizations, non-protocol specified medical visits, etc.) will be collected for all randomized participants. Specifically, healthcare resource utilization is evaluated based on the number of medical care encounters such as hospital admissions and their duration, outpatient visits, diagnostic tests and procedures, concomitant medications, and reasons for the encounters. This data will be self-reported by participants at the frequency described in the schedule of assessments. Participants should recall any hospitalizations or non-protocol required healthcare visits (ie, participant seeking medical attention for any reason) that occurred between visits. This data may also be obtained through electronic sources such as electronic medical records, where available.

8. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study are detailed in Section 11.1.8.

8.1. Early Discontinuation of the Study

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the incidence or severity of AEs in this study or other studies with osivelotor indicating a potential health risk to participants.

In the instance of early termination of the study, the Sponsor will notify, in writing, the Investigators, regulatory authorities, and Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) and will specify the reasons(s) for the termination.

8.2. Discontinuation of Study Treatment

Participants will be discontinued from study drug for any of the following reasons:

- Participant is lost to follow-up.
- A participant that does not take the full loading dose assigned may be discontinued following a discussion with the Medical Monitor.
- At the discretion of the Investigator.
- Participant is noncompliant.
- Pregnancy.
- Withdrawal of consent (participants are free to discontinue treatment or withdraw from the study at any time and for any reason. The Investigator must withdraw participants from the study who request to be withdrawn). Additionally, parent/legal

guardian/legally authorized representative can withdraw consent at any time and for any reason.

Participants should return to the study site for an EOS visit approximately 12 weeks after the last dose of study drug per the Schedule of Assessments (SoA) and Procedures (Section 2.1).

8.2.1. Potential Cases of Acute Kidney Injury

Participants exposed to IMP demonstrating transient or sustained increase in Screat (with decrease in Screat-based eGFR or eCrCl) require expedited evaluation to differentiate AKI from DICI. DICI is defined as transporter-mediated effect related to altered renal tubular creatinine handling without histological injury.

AKI *may be due to one or more types of injury, including DIKI. Differentiation of DIKI from other causes of AKI and from DICI may require clinical, radiographic, histopathologic, and laboratory assessments, as well as nephrology consultation.*

Follow-Up Assessments

The participant should return to the site for evaluation as soon as possible, preferably within 48 hours of awareness of the abnormal results.

Evaluation should include physical examination, laboratory tests, detailed medical and surgical history, review of all medications (including recreational drugs and supplements [herbal]), family history, sexual history, travel history, blood transfusion, and potential occupational exposure to chemicals.

Laboratory assessments should include simultaneous serum cystatin C (Scys) and serum creatinine (Screat) tests. Estimates of eGFR, eCrCl and Screat-based eGFR and combined Screat-Scys-based eGFR should also be derived using the appropriate equation described in Section 11.5.

Assessments of urine albumin-to-creatinine ratio or urine volume may also be performed as appropriate.

If appropriate, nephrology consultation may be recommended to facilitate differentiation of renal parenchymal disease, pre-renal azotemia, and post-renal obstruction.

Differentiating Acute Kidney Injury from DICI

A confirmed Screat increase is defined as:
(i) ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours OR
(ii) confirmed Screat increase ≥1.5 times baseline (known or suspected to have occurred within the prior 7 days).

Based on the assessments performed, suspected AKI (including DIKI) may be differentiated from DICI as follows.

Pediatric Participants

	AKI (including DIKI) **Any one of the below**	**DICI**
Scys & Screat	Simultaneous, confirmed Scys increase and confirmed Screat increase	Confirmed Screat increase without confirmed increase in reflex Scys
Albuminuria	Confirmed albuminuria increase (see Section 11.5 for Grades A1 to A3 quantitation)	
Urine volume	Urine volume <0.5 mL/kg/h for 6 consecutive hours	

Adult Participants

	AKI (including DIKI) **Any one of the below**	**DICI**
Scys & Screat	Simultaneous, confirmed serum cystatin C (Scys) increase and confirmed Screat increase	Confirmed Screat increase without confirmed increase in reflex Scys AND Confirmed Screat-based eGFR decrease without confirmed combined Screat-Scys-based eGFR decrease.
eGFR	Decrease in Screat-based eGFR and combined Screat-Scys-based eGFR (when available)	
Albuminuria or proteinuria	Confirmed albuminuria increase (see Section 11.5 for Grades A1 to A3 quantitation)	
Urine volume	Urine volume <0.5 mL/kg/h for 6 consecutive hours	

Regardless of the presence or absence of increase in Screat, DIKI and other causes of AKI may be suspected if either (i) new-onset or worsening albuminuria or proteinuria are detected or (ii) urine volume (if measured) is <0.5 mL/kg/h for 6 consecutive hours.

All confirmed cases of clinically relevant decrease in kidney function should be considered potential cases of DIKI if no other reason for the kidney function abnormalities has been found.

See Appendix 2: Liver Safety: Suggested Actions and Follow-Up Assessments for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

8.2.2. Discontinuation due to Adverse Events

In addition to the dose modification and study stopping rules previously outlined in Section 7.5 and Section 8.1, respectively, any participant who experiences an AE may be withdrawn at any time from the study at the discretion of the Investigator. Participants withdrawn from the study due to an AE, whether serious or nonserious, should be followed by the Investigator until the clinical outcome of the AE is determined (ie, the event has

resolved or has stabilized). The AE(s) should be noted on the appropriate eCRFs. The Sponsor and/or contract research organization (CRO) Medical Monitor must be notified of the study participant discontinuation. If the AE relates to overdose of study treatment, see Section 7.6 for details of specific actions to be taken.

8.3. Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the Schedule of Assessments (SoA) Section 2.1. The SoA details the data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from the study treatment and the study at that time.
- If the participant/parent/legal guardian/legally authorized representative withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, they may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

8.4. Lost to Follow up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether 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, 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, they will be discontinued from the study.
- Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and

the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- Collection, processing, and shipping details for whole blood, plasma, serum, and other samples will be outlined in a separate laboratory manual.
- On study blood volume collections for participants <18 years old will not exceed 1% total blood volume (0.8 mL/kg based on 80 mL/kg blood volume) in any given 24-h period and 3% total blood volume (2.4 mL/kg based on 80 mL/kg blood volume) in any given 4-week period. Specific blood specimens (eg, exploratory measures) may be omitted at the discretion of the Investigator if warranted such as in the context of blood loss associated with standard clinical care, bleeding events, or if otherwise deemed appropriate. See Table 10 for the blood specimen assessment priority list.

9.1. Demographic/Medical History

The Investigator or designee will collect a complete medical history at the Baseline Visit. Demographics (sex, date of birth, race, ethnicity, height, and weight), SCD history, and current medications will be recorded.

9.2. Efficacy Assessments

Efficacy will be assessed through the following endpoints: annualized rate of VOC, change from baseline in hematological laboratory parameters (eg, hemoglobin, reticulocytes, lactate dehydrogenase, and unconjugated bilirubin), effects on inflammation, EPO levels, HRQOL assessments, and exploratory biomarkers (markers of hemolysis including haptoglobin, hemopexin, and soluble C3). Planned timepoints for all efficacy assessments are provided in the SoA (Section 2.1).

A VOC is defined as an acute episode of pain that:

- Has no medically determined cause other than a vaso-occlusive event, and
- Results in a visit to a medical facility (hospitalization, emergency department, urgent care center, outpatient clinic, or infusion center), and

- Requires parenteral narcotic agents, parenteral nonsteroidal anti-inflammatory drugs (NSAIDs), or an increase in treatment with oral narcotics.

Participant/parent/legal guardian/legally authorized representative will be instructed to visit the clinical site for VOCs requiring a visit to a healthcare facility. However, in cases where visits to other healthcare facilities are required for treatment of their VOCs (eg, emergency room, hospital, urgent care center, outpatient clinic or infusion center), participant/parent/legal guardian/legally authorized representative will be instructed to notify the clinical site within 48 hours when one of these visits occurs.

