CLINICAL STUDY REPORT SYNOPSIS

Study Title:	A Phase 2/3 Randomized, Multicenter Study of Osivelotor Administered Orally to Participants With Sickle Cell Disease and an Open-Label Pharmacokinetics Study in Pediatric Participants With Sickle Cell Disease
Study Number:	C5351004
Study Phase:	2/3
Regulatory Agency or Public Disclosure Identifier Number:	NCT #: NCT05431088 EU CT #: 2023-508766-14-00
Pediatric Investigational Plan Number:	EMEA-003241-PIP01-22
Study Intervention:	PF-07940367 or GBT021601 (Osivelotor)
Trade Name	Not Available
Indication:	Sickle Cell Disease
Study Sponsor:	Global Blood Therapeutics, Inc. a wholly owned subsidiary of Pfizer 181 Oyster Point Blvd. South San Francisco, CA 94080 USA
Study Initiation Date (FPFV):	22 Sep 2022
Primary Completion Date (PCD):	NA
Presentation of data in this CSR synopsis based on Interim Data Cutoff Date:	The analyses presented in this report are based on a database lock date of 16 May 2025
CSR Version and Report Date:	**Document Version**: Part A Interim CSR Version 1.0 — **Report Date**: 12 October 2025

GOOD CLINICAL PRACTICE STATEMENT

This study was conducted in compliance with GCP guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct, including the archiving of essential documents.

Number of Study Center(s) and Investigator(s):

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A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications:

Refer to Appendix 16.1.11 for the list of publications.

BRIEF DESCRIPTION OF THE TRIAL DESIGN AND METHODOLOGY

Part A (Adult Participants):

Part A was a Phase 2, randomized, open-label, dose-finding study to determine the optimal dose of osivelotor with 12 weeks of treatment in participants with SCD. The primary endpoint of Part A was the change from baseline in Hb.

In Part A, after the ICD was signed, adult participants were assessed for study eligibility during a 28-day Screening Period. On study Day 1, eligible participants were randomized based on a 1:1 (osivelotor 100 mg: osivelotor 150 mg) allocation and received a loading dose regimen of osivelotor (participants on 100 mg arm received 200 mg BID and participants on 150 mg arm received 300 mg BID, approximately 12 hours apart) over the first 4 days. Participants then received maintenance daily doses through Week 12.

Part A Substudy 2: Assessed whether there was benefit to a 200 mg dose level as well as explored exposure-response and safety at higher exposures, up to approximately 10 participants were to be enrolled in Substudy 2 (at selected sites) and were administered a once daily loading dose of 300 mg for 14 days followed by 200 mg once daily maintenance dose for another 10 weeks (through Week 12). At the time of this interim CSR for Part A, 3 participants had been enrolled and completed the 200 mg Substudy 2.

Number of Participants (planned and analyzed)

Table S1. Number of Participants (Planned and Analyzed)

Population	N	Definition
ITT	57	All randomized participants regardless of whether or not study drug was administered. Participants will be analyzed according to the dose arm to which they are assigned at randomization. **For Substudy 2:** All participants who sign the informed consent and enroll in Substudy 2 regardless of whether or not study drug was administered.
mITT	57	All randomized participants who received at least one dose of study drug and have at least one post baseline measurement. (Note: Post-baseline measurement is determined based on exposure, vital signs and lab data) Participants will be analyzed according to the dose arm to which they are assigned at randomization. **For Substudy 2:** All participants who sign the informed consent and enroll in Substudy 2 and received at least one dose of study drug and have at least one post baseline measurement.

