biossil

14 February 2025

Re: Cover Letter for ClinicalTrials.gov NCT02187003

This Cover Letter accompanies the final Protocol (Amendment 3; 01 April 2019) for the completed trial, NCT02187003.

Sincerely,

Signed by:
Debora Manning
7131A55FBB88471...

Debora Manning, MPH
Head of Regulatory
Biossil Inc.
debora@biossil.ai

A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RIVIPANSEL (GMI-1070) IN THE TREATMENT OF VASO-OCCLUSIVE CRISIS IN HOSPITALIZED SUBJECTS WITH SICKLE CELL DISEASE

Compound:	PF-06460031
Compound Name:	GMI-1070, Rivipansel
United States (US) Investigational New Drug (IND) Number:	[redacted]
European Clinical Trial Database (EudraCT) Number:	Not Applicable (N/A)
Universal Trial Number:	N/A
Protocol Number:	B5201002
Phase:	Phase 3

[redacted]

Document History

Document	Version Date	Summary of Changes
Original Protocol	30 June 2014	N/A
Amendment 1	20 March 2015	- Added Pfizer Study B5201001 results to Introduction; [redacted] - Revised description of rivipansel drug product appearance; - Specified requirement for study drug filtration at preparation and administration; - Added that syringe filters will be supplied by the sponsor; [redacted] - Editorial changes throughout.
Amendment 2	13 July 2016	[redacted]

[redacted]

Document	Version Date	Summary of Changes
		- Clarified that Readiness-for-Discharge assessments will occur at regular pre-defined intervals during the daytime hours (6am to 10pm) and removed the requirement for routine assessments during the night-time hours (10pm to 6am). Indicated that an ad hoc assessment would be required if a subject is considered to have achieved readiness-for-discharge during the night-time hours; - Extended the period of time a subject is able to screen into the Open Label Extension Study (B5201003) to 180 days from last visit in B5201002; - Removed the option to sign consent for the Open Label Extension Study (B5201003) at hospital discharge in Study B5201002; - Added eligibility criterion excluding subjects currently receiving, or expected to receive, transdermal analgesics; - Added eligibility criterion excluding subjects who were previously randomized into the current study; - Clarified that the adjudication committees will only evaluate adverse events occurring from the time of the subject's first dose of study drug to the subject's last study visit; - Removed requirement to completely shroud the study drug IV infusion line with tinted tubing covers; - Updated information regarding the compatibility of rivipansel with other IV fluids; - Restructured the concomitant treatment section (Section 5.8) to include newly added prohibited medications (transdermal analgesics and systemic steroids [when used exclusively for treatment of uncomplicated VOC]) as well as to

Document	Version Date	Summary of Changes
		clearly present permitted medications; - Added the option for sites to use results from local laboratory tests, conducted per standard of care and obtained within 24 hours prior to informed consent, to determine the subject's eligibility; - Clarified in Section 6, Study Procedures, that a pregnancy test is required to be performed on all female subjects of childbearing potential; - Clarified that if the subject is experiencing a VOC or other acute SCD-related event, the Day 35 Post-Discharge Follow-Up visit should be delayed until the acute event has resolved; - Clarified requirement to obtain photographs and blood samples in the event of an acute rash or cutaneous manifestation; [redacted] [redacted] - Extended the reporting period for SAEs to the Pfizer Drug Safety Unit to include the subject's last study visit; [redacted] - Updated web-link to the Bedside Schwartz eGFR calculator; - Incorporated other minor clarifications and editorial changes throughout.
Amendment 3	01 April 2019	- Aligned abbreviations with protocol content

Document	Version Date	Summary of Changes
		- Updated Table 1 and the associated footnotes to align with the edits made in the body of the protocol. - In Section 7.1.1, clarified determination of date and time when criterion 2 is met, to allow for situations where an acute complication starts after an "NA" response and is resolved prior to the next assessment, leading to a "YES" response at the first assessment after the last "NA" response. - Updated study schematic in Section 3.1 to reflect updated Cohort 1 planned enrollment based on combined Cohorts 1 and 2 study design for the primary analysis population. Also clarified that readiness-for-discharge should continue to be evaluated until subjects have left the hospital. -Updated Section 3.2 for planned enrollment numbers to reflect a combined Cohort 1 and Cohort 2 study design for the primary analysis population. [redacted] - Clarified in Section 3.4 that the study will be completed in approximately 48 months. - Clarified in Section 4.2, exclusion criteria #1 that subjects with fever ≥ 39°C (102.2°F) are excluded. - Clarified exclusion criteria regarding transdermal analgesics as per Section 5.8.2 of the protocol and further clarified Section 5.8.2 - Added reference to contact center vs help desk in Section 4.4 - Administrative update to clarify definition of investigational product as per ICH guidelines in

Document	Version Date	Summary of Changes
		Section 5 - Added reference to Pfizer Study Manager in Section 5.2 - Added reference to the Study Drug Administration Guidance Document in Section 5.5 - Clarified in Section 5.6 that when Investigational product temperature excursions will be considered protocol deviations according to current Pfizer Protocol template - Clarified that listing of IV pain medications in the protocol, Section 5.8.4, is not inclusive of all permitted IV pain medications - Clarified in Section 6 that a back-up process that can be utilized in the event issues are experienced with the eClinRO web-based data capture system - Clarified examples of screening lab samples in Section 6.1.2.1: eGFR to be calculated as per protocol and not as per local laboratory; pregnancy test results should be used to assess against Exclusion Criteria #20; and administrative updates [redacted] [redacted] - Clarified in Section 6.6 lost-to-follow-up requirements to align with Protocol Administrative Clarification letter (PACL) issued Oct 2017. - Confirmed in Section 7.1.1 that a back-up

Document	Version Date	Summary of Changes
		process may be utilized if the eClinRO system is unavailable when a member of the site staff attempts to access the system. - Added "temporal" as an acceptable method of temperature measurement in Section 7.2.2. [redacted] - Updated Section 9.1 to reflect Primary Analysis Population consisting of both Cohort 1 and Cohort 2 combined. Also clarify planned analyses of Cohort 1 and Cohort 2 related to observed hazard ratio and confidence interval. - Updates made to the sample-size rationale for the pediatric strata (Section 9.1) and to the reporting of confidence intervals (Sections 9.2.1 and 9.2.3) so that only 2-sided 95% confidence intervals are used in both places. This is to align with PACL issued in January 2017 related to these sections. - Updated Section 9.2 Primary Analysis Population to reflect Cohort 1 and Cohort 2 combined. - Updated Sections 9.1, 9.5 and 9.6 to remove the interim analysis of efficacy. This is to align with PACL issued in January 2017 related to these sections. Also updated these sections based on study progress to reflect an interim analysis was not required. -Updated Section 9.2 to clarify that details on the censoring rules for the time-to-event endpoints are provided in the Statistical Analysis

Document	Version Date	Summary of Changes
		Plans (SAP), and to streamline and simplify the analysis methods for subgroups and exploratory endpoints.- Clarified in Section 9.2.3 how subgroup analysis will be performed. - Removed specific outside organization weblinks for eGFR calculators and replaced with reference to study specific web-portal under study team control. - In addition to changes described above, administrative and editorial changes were made throughout the document for clarity, completeness and to improve readability.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and, institutional review boards (IRBs)/ethics committees (ECs).