VOCs are categorized as:

- Uncomplicated VOC: a VOC that is NOT classified as an ACS, hepatic sequestration, splenic sequestration, priapism, or dactylitis.
- Complicated VOCs:
  - Acute Chest Syndrome, defined as a finding of a new pulmonary infiltrate, but excluding atelectasis (as indicated by chest X-ray). Must also present with at least one of the following signs or symptoms: participant-reported chest pain, body temperature of more than 38.5°C, tachypnea, wheezing, or cough.
  - Hepatic sequestration, defined as findings of right upper quadrant pain, an enlarged liver, and an acute decrease in Hb concentration.
  - Splenic sequestration, defined as findings of left upper quadrant pain, an enlarged spleen, and an acute decrease in Hb concentration.
  - Priapism, defined as having a sustained penile erection requiring a visit to a medical facility.
  - Dactylitis, defined as the global swelling of a finger or a toe giving it a clinical sausage-shape presentation.

Instructions for recording VOC events and source document collection for VOC event adjudication are provided in Section 9.4.12.1.

For participants with a gap in dosing >42 consecutive days from completing the originating study, outcome measures will be evaluated at the end of the loading dose period (Week 1), then every 2 weeks for the first 2 months (up to Week 8), then every 4 weeks for 4 months (up to Week 24), then every 12 weeks thereafter.

For participants from Part A of C5351004 or any other open label osivelotor study, outcome measures will be evaluated every 12 weeks.

For participants from Part B of C5351004, or any other randomized, blinded, placebo controlled osivelotor study, outcome measures will be evaluated every 8 weeks for the first 24 weeks of treatment in the open label study, and every 12 weeks thereafter.

For pediatric participants from Part C of C5351004, outcome measures will be evaluated at Week 2 and Week 4, then every 4 weeks for the first 24 weeks of treatment, and then every 12 weeks thereafter.

9.3. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 2.1).

9.3.1. Physical Examination

A full physical examination will be conducted at the Baseline Visit. All subsequent physical examinations will be brief physical examinations. Full physical examination will include examination of the following: general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes, and nervous system. Brief physical examinations will include general appearance; eyes, skin, cardiovascular and respiratory system examinations; abdominal examination, and as needed, a symptom-directed examination.

An abnormal physical examination finding during the on-study period (ie, following dose administration) that is considered clinically significant and (1) requires the participant to be discontinued from the study, or (2) requires the participant to receive treatment will be recorded as an AE.

9.3.2. Vital Signs

Vital signs assessments will include respiratory rate (breaths per minute), systolic and diastolic blood pressure (mmHg), heart rate (beats per minute), and body temperature, which will be measured after a participant has rested for at least 5 minutes in the supine or recumbent position, as age appropriate and feasible, and will be collected as per Section 2.1.

Any clinically significant abnormal vital sign assessment requires at least one repeat measurement.

Vital signs abnormalities that are (1) considered clinically significant initially and on confirmation, (2) require a participant to be discontinued from the study, (3) require a participant to receive treatment, or (4) require a change or discontinuation from the study drug (if applicable) will be recorded as AEs.

9.3.3. Clinical Laboratory Tests

Blood and urine for clinical laboratory tests (Table 9) will be collected as outlined in the SoA (Section 2.1). A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests. The Baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the first dose of study drug.

Prior to initiation of treatment, if a participant has an out-of-range value for a clinical laboratory parameter that the Investigator believes is not clinically significant or that the Investigator does not believe is correct (eg, laboratory or specimen processing error), but the Investigator wants to confirm with a repeat laboratory test, a single repeat is allowed to confirm the initial result.

All out of-range values will be assessed by the Investigator as clinically significant or not clinically significant. For any laboratory test value outside the reference range that the Investigator considers clinically significant during the on-study period (ie, following dose administration), the Investigator will repeat the test to verify the out-of-range value and

clinical significance. Clinically significant laboratory abnormalities will be recorded in the AE eCRF (see Section 9.4.7.2).

For pediatric participants,

- Blood draws will be minimized (see Section 9.3.3.1).
- Encourage pain management techniques, for example, cold spray, lidocaine cream, Buzzy Bee, massage, guided imagery, heat/cold packs.
- Reduce fear by providing comfort items/swaddling, parental presence, medical play therapy so children know what to expect, distraction (toys, videos, music), and/or provide a reward system after necessary painful procedures.

See Section 11.4 for suggested actions and follow-up assessments regarding liver safety in the event of potential DILI.

See Section 11.5 for guidelines on laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

Additional safety laboratory tests may be conducted as needed by the Investigator to evaluate participant safety.

Table 9. Clinical Safety and Other Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	ALT	Albumin	EPO
Hb	Albumin	Bilirubin	FSH (postmenopausal females only)
RBC count	Alkaline phosphatase	Blood	Pregnancy –serum and urine (females who are post menarche and of child-bearing potential) [b]
Mean corpuscular volume	AST	Creatinine	
Mean corpuscular Hb	Bicarbonate	Glucose	
Mean corpuscular Hb concentration	Blood urea nitrogen	Ketones	
Reticulocyte count (absolute and %)	Calcium	Leukocytes	RBC deformability
Platelet count (estimate not acceptable)	Chloride	Microscopic analysis of sediment if clinically indicated	Flow Adhesion
White blood cell count including differential count (percent and absolute):	Creatine phosphokinase	Nitrite	RBC Mitochondrial Content
Neutrophils	Creatinine	pH	Peripheral Smear
Lymphocytes	Fasting glucose	Protein	Serum cystatin C
Monocytes	Globulin	Specific gravity	Haptoglobin
Basophils	Lactate dehydrogenase Magnesium	Urobilinogen	Hemopexin
Eosinophils	Phosphorous		Soluble C3
PT	Potassium		**Serology Panel (if clinically indicated):**
aPTT	Sodium		HIV antibody
INR	Total bilirubin (direct and indirect)		Hepatitis A virus IgM antibody
	Total protein		Hepatitis B virus surface antigen
	Uric acid		Hepatitis C virus antibody
	eGFR [a]		

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CKD-EPI, chronic kidney disease epidemiology; eGFR, estimated glomerular filtration rate; EPO, erythropoietin; FSH, follicle stimulating hormone; Hb, hemoglobin; HIV, human immunodeficiency virus; IgM, immunoglobulin M; INR, International Normalized Ratio; PT, prothrombin time; RBC, red blood cells.

a Using CKD-EPI equations (for adults 18 years and above), Cockcroft-Gault formula (for adolescents 12 to <18 years), Modified Schwartz Equation (for children 2 to <12 years), or Schwartz equation (for infants 6 months to <2 years), see Section 11.5.2.

b Tests will be conducted at the clinic.

9.3.3.1. Total Blood Volume

On study blood volume collections for participants <18 years old will not exceed 1% total blood volume (0.8 mL/kg based on 80 mL/kg blood volume) in any given 24-h period and 3% total blood volume (2.4 mL/kg based on 80 mL/kg blood volume) in any given 4-week period. Specific blood specimens (eg, exploratory measures) may be omitted at the discretion of the Investigator if warranted such as in the context of blood loss associated with standard

clinical care, bleeding events, or if otherwise deemed appropriate. See Table 10 for the blood specimen assessment priority list.

Due to volume restrictions in pediatric research, assessments will be prioritized in the following order:

Table 10: Blood Specimen Assessment Priority List

Priority	Test
1	Hematology
2	Chemistry
3	Pharmacokinetics
4	Erythropoietin
5	Blood Smear and RBC Deformability
6	Exploratory biomarkers

9.3.4. Pregnancy Testing

Pregnancy tests will be performed on female participants who are post menarche and of child-bearing potential as indicated in the Schedule of Assessments (Section 2.1). A woman is considered of child-bearing potential, ie. fertile, following menarche and until becoming post-menopausal unless permanently sterile. A serum pregnancy test will be conducted at Baseline only if there is a delay of >7 days in start of OLE from the originating study, otherwise a urine pregnancy test will be conducted at Baseline with urine pregnancy tests conducted thereafter as indicated in the Schedule of Assessments. If the Day 1 urine test is positive, a pre-dose serum pregnancy test should be performed and dosing should be postponed until a negative result is confirmed; if positive, the participant will be considered a screen failure.