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Table S1. Number of Participants (Planned and Analyzed)

Population	N	Definition
Safety	57	All participants who received at least one dose of study drug. Participants will be analyzed according to the study drug they actually received.
PK	57	All randomized participants who received at least one dose of study drug and have at least one concentration data point (plasma or whole blood) post dose. **For Substudy 2:** All enrolled participants who received at least one dose of study drug and have at least one concentration data point (plasma or whole blood) post dose.
PD	57	All randomized participants who received at least one dose of study drug and who have at least one PD assessment post dose. **For Substudy 2:** All enrolled participants who received at least one dose of study drug and who have at least one PD assessment post dose.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Key Inclusion Criteria (Part A):

1. Participant with SCD. Documentation of SCD genotype homozygous for sickle cell allele (HbSS) or double heterozygote for sickle hemoglobin (HbS) and β-0 thalassemia (HbSB) may be based on history of laboratory testing or must be confirmed by laboratory testing during Screening.
2. Hb ≥ 5.5 and ≤ 10.5 g/dL during Screening and considered stable by the Investigator.
3. For participants taking HU and/or L-glutamine, the dose must be stable for at least 90 days prior to signing the ICF or assent and with no anticipated need for dose adjustments during the study in the opinion of the Investigator.
4. Female participants of child-bearing potential must agree to use a highly effective method of contraception or practice abstinence from study start to 120 days after the last dose of study drug.
5. Female participants of child-bearing potential must have a negative pregnancy test before administration of study drug.
6. Age 18 to ≤65 years, inclusive at Screening.

Key Exclusion Criteria (Part A):

1. More than 10 VOCs within 12 months of Screening.
2. Female participant who is breastfeeding or pregnant.
3. Receiving regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventive transfusion) or has received an RBC or exchange transfusion for any reason within 90 days of Day 1.
4. Hospitalized for sickle cell crisis or other vaso-occlusive event within 14 days of signing the ICF.
5. Screening laboratory test of ALT > 4 × ULN for age.

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Study Interventions

The maximum duration of the study for adult participants in Part A was approximately 25 weeks (for main study and Substudy 1) or approximately 29 weeks for Substudy 2. Substudy 1 evaluated RBC lifespan through endogenous carbon monoxide levels and Substudy 2 evaluated a 200 mg maintenance dose. This includes a 28-day (4-week) Screening period, up to a 12-week Treatment period, and a follow-up period. Participants in the main study and Substudy 1 not enrolling in OLE were followed by an EOS visit 9 weeks after completion of treatment. Substudy 2 participants not enrolling in OLE had an EOS Visit 12 weeks after completion of treatment.

After the ICD was signed, participants were screened for eligibility in the study from Day -28 through Day -1. Eligible participants were randomized on Day 1 based on a 1:1 (osivelotor 100 mg: osivelotor 150 mg) allocation and received their initial dose (loading dose) at the clinical site.

As of Protocol Amendment 3, the SMC recommended that participants continue to be randomized in a 1:1 manner (osivelotor 100 mg: osivelotor 150 mg) and that Substudy 2 be included to evaluate the benefit of a 200 mg daily maintenance dosing at select sites. At the time of this interim CSR, 3 participants completed Substudy 2 and no additional participants were enrolled in this substudy.

Table S2. Study Intervention Lot Numbers

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/Potency	Dosage Form
PF-07940367 (GBT021601) 100 mg Tablet	21-0149	N/A	100 mg	TABLET
PF-07940367 (GBT021601) 25 mg Tablet	21-0148	N/A	25 mg	TABLET
PF-07940367 (GBT021601) 100 mg Tablet	22-0112	N/A	100 mg	TABLET
PF-07940367 (GBT021601) 100 mg Tablet	21-0073	N/A	100 mg	TABLET
PF-07940367 (GBT021601) 25 mg Tablet	21-0071	N/A	25 mg	TABLET

Global Substantial Modifications

Table S3. Global Substantial Protocol Modifications Relevant to Part A

Date of Protocol Amendment	Amendment
Amendment 8 (France/Germany country-specific 17 Jul 2024)	Not implemented globally. No participants enrolled under Amendment 8.