Abbreviations

This is a list of abbreviations used in the protocol.	
Abbreviation	**Term**
ACS	acute chest syndrome
ACS-SEAC	acute chest syndrome safety endpoint adjudication committee
AE	adverse event
AGEP	acute generalized exanthematous pustulosis
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
BiPAP	bilevel positive airway pressure
[redacted]	[redacted]
BUN	blood urea nitrogen
CaPS	CDISC and Pfizer Standards
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CL_r	renal clearance
C_{max}	maximum observed drug concentration
CM-SEAC	cutaneous manifestation safety endpoint adjudication committee
CPAP	continuous positive airway pressure
CRF	case report form
CSA	clinical study agreement
D5	5% dextrose
D5W	5% dextrose in water
dL	Deciliter
EC	ethics committee
ECG	Electrocardiogram
eClinRO	electronic Clinician Reported Outcome
eCRF	electronic case report form
ED	emergency department
EDMC	external data monitoring committee
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
[redacted]	[redacted]
EU	European Union
EudraCT	European Clinical Trials Database
F1.2	prothrombin fragment 1.2
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FSFV	first subject first visit
FSH	follicle-stimulating hormone

GCP	Good Clinical Practice
gm	Gram
Hb C	hemoglobin C
Hb F	fetal hemoglobin
Hb S	hemoglobin S
Hb SD	hemoglobin SD
HPLC	high performance liquid chromatography
[redacted]	[redacted]
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	Identification
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
ITT	intent to treat
IUD	intrauterine device
IV	Intravenous
KCl	potassium chloride
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LDH	lactate dehydrogenase
LFT	liver function test
LSLV	last subject last visit
LTFU	lost to follow up
mEq/L	milliequivalents per liter
mg	Milligram
mL	Milliliter
mmHg	millimeter of mercury
msec	Millisecond
N/A	not applicable
NIH	National Institutes of Health
[redacted]	[redacted]
NS	normal saline, 0.9% sodium chloride
NSAID	nonsteroidal anti-inflammatory
O_2	Oxygen
PaO_2	partial pressure of oxygen
PBS	phosphate buffered saline
PCA	patient controlled analgesia
PCD	primary completion date
PIN	personal identification number
PK	Pharmacokinetic
PT	prothrombin time
q12hr	every 12 hours

QTc	corrected QT interval
RBC	red blood cell
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sickle cell disease
SCD-SS	sickle cell disease SS
SCD-SC	sickle cell disease SC
SCD-Sβ^+-thal	sickle cell disease β^+-thalassemia
SCD- Sβ^0-thal	sickle cell disease β^0-thalassemia
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOP	standard operating procedure
$sPLA_2$	secretory phospholipase A_2
SRSD	single reference safety document
$t_{1/2}$	half-life
[redacted]	[redacted]
TEAE	treatment emergent adverse event
[redacted]	[redacted]
ULN	upper limit of normal
US	United States
UTN	Universal Trial Number
[redacted]	[redacted]
VOC	vaso-occlusive crisis
WBC	white blood cell

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

Table 1. Schedule of Activities

Study Procedure	Pre-VOC/ Study Entry Screening	Monthly Contacts[o]	VOC/ Treat-ment - Ready Screening	Double-Blind Treatment				Post-Treatment Daily Assess-ments	Discharge	Post-Discharge Daily Assessments	Post-Discharge Follow-Up Phone Call[x]		Post-Discharge Follow-Up Visit[x]
				Loading Dose	First 24 Hours[p]	Daily Assess-ments	End of Treat-ment[v]						
Visit Number			**Visit 1: During Hospitalization**								**2**	**3**	**4**
Study Day			**Day 1 through 8**							**Post-Discharge Day 1 up to Day 10**	**Post-Discharge Day 7±3**	**Post-Discharge Day 21 ±5**	**Post-Discharge Day 35 ±5**
Informed consent/ assent	(X)[n]		(X)[n]										
Enter subject into electronic system to document entry into Screening period	(X)		X										
Affirmation of informed consent			(X)[n]										
Demographics			X										
Medical History			X										
SCD History			X										
Complete Physical Examination			X										
Targeted Physical Examination						X[s]	X[s]		X				X
Height, weight			X										
Vital Signs[a]			X			X[tt]	X[t]	X[t]					X

Study Procedure	Pre-VOC/ Study Entry Screening	Monthly Contacts[o]	VOC/ Treat-ment - Ready Screening	Double-Blind Treatment				Post-Treatment Daily Assess-ments	Discharge	Post-Discharge Daily Assessments	Post-Discharge Follow-Up Phone Call[x]		Post-Discharge Follow-Up Visit[x]
				Loading Dose	First 24 Hours[p]	Daily Assess-ments	End of Treat-ment[v]						
Visit Number			**Visit 1: During Hospitalization**								**2**	**3**	**4**
Study Day			**Day 1 through 8**							**Post-Discharge Day 1 up to Day 10**	**Post-Discharge Day 7±3**	**Post-Discharge Day 21 ±5**	**Post-Discharge Day 35 ±5**
Clinical Laboratories[b]			X				X						X
Urinalysis[c]			X				X						X
Pregnancy Test[d]			X				X						X
Contraception check			X								X	X	X
[redacted]													
Hemoglobin Electrophoresis[g]			(X)										
[redacted]													