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

9.3.5. Fertility and Contraceptive Requirements

9.3.5.1. Female Participants of Childbearing Potential

Female participants who are of child-bearing potential are required to use highly effective methods of contraception or practice abstinence from study start to 84 days after the last dose of study drug.

Highly effective contraception methods are defined as the following:

a. Estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation OR progestogen only hormonal contraception associated with inhibition of ovulation by oral, implantable, or injectable route of administration
b. An intrauterine device

c. An intrauterine hormone-releasing system
d. Females with bilateral tubal occlusion
e. Surgically sterile male partner (eg, vasectomy)
f. True sexual abstinence, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. Periodic abstinence (eg, calendar, ovulation, symptom-thermal, post-ovulation methods), and withdrawal are not acceptable methods of contraception.

9.3.5.2. Instructions for Male Participants Capable of Fathering a Child

It is important that the female partners of male participants do not become pregnant during the study and for a total period of 84 days after the male participant has taken the last dose of osivelotor.

As a precaution, all male participants who are sexually active and not surgically sterile should avoid fathering a child by either true abstinence or the use of barrier methods of contraception plus highly effective contraception for their female partner if of childbearing potential.

9.3.5.3. Acceptable Forms of Contraception for Male Participants with Female Partners Capable of Reproduction

Male participants who are not surgically sterile with partners of childbearing potential must agree to use a highly effective method of birth control during the study and for 84 days after the last dose of study drug. A highly effective method of contraception is defined as one that results in a low documented failure rate when used consistently and correctly such as: condom plus use of an intrauterine device; intrauterine system or hormonal method of contraception (oral, injected, implanted, or transdermal) for their female partner; or sexual abstinence.

Male participants who are not surgically sterile with a partner who is pregnant must agree to condom use or maintain sexual abstinence during the study and for 84 days after the last dose of study drug.

9.4. Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

9.4.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a participant administered a pharmaceutical product during the course of a clinical investigation. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not thought to be related to the investigational product. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the participant/parent/legal guardian/legally authorized representative signs the ICF for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE.

Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Life-threatening AE or life-threatening suspected adverse reaction is an AE or suspected adverse reaction that, in the view of either the Investigator or Sponsor, places the study participant at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

An AE or suspected adverse reaction is considered to be "unexpected" if it is not listed in the Reference Safety Information section of the current IB or is not listed at the specificity or severity that has been observed.

The Investigator will assess each AE for seriousness, severity, and relationship to investigational product.

9.4.2. Definition of Serious Adverse Events or Serious Suspected Adverse Reactions

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

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

NOTE: Hospitalization planned prior to study enrollment (eg, for elective surgeries) is not considered to be an SAE. Any complications arising from a planned hospitalization may be considered an AE and should be reported as applicable. Hospitalizations that occur for pre-existing conditions that are scheduled after study enrollment are considered SAEs.

9.4.3. Severity of Adverse Events

Whenever possible, the severity of all AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0.

For AEs not adequately addressed in the NCI CTCAE, Version 5.0, the criteria presented in Table 11 should be used.

Table 11. Grading for Adverse Events not Covered in the NCI-CTCAE

Severity	Description
Grade 1 – Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 – Moderate	Minimal, local, or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living
Grade 3 – Severe	Medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
Grade 4 – Life-threatening	Life-threatening consequences; urgent intervention indicated
Grade 5 – Fatal	Death

Abbreviations: NCI-CTCAE, National Cancer Institute - Common Terminology Criteria for Adverse Events.

To make sure that there is no confusion or misunderstanding between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific event (ie, mild, moderate, or severe); the event itself, however, may be of relatively minor medical significance (eg, severe headache). This is not the same as "serious", which is based on the study participant/event outcome or action criteria associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

9.4.4. Relationship to Investigational Product

The relationship of an AE to the study drug should be determined by the Investigator according to the following definitions:

NOT RELATED: Evidence exists that the AE has an etiology other than the study drug and/or the temporal relationship of the AE/SAE to the investigational product administration makes the relationship unlikely. If an SAE is not considered to be related to study drug, then an alternative explanation should be provided.

RELATED: A temporal relationship exists between the event onset and the administration of the study drug and makes a causal relationship possible or probable. It cannot be readily explained by the participant's clinical state or concomitant therapies and may appear, with some degree of certainty, to be related based on the known therapeutic and pharmacologic actions of the drug. Good clinical judgment should be used for determining causal assessment.

9.4.5. Unexpected Adverse Reactions

An adverse reaction is "unexpected" if its nature and severity are not consistent with the information about the study drug provided in the PF-07940367 IB (Pfizer, 2023).

9.4.6. Adverse Event Reporting

9.4.6.1. General AE Reporting

All AEs/SAEs will be recorded from the time the study participant/parent/legal guardian/legally authorized representative signs the ICF/assent form until the EOS Visit or ET Visit, whichever comes first. The AE or SAE must be recorded on the CRF and the SAE reported using PSSA. The Investigator is responsible for evaluating all AEs/SAEs, obtaining supporting documents, and ensuring that documentation of the event is complete. Details of each reported AE/SAE must include at a minimum severity, relationship to study treatment, duration, and outcome.

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent/legal guardian/legally authorized representative provides informed consent, which is obtained before undergoing any study related procedure and/or receiving study intervention, through and including a minimum of 63 calendar days after the last administration of the study intervention. Follow-up by the investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

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

If a participant permanently discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using PSSA Pfizer's Serious Adverse Event Submission Assistant. The Sponsor/Medical Monitor(s) must be notified of the study participant discontinuation.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has concluded study participation, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using PSSA.

9.4.7.1. Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the eCRF rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be

medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded separately on the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

9.4.7.2. Abnormal Laboratory Values

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

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

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

9.4.8. Serious Adverse Events, Serious Adverse Drug Reactions, and Requirements for Immediate Reporting

All SAEs, regardless of causal attribution, must be reported by the Investigator/designee or site personnel within 24 hours of SAE awareness on the AE eCRF and reported to Pfizer Safety via PSSA. In the event that PSSA is not available, paper SAE report forms will be used to report the SAE and faxed or emailed to the Sponsor or CRO designee. The information reported on paper SAE report form should be entered into the EDC once available.

The Sponsor or designee may request additional source documentation pertaining to the SAE from the investigational site. Follow-up reports must be submitted within 24 hours of awareness and participant identifier information (eg, name, medical record number) must be redacted in the hospital discharge summaries, autopsy reports, and/or death certificates.

Follow-up SAE information must be submitted within 24 hours of awareness as additional information becomes available. All SAEs regardless of causal attribution must be followed to resolution or stabilization, or until reasonable attempts to determine resolution of the SAE are performed.

9.4.8.1. Reporting Suspected Unexpected Serious Adverse Reactions and Urgent Safety Issues

The Sponsor is responsible for reporting suspected unexpected serious adverse reactions (SUSARs) to regulatory agencies, competent authorities, IRBs/ECs, and Investigators as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than 7 calendar days of the Sponsor's first knowledge of the event and follow-up information submitted within an additional 8 calendar days, or as otherwise required per local laws and

regulations. All other SUSARs will be submitted within 15 calendar days of the Sponsor's first knowledge of the event. The Investigator is responsible for notifying the local IRBs or ECs of all SAEs that occur at his or her site as required by local regulations or IRB/EC policies, if this responsibility resides with the site.

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

9.4.9. Drug-induced Liver Injury

Participants will be monitored for signs of drug-induced liver injury (DILI).