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Table S3. Global Substantial Protocol Modifications Relevant to Part A

Date of Protocol Amendment	Amendment
Amendment 7 (MHRA UK country-specific 21 May 2024)	Not implemented globally. No participants enrolled under Amendment 7.
Amendment 6 (Current Global Protocol – 08 Feb 2024)	Added male contraception requirement and sperm donation restriction for Part B and C participants.
Amendment 5 (11 Dec 2023)	Updated contraception/abstinence requirement to extend from study start to 120 days and update to estimands.
Amendment 4.0 (01 Nov 2023)	Changed follow-up for participants in Part A Substudy 2 from 8 to 12 weeks. Statistical analysis/estimands for Part A revised. Added randomization stratification by geographic region.
Amendment 3.0 (23 May 2023)	Added Substudy 2 to Part A, minor revisions the secondary endpoints for Part A, revised the duration of study participation from Part A
Amendment 2.0 (10 Jan 2023)	Added a substudy to Part A to measure RBC lifespan, added language defining non-responder, updated the language around reporting SAEs to align with Pfizer standards
Amendment 1.0 (25 Feb 2022)	Revised the study design in Part A to a dose-finding study in up to 60 adult participants with 12 weeks of treatment. Revised the wording of the primary objective and primary endpoint. Revised the secondary objective and secondary endpoints. Revised the Duration of Study Participation. Increased the number of participants. Revised the Exclusion criteria. Updated the Dose Stopping Rules, the planned sample size and statistical analysis. Revised the duration of treatment.

Global Interruptions and re-starts

Not applicable

ENDPOINTS AND STATISTICAL METHODS

Table S4. Objectives, Endpoints, and Statistical Methods

Objectives	Endpoints	Analysis Type	Analysis Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Primary					
Part A: To assess the effects of osivelotor in adult participants with SCD as measured by change in Hb.	Change from baseline in Hb through Week 12.	Primary efficacy analysis and Subgroup analysis	mITT	• Early study treatment discontinuation: Analyzed data as collected. • New post-randomization HU use with no HU use at baseline, post-randomization transfusion, use of prohibited and/or restricted medications known to affect Hb/VOC: Hb measurements on or post the start date of these therapies were not included.	Descriptive Summary and MMRM
	Change from baseline in Hb	Sensitivity analysis	mITT	• Early study treatment discontinuation: Hb measurements post 3 days after	Descriptive Summary

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Table S4. Objectives, Endpoints, and Statistical Methods

Objectives	Endpoints	Analysis Type	Analysis Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
	through Week 12.			last study treatment dose were not included. • For participants who complete study treatment, Hb measurements post 3 days after last study treatment dose were not included. • New post-randomization HU use with no HU use at baseline, post-randomization transfusion, use of prohibited and/or restricted medications known to affect Hb/VOC: Hb measurements on or post the start date of these therapies were not included.	and MMRM
Secondary					
Part A: To evaluate the effects of osivelotor on Hb and clinical measures of hemolysis. To evaluate the safety and tolerability as well as the PK and PD properties of multiple dose osivelotor administration.	Proportion of participants with an increase from baseline of >1 g/dL in Hb through Week 12	Secondary analysis	mITT	This analysis excluded measurements on or after the start date of: new HU use post-randomization with no HU use at baseline, post-randomization transfusion, post-randomization use of prohibited and/or restricted medications known to affect Hb/VOC.	Descriptive summary and 95% CI using Clopper Pearson exact method
	Incidence of TEAEs, changes in laboratory assessments, ECGs, and vital signs	Secondary analysis	Safety	NA	Descriptive summary
	Change from baseline through Week 12 in hemolysis measures including indirect bilirubin, absolute reticulocytes, % reticulocytes and LDH	Secondary analysis	mITT	• Early study treatment discontinuation: Analyzed data as collected. • New post-randomization HU use with no HU use at baseline, post-randomization transfusion, use of prohibited and/or restricted medications known to affect Hb/VOC: Hb measurements on or post the start date of these therapies were not included.	Descriptive Summary and MMRM
	AUC_{0-8}, AUC_{0-24}, C_{max}, T_{max} for plasma and whole blood PK concentrations. The B:P ratio based on AUC_{0-8}, AUC_{0-24}, and	Secondary analysis	PK	• Missing PK data were not imputed • BLQ values will be treated as zero	Descriptive summary