Study Procedure	Pre-VOC/ Study Entry Screening	Monthly Contacts[o]	VOC/ Treat-ment - Ready Screening	Double-Blind Treatment				Post-Treatment Daily Assess-ments	Discharge	Post-Discharge Daily Assessments	Post-Discharge Follow-Up Phone Call[x]		Post-Discharge Follow-Up Visit[x]
				Loading Dose	First 24 Hours[p]	Daily Assess-ments	End of Treat-ment[v]						
Visit Number			**Visit 1: During Hospitalization**								**2**	**3**	**4**
Study Day			**Day 1 through 8**							**Post-Discharge Day 1 up to Day 10**	**Post-Discharge Day 7±3**	**Post-Discharge Day 21 ±5**	**Post-Discharge Day 35 ±5**
Inclusion/ Exclusion criteria			X										
Randomization			X										
Study Drug Administration[j]				X	X	X							
Readiness-for-Discharge Criteria)[k]					X	X	X	X	X				
Date and Time of Discharge									X				
[redacted]													
Telephone Contact		(X)									X	X	
Adverse Events	(X)	(X)	(X)	X	X	X[t]	X	X	X		X	X	X
Prior/Concomitant Medications			X	X	X	X[t]	X	X	X		X	X	X
Parenteral Opioids[l]			X	X	X	X[t]	X	X	X				
Prior/Concomitant Non-drug Treatments/ Procedures			X	X	X	X	X	X	X		X	X	X
[redacted]													
Informed consent/assent for Open-Label Extension Study[m]													(X)

Abbreviations: eClinRO = electronic Clinician Reported Outcome; [redacted] SCD = sickle cell disease; VOC = vaso-occlusive crisis

a. Temperature, respiratory rate, pulse, blood pressure, pulse oximetry.
b. Hematology and serum chemistry. See Table 3 in Section 7.2.3.
c. See Table 3 in Section 7.2.3.
d. Serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, is required to be performed on all female subjects of childbearing potential to confirm the subject does not meet Exclusion Criterion #20. A negative pregnancy test result is required before study drug may be administered; study drug may not be administered when the pregnancy test result is indeterminate or positive. Pregnancy tests may also be repeated as per request of IRB/ECs or if required by local regulations.
[redacted]
g. Sample will only be collected if subject's diagnosis of SCD (ie, laboratory result by hemoglobin electrophoresis, High Performance Liquid Chromatography [HPLC], or genotype analysis) cannot be source documented.
[redacted]
i. For subjects ≥12 years of age.
j. All eligible subjects should be dosed with study drug as early as possible, but the start of study drug dosing should be no later than 24 hours from the administration of the first dose of IV opioids. Dosing to continue every 12 (±2) hours until criterion 1 of the readiness-for-discharge criteria has been met, or up to 15 doses of study drug (1 loading dose and a maximum of 14 maintenance doses), whichever comes first.
k. Study site staff will assess specific readiness-for-discharge criteria. The criteria will be assessed in all subjects at pre-defined intervals (and ad hoc as necessary) from the start time of the loading dose until discharge. Readiness-for-discharge criteria should continue to be evaluated after they have been met until subjects have left the hospital to ensure no subsequent updates to the readiness-for-discharge evaluations are required. Routine assessments are to be performed during "daytime hours" only (defined as 6:01am to 10:00pm). Assessments are not to be performed during "night-time hours" (defined as 10:01pm to 6:00am), unless it becomes apparent that the subject has become ready-for-discharge during the "night-time hours", in which case an ad hoc assessment should be undertaken. In addition, an assessment should always be made at the time the decision is made to discharge the subject, regardless of the hour. Section 7.1.1.
l. All parenteral opioid administration will be collected daily (eg, subcutaneous, intravenous, etc), but specifically intravenous opioid administration will be recorded from the start of administration of the opioid (e.g. prior to the first dose of study drug) and approximately every 4 hours for the first 48 hours from the start time of the loading dose, then daily until discharge.
m. Informed consent/assent for the Open Label Extension Study may be obtained from the time of the Day 35 Post-Discharge Follow Up visit up to 180 days after the Day 35 Post-Discharge Follow-Up visit.
n. Investigators are asked to identify, through chart review, those subjects who may be appropriate for the study before they develop VOC. These subjects may be educated about the study while they are well, for example in the office setting, and approached for consent/assent (Pre-VOC/Study Entry Screening). Serious adverse events must be reported to Pfizer from the time of signing Pre-VOC/Study Entry informed consent. Formal assessment for eligibility into the study or enrollment/randomization will not be performed at this time. At the time of VOC, the subject will be asked if they want to continue participating in the VOC/Treatment-Ready Screening and if eligible, be randomly assigned to blinded study drug. The subject's affirmation must be documented. Other subjects may be initially approached for consent when presenting to the emergency room/clinic in VOC.
o. Contacts are to be conducted every 4 weeks (±7 days) from the time of signing the consent/assent to the VOC/Treatment-Ready Screening visit (may be a clinic visit instead of a phone call, if preferred).
p. During the first 24 hours from the start time of the loading dose.
q. Every 4 (±1) hours (while awake).
r. Assessment to be collected at 8 (±4) hours after start of loading dose, while subject is awake.

s. Performed daily through 24 hours after the last dose of study drug (if not discharged first).
t. Performed daily until time of discharge.
u. Every 4 (±1) hours (while awake) until 48 hours from the start time of the loading dose, then performed twice daily, at least 8 hours apart, until discharge.
v. End of Treatment procedures are to be performed within 24 hours after last dose. This will occur either on or before Day 8 or prior to discharge, whichever comes first.
[redacted]
x. Post Discharge Follow-up phone calls and study site visit are to occur 7 (±3), 21 (±5), and 35 (±5) days from the time of discharge from the hospital (Note: If the subject or investigator prefer, the Day 7 Post-Discharge and Day 21 Post-Discharge contact may be a clinic visit).
[redacted]

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

[redacted]

1. INTRODUCTION

Sickle cell disease (SCD) is one of the most prevalent genetic disorders in the United States (US), affecting approximately 100,000 people.[1] It is a chronic condition with substantial morbidity and mortality, and is responsible for more than 75,000 hospitalizations per year in the US with an average stay of 6.1 days.[2] Both children and adults are affected, and greater mortality is seen in those with more severe disease.

SCD refers to a group of autosomal recessive inherited disorders of the β-globin gene. A single nucleotide substitution results in the presence of valine instead of glutamic acid in the β-globin chain. The resulting polymerization of Hemoglobin S (Hb S) when deoxygenated is the primary indispensable event in the molecular pathogenesis of SCD.[3] Individuals homozygous for Hb S have sickle cell anemia (SCD-SS). Those who are compound (double) heterozygotes have 1 copy of Hb S and 1 copy of either Hb C (SCD-SC), Hb β^+-thalassemia (SCD-Sβ^+-thal), or Hb β^0-thalassemia (SCD-Sβ^0-thal).[4]

SCD is associated with a number of serious and potentially disabling conditions that have similar symptoms but vary in severity by genotype. Most notable is vaso-occlusive crisis (VOC), an extremely painful and serious consequence of SCD, presumably resulting from acute ischemic tissue injury.