Potential events of DILI will be defined as meeting all the following criteria (as specified in the FDA Guidance for *Drug-Induced Liver Injury: Premarketing Clinical Evaluation 2009* [FDA, 2009]).

Potential events of DILI will be reported as SAEs (Section 9.4.8). All participants with potential DILI will be closely followed until abnormalities return to normal or baseline or until all attempts to determine resolution of the event are exhausted.

See Appendix 2: Liver Safety: Suggested Actions and Follow-Up Assessments in the event of potential DILI.

9.4.10. Method of Detecting AEs and SAEs

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

9.4.11. 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. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.4).

9.4.12. Disease-related Events or Disease-related Outcomes Not Qualifying as AEs or SAEs

9.4.12.1. Adverse Events that are Vaso-Occlusive Crisis Events

VOC events are not reported as an AE/SAE and must be reported on the VOC page.

If the underlying cause of an SAE is determined to be a VOC, then the SAE will be entered on the VOC page and not reported as an SAE.

If the underlying cause of an SAE is determined not to be a VOC, then the SAE must be recorded in the SAE page and reported as an SAE.

The following disease-related events are common in participants with SCD, independent of exposure to study intervention, can be serious/life-threatening, and are defined as endpoints in this protocol:

- Uncomplicated VOC (defined as an acute episode of pain with no medically determined cause other than a vaso-occlusive event, results in a visit to a medical facility (hospitalization, emergency department, urgent care center, outpatient clinic, or infusion center), and requires parenteral narcotic agents, parenteral nonsteroidal anti-inflammatory drugs (NSAIDs), or an increase in treatment with oral narcotics, but is NOT classified as an acute chest syndrome, hepatic sequestration, splenic sequestration, dactylitis, or priapism.)
- Complicated VOC:
  - Acute chest syndrome
  - Hepatic sequestration
  - Splenic sequestration
  - Priapism requiring a visit to a medical facility
  - Dactylitis

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 VOC page in the participant's CRF within 72 hours. These disease-related events will be monitored by an independent data monitoring committee and 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 disease-related events):

- 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.

9.4.12.1.1. Procedures for Reporting and Documenting VOC Event Data

All VOCs, as defined in Section 9.4.12.1, are to be documented within the eCRF within 5 days of a site becoming aware of such event. Each VOC is to be recorded only once on the "Vaso-Occlusive Event" eCRF page. All VOCs are to be recorded throughout the entire treatment period, up to Week 48, and should continue until the Follow-Up Visit at Week 60 for participants who do not enroll in the OLE study (or earlier if participant discontinues from the study). The Investigator will classify and provide all the following information for each VOC as follows:

- Diagnosis, which will be limited to one of the pre-defined VOC events as described in Section 9.4.12.1:
  - Uncomplicated VOCs
  - Acute chest syndrome
  - Hepatic sequestration
  - Splenic sequestration
  - Priapism (requiring a visit to a medical facility)
  - Dactylitis
- Onset date,
- Stop date,
- Action taken (none, required concomitant medication, temporarily withheld study drug, permanent discontinuation of study drug, or other [explain]),
- Whether or not hospitalization or a visit to emergency department, urgent care center, outpatient clinic, or infusion center was required,
- Concomitant medications given, and
- Outcome (recovered without sequelae, resolved with sequelae, ongoing, unknown, death).

If a participant is hospitalized due to a VOC and during hospitalization develops a non-VOC event that meets the criteria for a SAE, then that event should be reported as a SAE. Any prolongation of a hospitalization due to a non-VOC event (even though they may have initially been hospitalized due to a VOC) is reportable as a SAE in the eCRF.

9.4.12.1.2. Source Document Collection for VOC Event Adjudication

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

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

- Clinical notes (including history and physical examination [PE] findings),
- Emergency Department notes (including history and PE findings),
- Hospital discharge summary,

- Clinical laboratory values (eg, Hb concentration values for diagnoses of hepatic or splenic sequestration),
- Physical examination findings,
- Concomitant medications, and
- Chest X-ray (required for reporting an ACS).

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

9.4.13. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy (EDP), exposure during breastfeeding (EDB), and occupational exposure.

Any such exposures to the study intervention under study are reportable to the Sponsor or designee within 24 hours of Investigator awareness.

9.4.13.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below is an example of environmental EDP:
  - A female family member of healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.
  - A male family member or healthcare provider who has been exposed to osivelotor by all possible routes of exposure, eg, ingestion, inhalation, or skin contact, then inseminates his female partner prior to or around the time of conception.

The Investigator must report EDP to the Sponsor or designee within 24 hours of the Investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below of information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner, the Investigator must report this information to Pfizer Safety using PSSA, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until at least 140 days after the last dose.
- If EDP occurs in the setting of environmental exposure, the Investigator must report information to Pfizer Safety using PSSA. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the Investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The Investigator will follow the pregnancy until completion (or until pregnancy termination) and notify the Sponsor or designee of the outcome as a follow-up to the initial report. The child born to a female participant or partner of a male participant exposed to study drug will be followed for 3 months after delivery. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criterial for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the Investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to the Sponsor or designee as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the Investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the Sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the Investigator will provide the participant with the 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 to provide to his partner.

9.4.13.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female nonparticipant is found to be breastfeeding while exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

The Investigator must report EDB to Pfizer Safety within 24 hours of the Investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed report is maintained in the Investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

9.4.13.3. Occupational Exposure

The Investigator must report any instance of occupational exposure to the Sponsor or designee within 24 hours of the Investigator's awareness using PSSA regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the Investigator site file.

9.4.14. Lack Of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE.**

9.4.15. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors are recorded and reported as follows:

Table 12. Reporting of Medication Errors

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported via PSSA to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Abbreviations: AE, adverse event; CT, clinical trial; CRF, case report form; PSSA, Pfizer's Serious Adverse Event Submission Assistant; SAE, serious adverse event.

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
  - The administration of expired study intervention;
  - The administration of an incorrect study intervention;
  - The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use;
  - The administration of an incorrect dosage.

Whether or not the medication error is accompanied by an AE, as determined by the Investigator, such medication errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s) are recorded on the AE page of the CRF.

In the event of a medication dosing error, Pfizer Safety should be notified within 24 hours.

Medication errors should be reported to Pfizer Safety within 24 hours via PSSA **only when associated with an SAE.**

9.5. Pharmacokinetics

Plasma and whole blood PK samples (1 x 4 mL per time point for participants from C5351004 Parts A and B; 1 x 2 mL per time point for participants from C5351004 Part C) will be collected according to the time points as specified in the SoA (Section 2.1).

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

9.6. Genetics

Genetics is not evaluated in this study.

9.7. Pharmacodynamics/Biomarkers

Predose blood samples for the following PD assessments will be collected at the timepoints specified in the SoA Section 2.1:

- Peripheral blood smears (to visually evaluate change in RBC sickling)
- RBC deformability
- RBC mitochondrial content
- Flow adhesion (adhesion of whole blood to microfluidic channels coated with vascular cell adhesion molecule or P-selectin)
- Exploratory biomarkers (markers of hemolysis including haptoglobin, hemopexin, and soluble C3)

These will be performed on samples from participants enrolled at sites in regions where these assessments are available.

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

9.8. Health-Related Quality of Life Assessments for Participants Enrolling from C5351004 Part A and Part B

PRO assessments will be completed electronically by the study participant at the beginning of the scheduled visit, before any medical procedures or interactions with the clinical staff take place.

Participants will be asked to provide responses to nine HRQOL surveys at sites where applicable. These survey measures include PROMIS SF Fatigue 13a, PROMIS SF Pain Interference 8a, PROMIS NRS Pain Intensity, PGI-S of fatigue, PGI-S of pain, PGI-C of fatigue, PGI-C of pain, EuroQol EQ-5D-5L, and WPAI+CIQ:SCD at sites where available.