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Table S4. Objectives, Endpoints, and Statistical Methods

Objectives	Endpoints	Analysis Type	Analysis Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
	C_{max}. C_{min} and B:P ratio based on C_{min} after multiple dose administration				
	% Hb occupancy through Week 12	Secondary analysis	PK	Missing data were not imputed	Descriptive summary
	Hb OEC as measured by p20 and p50 through Week 12	Secondary analysis	PD	NA	Descriptive summary
VOC Exploratory					
Part A: To evaluate the effects of osivelotor on VOCs	Annualized rate of VOC through Week 12	Exploratory analysis	mITT	For on-treatment analysis: • Excluded data after treatment end date. • Excluded data after start of new post randomization HU use with no HU use at baseline, start of prohibited and/or restricted concomitant medications known to affect Hb/VOC post randomization, exchange transfusion date.	Descriptive summary and Negative Binomial Model

SUMMARY OF RESULTS

Participant Disposition

A total of 57 participants were enrolled at 8 centers in 2 countries (Nigeria and US) for Part A.

Of the 57 participants who enrolled in Part A, 53 participants completed treatment and 4 discontinued.

- 7.0% (4/57) of all participants discontinued from treatment in Part A; 7.4% (2/27) in the 100 mg dose group, 7.4% (2/27) in the 150 mg dose group, and none (0/3) in the 200 mg dose group.
  - 2 participants discontinued treatment due to adverse events in the 100 mg dose group.
  - 1 participant discontinued treatment due to an adverse event and 1 participant discontinued treatment due to being lost to follow-up in 150 mg dose group.

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Demographic and Other Baseline Characteristics

Demographic and baseline characteristics were generally similar across treatment groups for the mITT population in Part A.

- The mean (min, max) age of all Part A participants (N=57) was 28.7 (18, 61) years; 28.4 (18, 53) years in 100 mg dose group, 28.2 (18, 59) years in the 150 mg dose group, and 36.0 (20, 61) years in the 200 mg dose group.
- 56.1% (32/57) of all Part A participants were female; 51.9% (14/27) in 100 mg dose group, 59.3% (16/27) in 150 mg dose group, 66.7% (2/3) in 200 mg dose group.
- All participants in Part A were African, Black, or African American.
- 73.7% (42/57) of all Part A participants were from Subsaharan Africa (SSA) compared to 26.3% (15/57) from North America; 77.8% (21/27) from SSA versus 22.2% (6/27) from North America in 100 mg dose group, 77.8% (21/27) from SSA versus 22.2% (6/27) from North America in 150 mg dose group, 0% (0/3) from SSA versus 100% (3/3) from North America in 200 mg dose group.
- Most participants (96.5% [55/57]) were of HbSS genotype.
- 36.8% (21/57) of participants were using HU at screening.
- VOCs within the past 12 months before screening:
  - 28.1% (16/57) of participants had no VOCs.
  - 71.9% (41/57) of participants had VOCs.
  - The pre-screening annualized VOC incidence rate was 1.82.
  - 68.4% (39/57)] experienced at least one acute painful crisis (uncomplicated).

Exposure

Osivelotor exposure in Part A safety population: Mean (min, max) treatment duration was similar across all dose groups: 12.0 weeks (10.1, 12.6) for the 100 mg dose group (N=27), 11.7 weeks (1.0, 13.1) for the 150 mg dose group (N=27), and 11.9 weeks (11.7, 12.1) for the 200 mg dose group (N=3). Note: For the 200 mg dose group, 2 out of 3 participants had a dose reduction.

Summary of Key Efficacy/VOC/Safety/PK/PD Results

Table S5. Summary of Key Efficacy/VOC/Safety/PK/PD Results

Endpoints	Results
Primary	
Change from baseline in Hb through Week 12	Hb change from baseline data suggest that osivelotor has the potential for robust, dose-dependent, and sustained efficacy.