Over the course of a year, about 60% of patients with SCD-SS will have at least 1 severe VOC[5], which typically presents as episodes of pain and inflammation, at 1 or more sites, in varying degrees of severity, and occurring at varying intervals throughout life. These pain crises, as VOC episodes are also known, are the clinical hallmark of SCD, are responsible for the vast majority of hospitalizations (>90%), and result in significant morbidity, mortality, and interruption of daily functioning. Other problems include ischemic and hemorrhagic stroke, acute chest syndrome (ACS), splenic sequestration, dactylitis, osteonecrosis, priapism, leg ulcers, and nephropathy.[3,6,7,8] Most SCD-related deaths occur during acute VOC, and are due to ACS or stroke.[9] Patients can become symptomatic with pain, infection, or splenic sequestration as early as 6 months of age; thus, VOCs are an important cause of morbidity throughout life, resulting in disruption to the individual's education, psychosocial development, and employment as well as causing severe pain, hospitalization, and premature death.

Current medical management of SCD includes use of hydroxyurea, which is used to increase fetal hemoglobin (Hb F) concentration and reduce the number of pain crises. Treatment of acute VOC includes mainly supportive measures such as opioid analgesics, hydration, oxygen, and transfusion. There is no mechanism-based treatment currently available, so this remains an unmet medical need. Most patients attempt pain management at home, and seek medical care only when this fails. Therefore, the majority of painful episodes do not come to medical attention.[10]

The etiology of VOC involves dual mechanisms: a mechanical component, by which the sickled red blood cells (RBCs) become caught in the post-capillary venules, and an associated inflammatory response in which white blood cells (WBCs) adhere to the endothelium.

The underlying pathogenesis of Red Blood Cell (RBC) Sickling is the deoxygenation of Hb S, which results in polymerization of the Hb, distortion of the RBC, and loss of deformability of the cell.[11] These "sickled" RBCs are a primary component of the occlusive process and cause vascular injury through interactions with endothelial cells.[6]

The other primary component is adhesive: stickiness of the cells which causes cell aggregates of WBC-RBC, WBC-WBC, and WBC-platelet to form. This adhesion is selectin-mediated and contributes to the VOC process. Cell aggregates block the vasculature and create a trap for the sickled RBCs, resulting in obstruction of blood flow[4,12]

Finally, vaso-occlusion resulting from sickled and adherent RBCs also causes slowing of blood flow in post-capillary venules, local tissue hypoxia, and further tissue inflammation, resulting in more deoxygenation and sickling of RBCs, and propagation of the occlusion, sometimes called secondary recruitment of sickled cells and occluded vessels.[3] Diapedesis (leukocyte migration into the tissues) and sickle-related microvascular occlusion also take place in postcapillary venules. Pain is the result of initial and ongoing occlusion and ischemia,[8] which results in higher mortality in patients with the SCD-SS genotype, compared to other genotypes.[9]

Of note is that soluble E-selectin, vascular cell adhesion molecules (VCAM)-1, and intracellular adhesion molecules (ICAM)-1 levels are higher in sickle cell patients at baseline than in normal volunteers. There is also some evidence to suggest that soluble E-selectin and ICAM-1 are increased in acute VOC when compared to baseline in patients with SCD.[13] In addition, increased soluble E-selectin levels have been shown to correlate with increased mortality in SCD patients.[14] Leukocytes adherent to the endothelial cell wall in postcapillary and collecting venules interact with sickled RBCs, leading to vaso-occlusion in sickle cell mice. However, sickle cell mice lacking E- and P-selectin were protected from developing vaso-occlusion.[15] Understanding of the role that selectins play in cell aggregation and the pathophysiology of VOC is increasing.[3,16]

Selectins are a family of adhesion molecules involved in trafficking and extravasation of leukocytes.[17] During the inflammatory response, leukocytes extravasate from the bloodstream and migrate to the sites of inflammation where they participate in the defense against pathogens or other inflammatory processes. This recruitment of leukocytes, which begins with the initial recognition and binding of the leukocytes to the endothelial cells that line the walls of the vasculature, is mediated by selectins.[18]

Three selectins are known to bind carbohydrate structures on cells in interactions characterized by fast kinetics that allow cell adhesion to proceed under the shear forces of blood flow.[19] P-selectin is located on platelets and is also pre-formed and stored in Weibel-Palade bodies within the endothelial cells. It is a "first responder" and is expressed at the endothelial cell surface within 30 minutes of an acute inflammatory response.[20] E-selectin is not pre-formed and stored, but requires de novo protein synthesis and is expressed on the endothelium 3 to 5 hours after activation.[21] Both of these selectins are responsible for the early recognition and adhesion of leukocytes to the vascular endothelium. L-selectin is located on a subset of leukocytes and participates in rolling and adhesion and plays a major role in homing to the lymph nodes.[17]

The natural ligands for the selectins are carbohydrate structures of the sialylated Lewis antigens present on scaffolds of glycoproteins and glycolipids (eg, PSGL-1, ESL-1, MAdCAM-1). Following initial selectin-mediated recognition and rolling, the leukocytes activate a second phase of adhesion while in close contact with the endothelium through integrin receptors. As these events mostly occur in a stepwise fashion, the selectins have been viewed as a target for upstream inhibition of the inflammatory response. By inhibiting the initial recognition, and thereby decreasing or preventing stickiness of RBC/WBC/endothelial cells in SCD, the pathophysiologic process of VOC may be interrupted and/or prevented. Damage caused by these infiltrating cells in an inflammatory response is therefore prevented and blood flow may be improved.

Inhibition of E-, P-, and L-selectins, a pan-selectin inhibition approach, offers potential promise as a useful therapeutic option.

Data in the literature support a key role for the selectins in VOC. In particular, Turhan et al (2002) have shown that E-selectin and P-selectin are key to the vaso-occlusion in a mouse model with the sickle genotype.[15] They have also suggested that drugs affecting leukocyte-endothelial interactions or leukocyte-sickle RBC aggregation may have an important role in treatment of VOC. In addition, Embury et al (2004) have shown the importance of P-selectin in contributing to microcirculatory abnormalities.[22] Kato et al (2005) have shown that increased soluble E-selectin levels in patients were associated with increased mortality over a 4-year period.[14]

GMI-1070 (rivipansel) is a pan-selectin antagonist, a compound found to inhibit selectin binding in vitro and to inhibit selectin-mediated effects in vivo. Selectin binding is a key early step in the inflammatory process leading to leukocyte adhesion and recruitment to inflamed tissue. Selectin binding has been shown to be involved in most – if not all – disease processes that involve inflammation. There are no other known approved therapeutic agents in this class.