Clinicians will also complete two HRQOL assessments (Clinical Global Impression of Change [CGI-C] and Clinical Global Impression of Severity [CGI-S]) on their global impression of participant improvement.

Qualitative interviews will be conducted with a subset of study participants by telephone or online/web conference after completion of study treatment as indicated in the Schedule(s) of Assessments and Procedures. Interviews will be targeted for completion within approximately 21 days after end of Part B study treatment. It will not be considered a protocol deviation if these interviews are conducted outside of this timeframe. These interviews are required for all eligible participants, including those who terminate early. Eligibility for participation will be outlined in a separate qualitative interview procedure document.

The goal of the interviews is to collect data regarding participants' disease- and treatment-related experiences, including the following:

- Disease-related symptoms and impacts prior to enrolling in the study
- Perceived changes in symptoms and impacts during the study
- Perspectives on relevance and clarity of HRQOL survey measure (eg, PROMIS, PGI-C and PGI-S survey measures).
- Meaningfulness of any changes experienced

The interviews will be conducted by trained moderators/interviews who are not employed or contracted by the study site. The duration of each interview will be approximately 60-90 minutes and will be audio recorded, transcribed, and de-identified. Following analysis of the qualitative data (ie, interview transcripts and field notes), a summary report that describes the study objectives, methods, sample, and aggregated results of the qualitative interviews will be developed separately from the CSR. These qualitative data will not be included in the CSR.

Planned timepoints for all HRQOL assessments are provided in the SoA (Section 2.1).

9.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9.10. Missed Assessments

Missed assessments should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the Investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

10. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the SAP, which will be maintained by the Sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

10.1. Statistical Hypothesis

No formal hypothesis will be assessed.

10.1.1. Estimands

The primary estimand is defined as follows:

Population: Patients with SCD as defined by the inclusion/exclusion criteria.

Endpoint(s):
- Incidence of TEAEs
- Changes in laboratory assessments
- Changes in vital signs

Intercurrent Events and Handling Strategy: No ICE is defined for this estimand. All data collected on or after obtaining informed consent will be included in the analysis.

Population-level Summary:
- Incidence of TEAEs – absolute and relative frequency
- Changes in laboratory assessments – descriptive summary of observed values at each visit and change from baseline.
- Changes in vital signs – descriptive summary of observed values at each visit and change from baseline.

10.1.2. Multiplicity Adjustment

No formal hypothesis will be tested and therefore no adjustments for multiplicity are planned.

10.2. Analysis Sets

The analysis population for reporting are defined in the following table:

Participant Analysis Set	Description
Enrolled	All participants who sign the inform consent document and enroll in this OLE study.

Participant Analysis Set	Description
Safety Analysis Set	All enrolled participants who have received at least one dose of study drug in this OLE study. Participants will be analyzed overall and according to the study treatment received in the parent study. This analysis set will be used for all safety, efficacy, PD/biomarker, HRQOL analyses.
PK Analysis Set	All enrolled participants who receive at least one dose of study drug and have at least one concentration data point (plasma or whole blood) post dose.

10.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses of the study endpoints and handling of missing, un-used, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

10.3.1. General Considerations

Data will be summarized using descriptive statistics as described in Sections 10.3.2 and 10.3.3. Data will be reported overall and also based on patient population and treatment received in the parent studies.

10.3.2. Primary Endpoint(s)/Estimand(s) Analysis

Primary Endpoints	Statistical Analysis Method
• Incidence of TEAEs • Changes in laboratory assessments • Changes in vital signs	Descriptive statistics of TEAEs, safety laboratory data and vital signs observed values and change from baseline will be provided. Safety data will be presented in tabular or graphical format and summarized descriptively, where appropriate.

10.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

Secondary Endpoints	Statistical Analysis Method
• Annualized rate of VOC	Annualized rate of VOC will be summarized using descriptive statistics and a negative binomial model. VOC data will be censored from the analysis after the following events: • New HU use post baseline; • Post baseline usage of prohibited/restricted medications known to affect Hb/VOC; • RBC exchange transfusion post baseline.
• Incidence of SCD related SAEs	Descriptive statistics of SCD related SAEs will be provided.
• Change from baseline in hematological laboratory parameters, including hemoglobin, reticulocytes, lactate dehydrogenase, and unconjugated bilirubin.	Change from baseline in hemoglobin, reticulocytes, lactate dehydrogenase, and unconjugated bilirubin will be summarized using descriptive statistics. • The following data will be excluded from the analysis: Data collected on or after the start of new HU use post baseline; • Data collected on or after the post baseline usage of prohibited/restricted medications known to affect Hb/VOC; • Data collected on or after start of post baseline RBC exchange transfusion; • Data collected from the start of post baseline RBC non-exchange transfusion for 18 weeks. (Data collected after the 18 weeks will be included in the analysis.)

10.3.4. Exploratory Endpoint Analysis

Results of exploratory endpoint analyses will be described in the CSR to the extent possible. Due to the exploratory nature of the endpoints, the associated data analyses may not be complete at the time of CSR preparation. If results of exploratory endpoint analyses cannot be included in the CSR, they will be disseminated to the scientific community to the extent possible through presentation at scientific meetings and/or publication in peer-reviewed scientific journals.

All plasma and whole blood concentration versus time data will be summarized using descriptive statistics and will be listed and summarized in tabular format. Graphical displays of mean and/or median concentration versus time plots may be prepared.

10.3.5. Other Analyses

PK parameters will be assessed by population PK analysis using nonlinear mixed-effects modeling and will be reported separately.

Pharmacogenomic or biomarker data from Retained Research Samples may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

10.4. Interim Analyses

No formal interim analysis will be conducted for this study.

10.5. Sample Size Determination

The sample size is based on the number of participants who will complete the parent studies and consent to continue to this study. Therefore, approximately 500 participants are anticipated to enroll in this long-term follow-up study.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Regulatory, Ethical, and Study Oversight Considerations

11.1.1. 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 Council for International Organizations of Medical Sciences international ethical guidelines
  - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines
  - Applicable local laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

11.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

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

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

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

11.1.4. Informed Consent Process

The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the participant (or their legally authorized representative) and answer all questions regarding the study. The participant (or their legally authorized representative) should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants (or their legally authorized representative [if allowed by local regulation]) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The Investigator must ensure that each participant (or their legally authorized representative) is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant (or their legally authorized representative) must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant (or their legally authorized representative).

The participant (or their legally authorized representative) must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The Investigator further must ensure that each study participant (or their legally authorized representative) is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

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

Participant (or their legally authorized representative) must be reconsented to the most current version of the IRB/EC-approved ICF(s) during their participation in the study as required per local regulations.

A copy of the ICF(s) must be provided to the participant (or their legally authorized representative).

11.1.5. Data Protection

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

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

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

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The Sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of Sponsor information or systems.

11.1.6. Dissemination of Clinical Study Data

The Sponsor fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulation. In addition, the Sponsor reports study results outside of the requirement of local laws/regulations pursuant to its standard operating procedures.

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

www.clinicaltrials.gov

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

EudraCT/CTIS

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

www.pfizer.com

The Sponsor posts clinical study report (CSR) synopses and plain-language study results summaries on www.pfizer.com for GBT/Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

The Sponsor complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

The Sponsor provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. The Sponsor will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

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

11.1.7. Data Quality Assurance

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

Guidance on completion of CRFs will be provided in the CRF Completion Requirement document.

The Investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

Quality tolerance limits (QTLs) are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

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

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan maintained and utilized by the Sponsor or designee.