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Table S5. Summary of Key Efficacy/VOC/Safety/PK/PD Results

Endpoints	Results
	Osivelotor achieved an increase in Hb through Week 12 compared to baseline. • For all osivelotor dose groups in Part A: Hb increase over baseline was observed as early as Week 1, the mean change from baseline was over 2 g/dL by Week 2 [MMRM point estimates (95% CI) for 100 mg (n=25): 2.34 g/dL (1.91, 2.77); 150 mg (n=25): 3.08 g/dL (2.65, 3.52)] [descriptive mean (min, max) for 200 mg (n=3): 3.37 (2.70, 4.30)], and Hb levels were maintained through Week 12 with minor fluctuations [MMRM point estimates (95% CI) for 100 mg (n=24) : 2.58 g/dL (2.05, 3.11); 150 mg (n=23): 3.35 g/dL (2.81, 3.89)] [descriptive mean (min, max) for 200 mg (n=3): 4.17 (2.90, 6.50)]. • Subgroup analyses were consistent with those of the primary analysis. • Sensitivity analyses were consistent with those of the primary analysis.
Secondary	
Proportion of participants with an increase from baseline of >1 g/dL in Hb through Week 12	Hb response (an increase in Hb from baseline by >1 g/dL) was observed as early as Week 1 for all dose groups. By Week 2, most participants were responders, and the response was maintained through Week 12 (EOT). In the combined 100+150 mg osivelotor group, 72.2%, 96.0%, and 95.7% of participants were Hb responders at Week 1, Week 2, and Week 12, respectively.
Incidence of TEAEs, changes in laboratory assessments, ECGs, and vital signs	Osivelotor was generally safe and well-tolerated. • Overall, most participants' TEAEs were of Grade 1 [22.8% (13/57)] or Grade 2 [38.6% (22/57)] maximum severity in Part A; 7 (12.3%) participants had a Grade 3 event, 1 (1.8%) participant had a Grade 4 event, and 2 (3.5%) participants had a Grade 5 event. • 17.5% (10/57) of participants had treatment-related TEAEs with 18.5% (5/27) and 14.8% (4/27) of participants in the 100 mg and 150 mg osivelotor dose groups respectively and 33.3% (1/3) of participants in the 200 mg dose group. • A higher percentage of participants in the 100 mg dose group (25.9% [7/27]) had at least one treatment-emergent SAE, than in the 150 mg dose group (7.4% [2/27]). 1 out of 3 participants had at least one treatment-emergent SAE in the 200 mg dose group. • Overall, 5.3% (3/57) of participants experienced a TEAE leading to study treatment discontinuation: 2 participants (7.4%) in the 100 mg dose group due to Malaria and Sepsis (one participant each), and 1 participant (3.7%) in the 150 mg dose group due to Malaria and Cerebrovascular accident. • Overall, one participant (1.8%) out of 57 experienced a treatment-related SAE of Atrial fibrillation which was reported in the 200 mg osivelotor dose group. No participants in the 100 or 150 mg dose groups experience a treatment-related SAE.

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Table S5. Summary of Key Efficacy/VOC/Safety/PK/PD Results