This study is designed to evaluate the efficacy and safety of rivipansel as treatment for VOC in hospitalized subjects with SCD.

1.1. Mechanism of Action/Indication

Rivipansel is being developed as a pan-selectin antagonist for the treatment of VOC in subjects with SCD (including SCD-SS, SCD-SC, SCD-Sβ^+-thalassemia, and SCD-Sβ^0-thalassemia).

1.2. Background and Rationale

1.2.1. Drug Development Rationale

Both P-selectin and E-selectin are responsible for the early recognition and adhesion of leukocytes to the vascular endothelium. L-selectin is located on a subset of leukocytes and participates in rolling and adhesion and plays a major role in homing to the lymph nodes.

By inhibiting the initial recognition, and thereby decreasing or preventing stickiness of RBC/WBC/endothelial cells in SCD, the pathophysiologic process of VOC may be interrupted and/or prevented. Damage caused by these infiltrating cells in an inflammatory response is therefore prevented and blood flow may be improved.

Rivipansel is a pan-selectin antagonist developed at GlycoMimetics that inhibits selectin binding *in vitro* as well as selectin-mediated effects *in vivo*. Inhibition of selectins offers potential promise as a useful therapeutic option for patients with SCD. Rivipansel has potent anti-inflammatory effects in a number of animal models, including the sickle cell mouse, in which it has been shown to normalize blood flow, reduce blood cell aggregation, and to improve survival in a model of VOC. In addition, the Phase 2 study (GMI-1070-201) data have shown that such effects in SCD patients have led to a reduction in the length and intensity of SCD pain crises. Treatment of VOC with mechanism-based therapies is an area of unmet medical need in both adult and pediatric patients with SCD. Both pediatric and adult patients would be expected to benefit substantially from a therapy that could treat VOC and therefore measurably reduce the associated suffering and adverse clinical outcomes.

1.2.2. Pre-Clinical Development of Rivipansel

For information on nonclinical pharmacology, pharmacokinetics and product metabolism in animals, and toxicology studies, please refer to the Investigator's Brochure.

1.2.3. Clinical Experience with Rivipansel

Clinical information is available from three completed Phase 1 studies, and a completed Phase 2 study, all conducted by GlycoMimetics. Additionally, data are available from a completed Pfizer sponsored Phase 1 study to assess the effect of rivipansel on corrected QT interval (QTc).

GlycoMimetic Studies

In the first Phase 1 study (GMI-1070-101), healthy volunteer subjects received single intravenous (IV) doses of 2, 5, 10, 20, or 40 mg/kg rivipansel or placebo. In the second Phase 1 study (GMI-1070-102), healthy volunteer subjects received multiple IV doses of 5, 10, or 20 mg/kg rivipansel or placebo every 8 hours for a total of 13 doses. An additional group of subjects received a loading dose of 40 mg/kg, followed by multiple doses of 20 mg/kg rivipansel every 8 hours for a total of 6 doses. These studies evaluated a total of 72 healthy adult subjects (54 active, 18 placebo).

Pharmacokinetic (PK) data are available from these studies in healthy volunteers. Mean values for C_{max}, area under the curve $(AUC)_{(0\text{-}t)}$, and $AUC_{(inf)}$ increased in a dose-proportional manner, providing evidence of linear pharmacokinetics. After a single 20 minute infusion of 20 mg/kg, the mean ± standard deviation C_{max} was 256±43.7 mg/L. The time of peak concentrations corresponds to the time of the end of infusion and the collection of the first blood sample for determination of GMI-1070. The volume of distribution was consistent across dose levels, 0.130 to 0.181 L/kg. Clearance was consistent across dose levels (0.211 to 0.284 mL/min/kg) and the mean elimination half-life ($t_{½}$) ranged from 6.67 hours to

7.41 hours. Urine collection after the multiple dose administration showed a minimum of 89% of the dose was recovered intact in the urine, and CL_r was less than filtration clearance, consistent with tubular reabsorption.

The third Phase 1 study (GMI-1070-103) was an open-label study of IV rivipansel in 15 adult subjects with stable SCD who received a 20 mg/kg loading dose of IV rivipansel, followed 10 hours later by a 10 mg/kg dose of IV rivipansel. The pharmacokinetics were observed to be consistent with those in the healthy volunteers.

In these three Phase 1 studies there were no clinically significant electrocardiogram (ECG) or physical examination findings. With one exception, all adverse events in subjects receiving rivipansel were Grades 1 or 2. Severe symptomatic anemia (Grade 4) that occurred in 1 subject with stable SCD was considered to be remotely related to the study medication, and resolved with therapy. No serious adverse events were reported in these studies.

A randomized, placebo-controlled Phase 2 trial (GMI-1070-201), evaluating the efficacy, safety, and pharmacokinetics of multiple IV doses of rivipansel in 76 subjects 12 to 60 years of age who were hospitalized for sickle cell VOC is now complete. This study included two dosing schedules; the first cohort received 20 mg/kg loading dose, then 10 mg/kg every 12 hours for up to 7 days, (maximum 15 doses) and the second cohort received 40 mg/kg loading dose, then 20 mg/kg every 12 hours for up to 7 days, (maximum 15 doses).

In the phase 2 study, the primary endpoint, time to resolution of VOC, was shorter for the rivipansel treated group versus the placebo group. The mean time to VOC resolution was 110 hours and 148 hours for the rivipansel treated group and the placebo group, respectively. Treatment with rivipansel was also associated with improvement in clinical measures of VOC. The rivipansel treatment group had a shorter median time to transition from parenteral to oral pain medications, time to discharge from the hospital, and time to first sustained reduction in VAS pain score. Mean use of opioid analgesics during hospitalization was also lower in the rivipansel treated group.