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

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

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

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

11.1.8. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor, including (but not limited to)

regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

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

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

11.1.9. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the Investigator and the Sponsor reporting the primary endpoint(s) of the study covering all study sites. The Investigator agrees to refer to the primary publication in any subsequent publications. The Sponsor will not provide any financial compensation for the Investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The Investigator will provide the Sponsor an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to the Sponsor 30 days before submission. If any patent action is required to protect intellectual property rights, the Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from the Sponsor. This allows the Sponsor to protect proprietary information and to provide comments, and the Investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or

Sponsor-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and the Sponsor will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The Investigator will disclose any relationship with the Sponsor and any relevant potential conflicts of interest, including any financial or personal relationship with the Sponsor, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

11.1.10. Sponsor's Medically Qualified Individual

The Sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the Investigator Site File.

Participants are provided with a Pfizer study information card at the time of informed consent which includes contact information for their investigator in case of study-related medical questions. The study information card contains, at a minimum, (a) study number, (b) participant's study identification number, and (c) principal investigator contact information.

11.2. Supporting Documentation

11.3. Appendix 1: Detailed Dosing Information For Osivelotor

Dose for Participants Enrolling from Part A of C5351004

Table 13. Dose for Participants Enrolled Directly from Part A of C5351004

Maintenance Dose in Part A of C5351004	Maintenance Dose in C5351005[a]
100 mg QD	Stay at 100 mg QD
	Increase to 150 mg QD
150 mg QD	Stay at 150 mg QD
	Decrease to 100 mg QD
Up to 200 mg QD	Stay at up to 200 mg QD
	Decrease to 150 mg QD
	Decrease to 100 mg QD

Abbreviations: QD, once daily.
a Until the analysis is completed from Part A of C5351004, the original dose from Part A of C5351004 should be continued in C5351005. After the optimal efficacious dose is determined in C5351004, participants may have their dose adjusted to the optimal efficacious dose in C5351005.

If there is a delay in dosing for participants from Part A of the C5351004 study prior to entry into this OLE study, a modified loading dose will be administered depending on the dose received in the previous study as follows:

Table 14. Modified Loading Dose for Those with a Gap in Treatment from C5351004 Part A, Part B, and Part C

Amount of Consecutive Days with Missed Doses	100 mg Maintenance Dose	150 mg Maintenance Dose	200 mg Maintenance Dose
>3 to <7 consecutive days of missed doses	200 mg QD x 3 days	300 mg QD x 3 days	300 mg QD x 4 days
7 to <14 consecutive days of missed doses	200 mg QD x 5 days	300 mg QD x 5 days	300 mg QD x 7 days
14 to <42 consecutive days of missed doses	200 mg QD x 7 days	300 mg QD x 7 days	300 mg QD x 10 days
42 consecutive days of missed doses or greater	200 mg QD x 7 days	300 mg QD x 7 days	300 mg QD x 14 days

Abbreviations: BID, twice daily; QD, once daily.

Dose for Participants Enrolled from Part B of C5351004

Table 15. Dose for Participants Enrolled from Part B of C5351004

Maintenance Dose in Part B of C5351004	Maintenance Dose in C5351005	Loading Dose in C5351005
150 mg dose or placebo	150 mg dose selected for Part B of C5351004	Not applicable

Dose for Participants Enrolled from Part C of C5351004

Table 16. Dose for Participants Enrolled from Part C of C5351004

Maintenance Dose in Part C of C5351004	Maintenance Dose in C5351005	Loading Dose in C5351005
Participants will be administered a dose that provides generally equivalent exposure to 150 mg QD in adult SCD participants	Remain on the dose selected in Part C of C5351004	Not applicable

Abbreviations: TBD, to be determined.

11.4. Appendix 2: Liver Safety: Suggested Actions and Follow-Up Assessments

11.4.1. Drug-induced Liver Injury

Participants will be monitored for signs of drug-induced liver injury (DILI).

Potential events of DILI will be defined as meeting all of the following criteria (as specified in the Food and Drug Administration (FDA) Guidance for *Drug-Induced Liver Injury: Premarketing Clinical Evaluation 2009* [FDA, 2009]).

- ALT >4 × ULN or aspartate aminotransferase (AST) >3 × ULN
- No other reason can be found to explain the combination of laboratory value increases (eg, acute viral hepatitis; alcoholic and autoimmune hepatitis; hepatobiliary disorders; nonalcoholic steatohepatitis; cardiovascular causes; concomitant treatments)

Potential events of DILI will be reported as SAEs. All participants with potential DILI will be closely followed until abnormalities return to normal or baseline or until all attempts to determine resolution of the event are exhausted.

11.4.2. Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are

"susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are "adaptors" or are "susceptible."

Liver function test (LFT)s are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili 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 T bili 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. In SCD, hyperbilirubinemia is due to a combination of acute hepatobiliary disease (ie, acute SC hepatic crisis, acute hepatic sequestration or acute intrahepatic cholestasis) as well as chronic hepatobiliary manifestations (ie, cholelithiasis, choledocholithiasis, and SCD cholangiopathy) (Shah, R 2017).

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 T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili 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** T bili 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 T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Because knowledge of the total and unconjugated bilirubin, may suggest the treatment assignment, these measurements will be redacted to the Investigator and monitored on a

regular basis by an unblinded team. Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

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

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

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

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

11.5. Appendix 3: Kidney Safety Monitoring Guidelines

11.5.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline Screat measurement to estimate kidney function [Screat-based eGFR] or creatinine clearance [eCrCl]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Screat increase. If Screat increase is confirmed after baseline, then reflex measurement of Scys is indicated.

ADULTS: Currently, 2021 CKD-EPI eGFR equations (Screat-only based and combined Screat plus Scys-based) are valid for use in adults only. At baseline Screat and Scys values are needed to calculate 2021 CKD-EPI eGFR by Screat-only based equation (see Table in Section 11.5.2.1) and by combined Screat plus Scys-based equation. When post-baseline Screat increase ≥0.3 mg/dL is confirmed, then reflex Scys measurement is needed to enable post-baseline comparison of eGFR changes (Screat-only based eGFR and combined Screat plus Scys eGFR).

PEDIATRICS: Currently, no Screat plus Scys eGFR equations have been universally adopted for pediatrics. Therefore, comparison of baseline Screat and Scys to post-baseline Screat and reflex Scys are utilized to support differentiation of AKI from DICI.

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

11.5.2. Age-Specific Kidney Function Calculation Recommendations

At Screening, eGFR will be calculated using 2021 CKD-EPI eGFR equations (for adults 18 years and above), eCrCl will be calculated using Cockcroft-Gault formula (for adolescents 12 to <18 years), and eGFR will be calculated using Modified Schwartz Equation (for children 2 to <12 years), or Bedside Schwartz equation (for infants 6 months to <2 years).

11.5.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations (Inker, Eneanya et al. 2021)

eGFR (mL/min/1.73m²)

2021 CKD-EPI Screat Only	Screat *(mg/dL)*	Scys *(mg/L)*	Recommended eGFR Equation
Female	if ≤0.7	NA	$eGFR = 143 \times (Screat/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if >0.7	NA	$eGFR = 143 \times (Screat/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ≤0.9	NA	$eGFR = 142 \times (Screat/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if >0.9	NA	$eGFR = 142 \times (Screat/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Screat-Scys Combined	**Screat *(mg/dL)***	**Scys *(mg/L)***	**Recommended eGFR Equation**

Female	if ≤0.7	if ≤0.8	$eGFR = 130 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ≤0.7	if >0.8	$eGFR = 130 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if >0.7	if ≤0.8	$eGFR = 130 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if >0.7	if >0.8	$eGFR = 130 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ≤0.9	if ≤0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ≤0.9	if >0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if >0.9	if ≤0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if >0.9	if >0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

11.5.2.2. Adolescents (12 Years to <18 Years) — Cockcroft-Gault Formula

eCrCl (mL/min)

Males: eCrCl = [(140 - age) × body weight (in kg)] / [Screat (in mg/dL) × 72]

Females: eCrCl = 0.85 × [(140 - age) × body weight (in kg)] / [Screat (in mg/dL) × 72]

11.5.2.3. Children (2 Years to <12 Years) — (Modified) Schwartz Equation

eCrCl normalized to BSA (mL/min/1.73 m^2)

eCrCl = (K × Ht) / Screat

Ht in cm; Screat in mg/dL.