Endpoints	Results
	• Laboratory abnormalities reported as TEAEs were infrequent, typically Grade 1 or Grade 2 and in general were consistent with SCD-related conditions. None were treatment related. • With the exception of Hb and measures of hemolysis (% reticulocyte, absolute reticulocytes, indirect bilirubin and LDH), mean changes from baseline over time in laboratory values observed through Week 12 were generally small and not clinically meaningful. • There were no clinically meaningful findings in vital sign measurements, liver function (including potential Hy's Law cases), or eGFR (kidney function). No clinically meaningful ECG findings in the 100 and 150 mg dose groups. 1 SAE of Atrial fibrillation occurred in the 200 mg group.
Change from baseline through Week 12 in hemolysis measures including indirect bilirubin, absolute reticulocytes, % reticulocytes, and LDH.	Osivelotor resulted in a favorable decreasing trend over time through Week 12 for hemolysis markers (indirect bilirubin, LDH, reticulocytes, and % reticulocytes).
AUC_{0-8}, AUC_{0-24}, C_{max}, T_{max} for plasma and whole blood PK concentrations. The B:P ratio based on $AUC_{0-8,}$ AUC_{0-24}, and C_{max}. C_{min} and B:P ratio based on C_{min} after multiple dose administration.	Dose-dependent increases in osivelotor PK exposure were observed.
% Hb occupancy through Week 12	Dose-dependent increases in % Hb occupancy were observed following treatment with osivelotor.
Hb OEC as measured by p20 and p50	Osivelotor treatment dose-dependently decreased p20 and p50, demonstrating a leftward shift in the OEC. These changes indicate an increase in Hb-O_2 affinity, confirming the pharmacodynamic activity of osivelotor.
VOC Exploratory	
Annualized rate of VOC through Week 12.	VOCs (total, uncomplicated, and complicated), and model-based annualized VOC rate: Combined 100+150 mg osivelotor (N=54): • Participants with VOCs: 25.9% (14/54) • Total VOCs: 17 (16 uncomplicated and 1 complicated) • Model-based annualized VOC rate: 1.33 events/year (95% CI: 0.79, 2.22) 200 mg osivelotor (N=3) • Participants with VOCs: 33.3% (1/3) • Total VOCs: 1 (1 uncomplicated and 0 complicated) • Due to limited sample size, the model-based annualized VOC rate was not calculated for the 200 mg dose group

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Table S5. Summary of Key Efficacy/VOC/Safety/PK/PD Results

Endpoints	Results
	Based on an ad hoc analysis of the combined 100+150 mg osivelotor (N=54), there was no increase in VOCs after starting osivelotor treatment compared to the period before treatment initiation.

CONCLUSIONS

Treatment with osivelotor in Study C5351004 Part A resulted in an increase in Hb and amelioration of hemolysis, with no increased risk for VOCs, and an acceptable safety profile (limited off-target effects).

Limitations and Caveats

This interim report includes all data from Part A and was prepared using summary data from a database lock of 16 May 2025. The data presented represent the latest data as of the time of report preparation. Part B of the study is ongoing, and a final report will be written for Part B after completion of the study.

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AUC	area under the concentration-time curve
AUC_{0-8}	AUC from time 0 to 8 hours following the first dose
AUC_{0-24}	AUC from time 0 to 24 hours following the first dose
B:P	blood to plasma ratio
BID	twice a day
BLQ	below limit of quantification
CI	confidence interval
C_{max}	maximum observed concentration
C_{min}	trough concentration
CSR	Clinical Study Report
ECG	electrocardiogram or electrocardiography
eCRF	electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
FPFV	first participant first visit
GCP	Good Clinical Practice
Hb	hemoglobin
HbS	hemoglobin S
HbSB-0	Hemoglobin β-0 thalassemia
HbSS	homozygous for sickle cell allele
HU	hydroxyurea
ICD	Informed Consent Document
ICF	informed consent form
ITT	intent-to-treat

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Abbreviation	Term
LDH	lactate dehydrogenase
MHRA	Medicines and Healthcare Products Regulatory Agency
mITT	modified intent-to-treat
MMRM	mixed-model for repeated measures
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
N	total number, total sample size
NA	not applicable
N/A	not available
No.	number
OEC	oxygen equilibrium curves
OLE	open-label extension
p20	partial pressure of oxygen at which hemoglobin is 20% saturated with oxygen
p50	partial pressure of oxygen at which hemoglobin is 50% saturated with oxygen
PCD	Primary Completion Date
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PSSA	Pfizer's Serious Adverse Event Submission Assistant
QC	quality control
QD	once daily
RBC	red blood cell
SAE	serious adverse event
SCD	sickle cell disease
SMC	Safety Monitoring Committee
SSA	Sub-saharan Africa
TCD	transcranial doppler
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
T_{max}	time to reach C_{max}
UK	United Kingdom
ULN	upper limit of normal
US	United States
VOC	Vaso Occlusive Crisis
vs	versus