Total treatment-emergent adverse event (TEAE) rates were comparable across groups. Serious Adverse Events (SAE) and those SAEs "related to treatment" were also comparable across groups. Eleven (11, 14.4%) subjects discontinued study drug treatment due to adverse events (8 [10.5%] subjects in the active group, and 3 [3.9%] subjects in the placebo group). No subjects discontinued participation in the study due to adverse events. A total of 28 serious adverse events (SAEs) were reported, encompassing 29 event terms across 23 subjects. A 30% SAE rate was seen in both active and placebo groups. The most common SAE in both treatment groups was re-hospitalization for VOC. One (1) SAE of acute generalized exanthematous pustulosis (AGEP) rash was seen in a subject who received the high dose; other less severe rash events were distributed across treated and placebo groups. No subjects died.

Of note, the drug product formulation that will be used in this study is a 30 mg/mL solution for injection in which the concentration is 30 mg/mL based on the active moiety of rivipansel. The drug product used in the Phase 1 and Phase 2 studies described previously (conducted by GlycoMimetics) was a 30 mg/mL solution for injection based on the salt of rivipansel which is equivalent to 28.28 mg/mL of the active moiety rivipansel.

Pfizer Sponsored Studies

A Phase 1 placebo and active controlled study to evaluate the effect of intravenous rivipansel on QTc interval in 48 healthy African-American adult subjects (Pfizer Study B5201001) has been completed. The rivipansel dose in the study was 4 grams (expressed as active moiety) as a single intravenous infusion and the active control was a single dose of moxifloxacin 400mg orally.

The study was deemed negative; the statistical analyses of the ECG measurements demonstrated a lack of a QTc effect with rivipansel compared to placebo as the upper bound of the 2-sided 90% confidence interval (CI) for mean differences between rivipansel and placebo at all 11 post-dose time points was below the International Council for Harmonisation (ICH) E14 criteria of 10 milliseconds (msec). The highest observed upper bound of the 2-sided 90% CIs was 3.22 msec at 3 hours post-dose. The moxifloxacin positive control performed as expected, thus the study should be deemed adequately sensitive.

Single doses of rivipansel were well tolerated in these healthy male African-American subjects with an adverse event profile largely consistent with that which had been reported in the previous studies undertaken by GlycoMimetics. The only new event reported was alanine aminotransferase (ALT) elevation that occurred in a single male subject after receiving rivipansel. The ALT elevation was moderate (maximum ALT 3 times the upper limit of normal [xULN]), was not associated with any clinical signs or symptoms and recovered to normal levels on subsequent follow-up. The event was confounded by the subject having a mildly elevated ALT at baseline (<1.5xULN) and having reported a previous episode of transient "liver function test" elevation which occurred while participating in another healthy volunteer drug study, undertaken at a different clinical research unit.

1.2.4. Study Rationale

Rivipansel is a glycomimetic inhibitor of E-, P-, and L-selectins *in vitro*. Rivipansel has been shown to inhibit inflammation in several animal models of disease, including the mouse model of vaso-occlusive crisis (VOC) of sickle cell disease (SCD). It has also been shown to consistently improve multiple clinically meaningful measures of the VOC experience, for both the pediatric and adult subjects enrolled in the Phase 2 study (GMI-1070-201). This Phase 3 study will continue to examine rivipansel for the treatment of VOC in patients with SCD.

1.2.5. Dose Rationale

Rivipansel is administered intravenously. In this current Phase 3 study, rivipansel IV solution for injection contains 30 mg/mL of active moiety rivipansel.

The dosing regimen in this Phase 3 study is as follows:

- Subjects aged 12 and over who weigh >40 kg, will receive study drug as a loading dose of 1680 mg followed by a maintenance dose of 840 mg every 12 ± 2 hours.

- Subjects aged 6 to 11 years, or any subject who weighs ≤40 kg, will receive weight-based dosing (mg/kg) administered as a loading dose of 40 mg/kg (maximum of 1680 mg) followed by a maintenance dose of 20 mg/kg (maximum of 840 mg) every 12 ± 2 hours.

The selection of the dose in this Phase 3 study was based on efficacy, safety, and pharmacokinetic results from the Phase 2 study, where a low dose (20 mg/kg loading dose/10 mg/kg every 12 hours) and a high dose (40 mg/kg loading dose/20 mg/kg every 12 hours) were studied (the doses were studied in a sequential fashion). In the Phase 2 study, the differences between the median time to discharge for rivipansel and placebo treatment groups were similar for the low rivipansel dose (56 hours) and the high dose (55 hours). Phase 2 treatment-emergent adverse events (AEs) by dose, as well as other safety data, indicates there were no apparent safety differences for either the low or high dose relative to placebo. The pharmacokinetic data from the Phase 2 study support fixed flat dosing for subjects 12 years of age and above. Furthermore, fixed flat dosing is a common approach for the administration of small molecules with a favorable safety margin, and offers a simpler approach with the potential for fewer dosing errors. Pharmacokinetic modeling and simulations predict that the dose will result in exposures similar to that observed with the low dose in the Phase 2 study and a minimum plasma concentration above 10 μg/mL will be maintained throughout the dosing interval. This concentration has shown improved blood flow, rolling flux and survival rate in a SCD mouse efficacy model.[23] In order for subjects ≥ 12 years of age not to exceed the high dose of 40/20 mg/kg studied in the Phase 2 study, the weight cut off was chosen to be 40 kg. Based on the similarity of efficacy and safety results between the 2 doses studied in the Phase 2 study, only a single dose will be studied.

Weight-based dosing for subjects 6 to 11 years of age will be used in this study. This is the most conservative approach given that children in this age range have not been previously studied. In the Phase 2 study, GMI-1070-201, subjects ≥12 years old with the regimen of 20 mg/kg loading dose followed by 10 mg/kg every 12 hours were studied and the dose was found to be efficacious. Because the exposures resulting from this dosing should result in similar efficacy in the younger subjects, modeling and simulation exercises were performed to identify dosing regimens that predict similar exposures. The simulations showed that for children 6 to 11 years old, a 40 mg/kg loading dose (maximum 1680 mg) followed by 20 mg/kg every 12 hours (maximum 840 mg) will result in concentrations similar to those observed with the 20/10 mg/kg dosing in the GMI-1070-201 study.

1.3. Summary of Benefit Risk Assessment

The available safety results from non-clinical and clinical studies support further investigation of rivipansel in subjects.

The beneficial effects of rivipansel are postulated to be the result of mechanism-based resolution of VOC via the inhibition of selectin-mediated adhesion of leukocytes to the endothelium. This prevents propagation of the vaso-occlusion and promotes early resolution of the VOC episode.

Additional information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

- To demonstrate the efficacy of rivipansel in treating a single episode of VOC in hospitalized subjects with SCD.

2.1.2. Secondary Objective

- To evaluate the safety of rivipansel when used to treat a single episode of VOC in hospitalized subjects with SCD.