K (proportionality constant): Female child <12 years: K = 0.55. Male child <12 years: K = 0.70.

11.5.2.4. Infants (1 Month to <2 Years) and Neonates (<1 Month) — (Bedside) Schwartz Equation

eGFR (mL/min/1.73 m^2) = 0.413 × (Ht/Screat)

Ht in cm; Screat in mg/dL.

11.5.3. Kidney Function Calculation Tools

The sponsor has provided the following resources to investigational sites when required to calculate age-specific kidney function at Screening, Baseline, and post-Baseline visits. Site calculations of kidney function can be performed manually, using the age appropriate formulae (see Section 11.5.2) and can use recommended online kidney function calculators to reduce the likelihood of a calculation error.

The United States National Kidney Foundation Online Calculators.

- Adults (18 years and above) - 2021 CKD-EPI Creatinine Online Calculator (eGFR): https://www.kidney.org/professionals/KDOQI/gfr_calculator

- Adolescents (12 years to <18 years) - Cockcroft-Gault Formula (eCrCl): https://www.kidney.org/professionals/kdoqi/gfr_calculatorCoc

- Investigational sites are responsible to ensure that the accurate age-specific equation is selected and that the correct units are used for serum creatinine (mg/dL only), serum cystatin C (mg/L only), total body weight (kg only), and age (years). Investigators are expected to (i) review and confirm correctness of the kidney function calculation results and (ii) evaluate the calculated value within the context of historical information available to them in the participant's medical record. Investigators are responsible for the clinical oversight of the participant eligibility process, kidney function calculation, and dose selection and adjustments per study protocol. Investigators are encouraged to direct questions or uncertainties regarding kidney function and dosing to the Pfizer Clinical Team and Medical Monitor, if needed.

11.5.4. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to CTCAE criteria for both pediatric and adult participants.

CTCAE Term (2017)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
AKI	NA	NA	Hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
AKI: A disorder characterized by acute loss of kidney function (within 2 weeks) and is traditionally classified as pre-renal (low blood flow into kidneys), renal (kidney damage), or post-renal causes (ureteral or bladder outflow obstruction.					
Creatinine increased	>ULN to 1.5 x ULN	>1.5 to 3.0 x baseline OR >1.5 to 3.0 x ULN	>3.0 to 6.0 x baseline OR >3.0 to 6.0 x ULN	>6.0 x ULN	NA
CKD	eGFR ≥60 to 89 mL/min/1.73m² OR eCrCl ≥60 to 80 mL/min	eGFR 30 to 59 mL/min/1.73m² OR eCrCl 30 to 59 mL/min	eGFR 15 to 29 mL/min/1.73m² OR eCrCl 15 to 29 mL/min	eGFR <15 mL/min/1.73m² OR eCrCl <15 mL/min OR dialysis indicated	Death
Proteinuria	ADULTS: Proteinuria 1+ OR Proteinuria >0.5 to <1.0 g/24 h	ADULTS: Proteinuria 2+ or 3+ OR Proteinuria 1.0 to <3.5 g/24 h PEDIATRICS: Urine Protein-	ADULTS: Proteinuria 4+ OR Proteinuria ≥3.5 g/24 h PEDIATRICS: Urine Protein-to-Creatinine	NA	NA

CTCAE Term (2017)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
		to-Creatinine Ratio (UPCR) 0.5 to 1.9	Ratio (UPCR) >1.9		

CKD: A disorder characterized by gradual and usually permanent loss of kidney function resulting in kidney failure.

11.6. Appendix 4: Prohibited and Restricted Concomitant Medications That May Result in DDI

The prohibited concomitant medications listed below (Table 17) should not be taken with osivelotor for the period of time at least equal to the required washout period listed in the table and throughout the conduct of the study. Restricted concomitant medications may be used but with the following restrictions (Table 18).

The Pfizer study team is to be notified of any prohibited or restricted medications taken during the study. After consulting with the sponsor, the investigator will make a judgment on the ongoing participation of any participant with prohibited or restricted medication use during the study.

This list of drugs prohibited and restricted for potential DDI concerns with the IMP may be revised during the course of the study with written notification from the sponsor to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs) if the overall benefit/risk assessment is not impacted or if the changes do not significantly impact the safety of participants or the scientific value of the trial.

This is not an all-inclusive list. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Table 17. Examples of Prohibited Concomitant Medications

Drug Category	Drugs	Washout Period Requirement Prior to First Dose of Osivelotor
Herbal Preparations and Dietary Supplements	Preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. Note: prescription or nonprescription vitamins are an exception	14 days prior to first dose of osivelotor
CCI [redacted]		5 elimination half-lives or 14 days, whichever is longer

Table 17. Examples of Prohibited Concomitant Medications

Drug Category	Drugs	Washout Period Requirement Prior to First Dose of Osivelotor
CCI [redacted]		
		5 elimination half-lives or 14 days, whichever is longer
		5 elimination half-lives or 14 days, whichever is longer
Prohibited Juices	Participants are not permitted to consume grapefruit, grapefruit juice, and/or Seville oranges	14 days prior to first dose of osivelotor

Abbreviations: CCI [redacted]
Note: This is not an exhaustive list. Country-specific lists may be used if available.
For an updated list, refer to the following link: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

Table 18. Examples of Restricted Concomitant Medications

Drug Category	Drugs	Restrictions
CCI [redacted]		Osivelotor must be administered at least 4 hours before CCI [redacted] are administered
		Participants should avoid sensitive CCI [redacted] If not possible, consider dose adjustment.
		Use caution with sensitive CCI [redacted] and consider dose adjustment, as needed.

Abbreviations: CCI [redacted]
Note: **This is not an exhaustive list.** Country-specific lists may be used if available.
For an updated list, refer to the following link: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use.

11.7. Appendix 5: 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 amendments can be found below:

Amendment 3.0 (22 June 2023)

Change	Rationale	Section(s) affected
Removed the personal identifiable information for the sponsor's medical officer from the title page and removed the statement of approval and compliance	Per pfizer protocol templates, there should be no personal identifiable information in the protocol. That information will be documented separately.	Title page Statement of approval and compliance
Increased the number of study sites to approximately 60 globally	For consistency with the number of sites in the originating studies	Synopsis
Added promis sf-fatigue 13a, promis sf-pain interference 8a, promis numeric rating scale-pain intensity, euroqol eq-5d-5l, and work productivity and activity impairment assessments to the quality-of-life assessments	This information is being collected in the originating study (gbt021601-021) and will continue to be collected in the open-label extension study to monitor patient reported outcomes	Synopsis Schedule of assessments and procedures Section 3 Section 8.8
Added specific detail that the pgi-c and pgi-s assessments will be for fatigue and pain, and that the cgi-c and cgi-s assessments will be for scd	For consistency with the originating study	Synopsis Schedule of assessments and procedures Section 3 Section 8.8
Revised the outcome measure of "trough and 1- to 2-hour blood and plasma concentrations" to "blood and plasma concentrations"	To provide for assessment of pk at various time points as outlined in the schedule of assessments	Synopsis Schedule of assessments and procedures Section 3
Added that events representing scd-related complications such as vaso-occlusive crisis (voc), (ie, acute chest syndrome (acs), hepatic sequestration, splenic sequestration, priapism, and dactylitis) will also be reported as measures of efficacy	For clarity on the measures of efficacy	Synopsis Section 8.2
Removed the criteria that if the day 1 visit does not occur on the same day as the end of treatment visit from the originating study, the day 1 visit must occur within 30 calendar days of completion of the originating study	There have been site activation delays that limited the ability of participants to enroll in the open label extension study so in order to allow those participants to	Synopsis Schedule of assessments and procedures Section 4.1