[redacted]

2.2. Endpoints

2.2.1. Efficacy Endpoints

2.2.1.1. Primary

- Time to readiness-for-discharge, defined as the difference between the readiness-for-discharge date and time (see Section 7.1.1) and the start date and time of the first infusion of study drug (in hours).

2.2.1.2. Secondary

2.2.1.2.1. Key Secondary:

- Time to discharge, defined as the difference in hours between the time and date of the hospital discharge order by a qualified healthcare provider and the time and date of the initiation of the first infusion of study drug.

- Cumulative IV opioid consumption (standardized using morphine equivalents) from the time of the loading dose of study drug to discharge.

- Time to discontinuation of IV opioids.

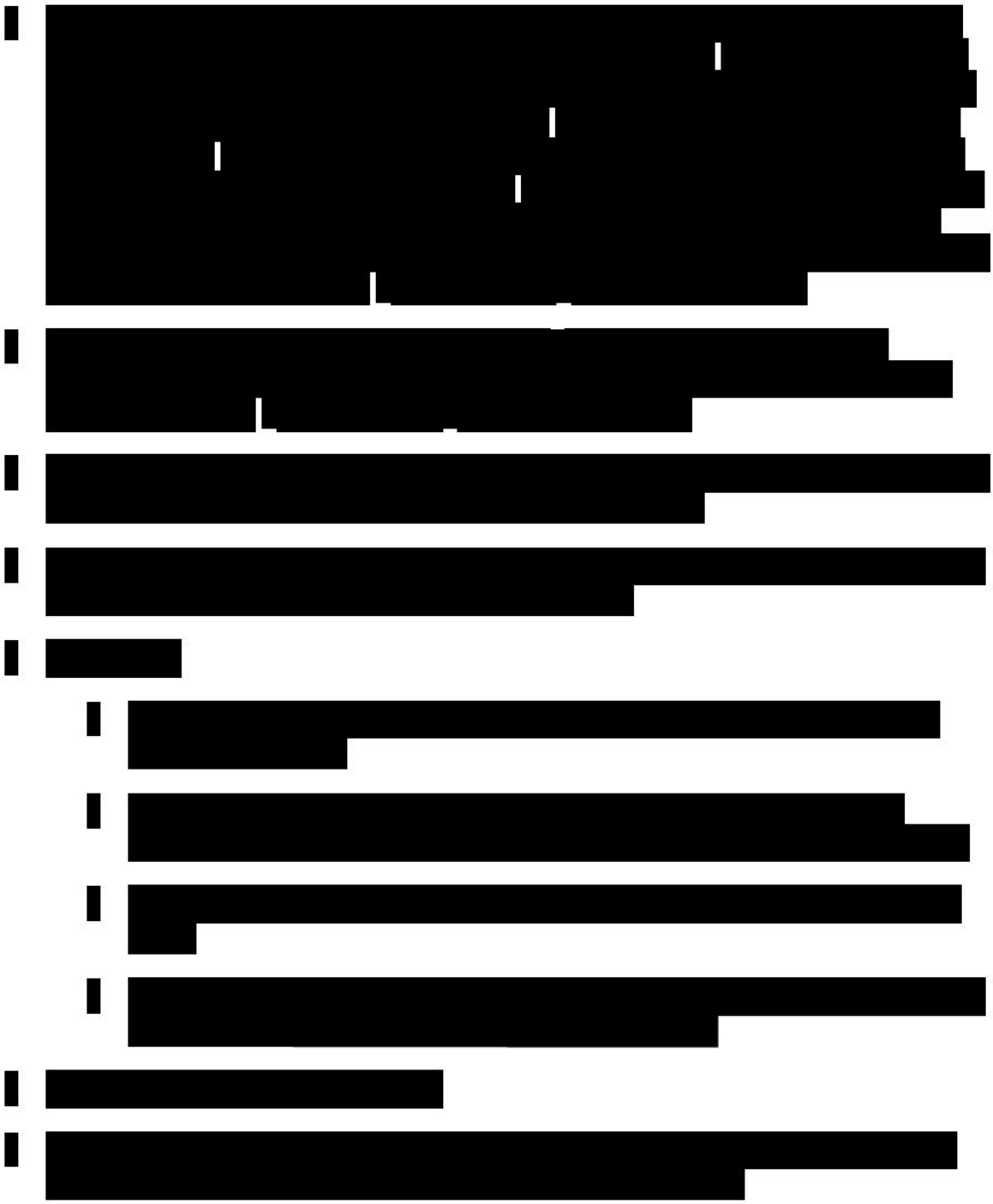
2.2.1.2.2. Other secondary

- Cumulative IV opioid consumption (standardized using morphine equivalents) within the first 24 hours post-loading dose of study drug.
- Percent of subjects re-hospitalized for VOC within 3 days of discharge.

2.2.2. Safety

- Incidence and severity of adverse events during study.
- Incidence of clinical laboratory abnormalities and change from baseline in clinical laboratory values at end of treatment.
- Incidence of clinically significant changes in physical examination.
- Change from baseline in vital signs over the study.
- Incidence of adjudicated ACS.
- Incidence of adjudicated severe and/or generalized cutaneous manifestations.
- Percent of subjects re-hospitalized for VOC within 7, 14 and 30 days of discharge.

[redacted]



3. STUDY DESIGN

3.1. Study Overview

This Phase 3 randomized, double-blind, placebo-controlled, parallel group, multicenter study is designed to demonstrate the efficacy of rivipansel in treating subjects with SCD who are ≥6 years of age experiencing an acute VOC event necessitating hospitalization. This study has two cohorts: Cohort 1 includes one adult stratum (≥18 years old) and one pediatric stratum (12-17 years old), Cohort 2 includes one pediatric stratum (6-11 years old). The primary analysis population will be Cohort 1 and Cohort 2 combined (see Section 9.1) but the two cohorts will also be analysed separately.

There are two entry points into this study. The first point of entry is referred to as "Pre-VOC/Study Entry Screening" and occurs while the subject is well. The second entry point is while the subject is experiencing a pain crisis and is termed "VOC/Treatment-Ready Screening".

Pre-VOC/Study Entry Screening: Investigators may choose to identify, through chart review, those subjects who may be appropriate for the study before they develop VOC. These subjects may be educated about the study when they are well, such as in the office setting, and approached for consent/assent while not experiencing a pain crisis. These subjects will receive monthly telephone calls from the study site staff (or attend clinic visits, if preferred) until the time of their next VOC necessitating hospitalization. At the time of VOC, the subject will be asked if they want to continue participating in the VOC/Treatment-Ready Screening and if eligible, be randomly assigned to blinded study drug. The subject's affirmation must be documented.