Change	Rationale	Section(s) affected
	continue on study drug, the 30-day window is being removed	Section 5.1
Added that if during the period between day 1 of this study and completion of the originating study, no dose is received for greater than 3 consecutive days, an appropriate loading dose should be administered prior to continued maintenance dosing	Blood concentration of drug will drop below steady state levels following a gap in dosing. In order to bring participants back up to steady state levels (the therapeutic window), a new loading dose will be administered	Synopsis Section 2.2 Section 4.1 Section 4.3 Appendix 1
Added a visit at week 1 (the end of the loading dose period) for participants with a gap in dosing >42 consecutive days from completing the originating study	To dispense new study drug and switch from the loading dose to the maintenance dose	Synopsis Schedule of assessments and procedures Section 4.1 Section 8.2
Added to the inclusion criteria 1 that participants who completed treatment from the originating study but were not able to rollover into study gbt021601-022 due to a delay in study site activation will be eligible provided other eligibility criteria are met	For consistency with the removal of the requirement to have been on the previous study within 30 calendar days	Synopsis Section 5.1
Revised the pregnancy testing to be a urine test at baseline unless there is a delay in start of ole of >7 days (in which case a serum pregnancy test would be administered)	To clarify that serum pregnancy tests are only required if there is a gap of >7 days in start of ole or to confirm a positive urine test	Schedule of assessments and procedures
Added a qualitative interview to the quality-of-life measurements which will be conducted with participants by telephone or online/web conference at the baseline visit	To collect data regarding participants' disease- and treatment-related experiences	Schedule of assessments and procedures Section 8.8
Added that additional nonclinical information can be found in the investigator brochure	For clarity on where to find more information	Section 2.1
Updated the clinical experience section	To provide more up to date information on the clinical studies	Section 2.1
Added individual level stopping rules for participants rolling over from the 200 mg treatment arm from part a of study gbt021601-021	For consistency with the originating study	Section 6.5.1
Revised the language in the treatment of overdose	For consistency with pfizer processes	Section 6.6

Change	Rationale	Section(s) affected
Added a table with examples of prohibited or restricted concomitant medications	For clarity	Section 6.7.1 table 9
Added a section regarding environmental exposure, exposure during pregnancy or breastfeeding, occupational exposure, and medication errors	For consistency with pfizer processes and for additional clarify	Section 8.4.13 Section 8.4.13.1 Section 8.4.13.2 Section 8.4.13.3 Section 8.4.14
Added to the outcome measures "it is intended that day 1 coincides with the final visit from the originating gbt021601 study. End of treatment (eot) assessments from the originating study will serve as baseline assessments for this study. If day 1 for this study is greater than 7 days from the completion of the originating study, new baseline assessments will be obtained. Additional assessments that may not have been included in the prior eot assessments are outlined in the schedule of assessments and will need to be completed prior to study drug administration."	To clarify that there are two potential baseline assessments (either from the originating study, or at the start of the ole)	Section 9.2.1
Added a section on reporting of safety issues and serious breaches of protocol	For consistency with pfizer processes and for additional clarify	Section 10.1.3
Revised the informed consent process, data protection, dissemination of clinical study data, data quality assurance, study and site start and closure, publication policy, sponsor's medically qualified individual	For consistency with pfizer template language and processes	Section 10.1.4 Section 10.1.5 Section 10.1.6 Section 10.1.7 Section 10.1.8 Section 10.1.9 Section 10.1.10
Updated appendix 1 guidelines for dose for participants rolling over with a gap in dosing	For additional clarity on dose information	Appendix 1
Added appendix 2 on liver safety	To provide guidance on monitoring, reporting, and managing potential drug-induced liver injury	Appendix 2

Abbreviations: pgi-c, patient global impression of change; pgi-s, patient global impression of severity; promis, patient-reported outcome measurement information system; scd, sickle cell disease; sf, short form.

Amendment 2.0 (11 Oct 2022)

Change	Rationale	Section(s) affected
Changed the sponsor contact from PPD to PPD .	Dr. PPD is the new clinical science lead for the gbt021601-022 study.	Title page Statement of approval and signature
Increased the frequency of study visits for participants rolling into the gbt021601-022 study from the gbt021601-012 study.	Due to quality issues at the site of the gbt021601-012 study, additional visits and assessments for these participants rolling into the open label extension study from the gbt021601-012 study were included to closely monitor the safety and pk of the participants.	Section 1.1 Section 1.2 Section 2.2 Section 2.3 Section 4.1 Section 4.3 Section 8.2 Appendix 1 – table 12
Updated the test product information from gbt021601 may be provided as a coated dispersible tablet to "an appropriate oral formulation for pediatric participants who cannot swallow the regular tablet"	The pediatric formulation is still being developed.	Section 1.1 Section 6.1
Revised the serious adverse event reporting from paper forms to the electronic case report forms via the electronic data capture system.	All adverse event reporting should now be captured electronically to minimize error.	Section 8.4.6

Amendment 1.0 (19 July 2022)

Change	Rationale	Section(s) affected
Revised the baseline visit to coincide with the day 1 visit and added clarification language to assessments done at that visit.	It is intended for the day 1 baseline visit to coincide with the final visit from the originating gbt021601 study.	Section 1.1 synopsis Section 1.2 schedule of assessments (table 1, table 2, table 3) Section 4.1 overall design

11.8. Appendix 6: Abbreviations

Abbreviation	Term
A1 to A3	albuminuria (KDIGO albuminuria severity standardization)
ACS	acute chest syndrome
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BID	twice daily
BSA	body surface area
CBD	cannabidiol
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CCI	[redacted]
DDI	drug-drug interaction
DICI	drug-induced creatinine increase
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
DSM-V	Criteria for Substance Use Disorders
EC	Ethics Committee
ECC	Emergency Contact Card
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding

Abbreviation	Term
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EMEA	Europe, Middle East, and Africa
EOS	end of study
EOT	end of treatment
EPO	erythropoietin
ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GBT	Global Blood Therapeutics, Inc
GCP	Good Clinical Practice
h	hour
Hb	hemoglobin
HbS	sickle hemoglobin
HIV	human immunodeficiency virus
HRQOL	Health-related quality of life
HSCT	hematopoietic stem cell transplantation
Ht	height
HU	hydroxyurea
IB	Investigator's Brochure
ICE	Intercurrent events
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IND	Investigational New Drug
IMP	Investigational medicinal product

Abbreviation	Term
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive response technology
K	Proportionality constant
LDH	lactate dehydrogenase
LFT	liver function test
MAD	Multiple ascending dose
MOA	Mechanism of action
MQI	Medically Qualified Individual
NA	Not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIRS	near infrared spectroscop
NIMP/AxMP	Non Investigational Medicinal Product/Auxiliary Medicinal Product
NRS	numeric rating scale
NSAIDs	nonsteroidal anti-inflammatory drugs
CCI [redacted]	
OLE	open-label extension
Oxy-Hb	Oxygen-hemoglobin
PACL	Protocol Administrative Change Letter
PD	pharmacodynamic
PE	Physical examination
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
CCI [redacted]	
PIP	Pediatric Investigation Plan
PK	pharmacokinetic
PPK	population pharmacokinetic
PRO	Patient-Reported Outcome
PROMIS	Patient-Reported Outcome Measurement Information System
PSP	Pediatric Study Plan
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time

Abbreviation	Term
QD	once daily
QTLs	Quality tolerance limits
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	sickle cell
SCD	sickle cell disease
Screat	serum creatinine
Scys	serum cystatin C
SF	short form
SoA	schedule of assessments
SOC	Standard of care
SRSD	Single Reference Safety Document
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	Half-life
T bili	total bilirubin
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time of maximum concentration
TME	targeted medical events
ULN	upper limit of normal
US	United States
VOC	vaso-occlusive crisis
WPAI+CIQ:SCD	Work Productivity and Activity Impairment plus Classroom Impairment Questionnaire: Sickle Cell Disease v2.0

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