VOC/Treatment-Ready Screening: In addition to approaching subjects prior to VOC, investigators are encouraged to identify subjects with VOC in settings that could include emergency department, clinic, day hospital or other acute care outpatient facilities, who are planned or likely to be admitted to the hospital, and approach them for consent/assent and eligibility criteria early in the process of treatment for VOC.

Subjects with acute VOC who complete the VOC/Treatment-Ready screening assessments and meet all eligibility criteria are enrolled into the study and will be randomized in a 1:1 ratio to receive multiple IV doses of rivipansel or placebo for the treatment of VOC. Randomization will be stratified by age (6-11, 12-17, and ≥18 years of age) and genotype (category 1: HbSS, $HbS\beta^0$ thalassemia and HbSD; category 2: HbSC, $HbS\beta^+$ thalassemia and HbS-Variant [other than HbSD]).

Dosing of eligible subjects with acute VOC will be initiated as early as possible, but no later than 24 hours from the administration of the first dose of IV opioids. For subjects aged 12 and over who weigh >40 kg, study drug will be administered as a loading dose of 1680 mg followed by a maintenance dose of 840 mg every 12 ± 2 hours. Subjects aged 6 to 11 years, or any subject who weighs ≤40 kg, will receive a loading dose of 40 mg/kg (maximum of 1680 mg) followed by a maintenance dose of 20 mg/kg (maximum of 840 mg) every 12 ± 2 hours. Study drug will be administered until criterion 1 of the

readiness-for-discharge criteria (see below) has been met, or up to 15 doses of study drug (1 loading dose and a maximum of 14 maintenance doses), whichever comes first.

The primary endpoint is time to readiness-for-discharge, where readiness-for discharge is met when all of the applicable 6 criteria are documented to have occurred – the criteria are to be assessed in relation to treatment for this VOC event and acute complication(s) directly related to this VOC event:

1. Only oral pain medication is required.
2. Acute complications related to VOC (such as ACS, stroke, priapism) have resolved to the extent that management can be in an outpatient setting, if applicable.
3. IV opioids have been discontinued.
4. IV hydration has been discontinued, if applicable.
5. IV antibiotics have been discontinued, if applicable.
6. RBC transfusion is no longer required for the treatment of this VOC, if applicable.

The readiness-for-discharge criteria will be assessed in all subjects at pre-defined intervals (and ad hoc as necessary) from the start time of the loading dose until discharge. Readiness-for-discharge criteria should continue to be evaluated after they have been met until subjects have left the hospital, to ensure no subsequent updates to the readiness-for-discharge evaluations are required. [redacted]

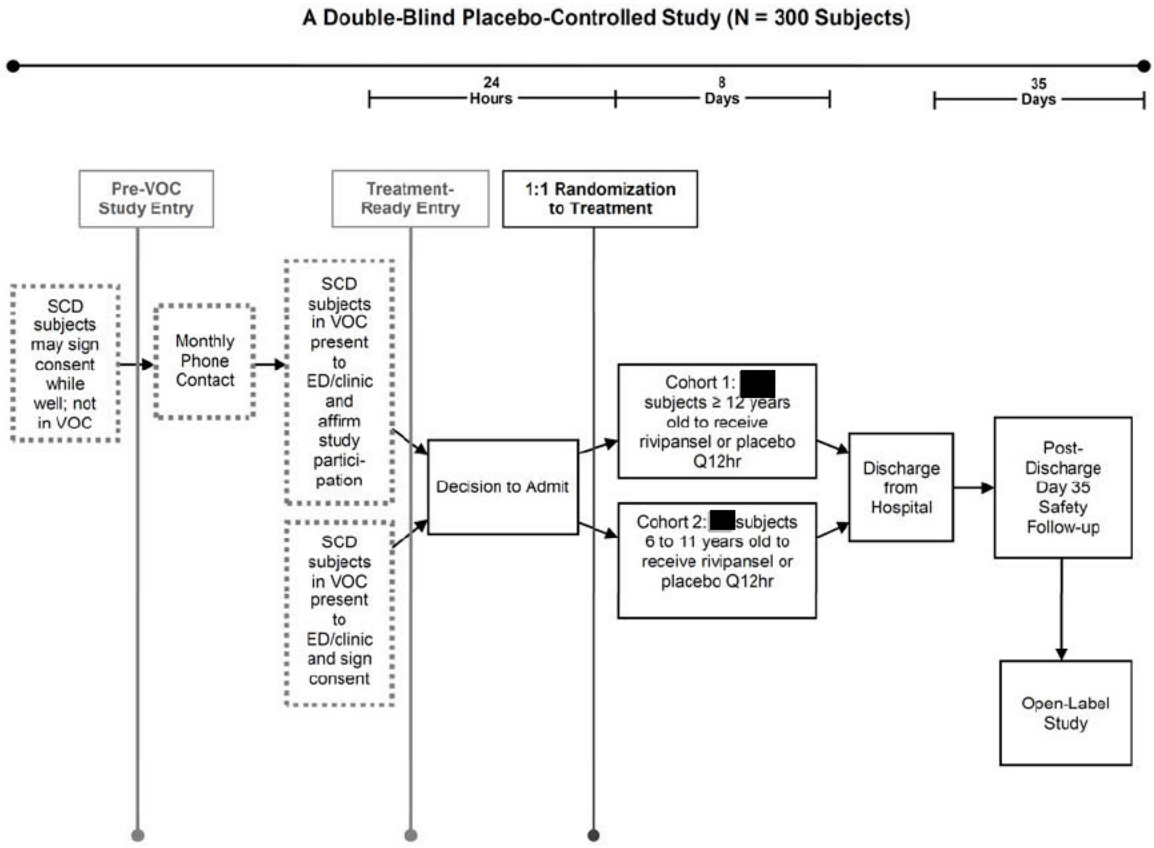
Subjects may be educated about the open-label extension study, B5201003, at the time of discharge from the hospital and approached for consent/assent from the time of the Day 35 Post-Discharge Follow-Up visit of the B5201002 study up to 180 days after the Day 35 Post-Discharge Follow-Up visit.

Safety, including clinical and laboratory examinations, efficacy, [redacted] will be obtained throughout the study according to the Schedule of Activities (see Table 1).

[redacted]

Electronic devices (eg, smart phone, tablet, or computers) will be utilized by study site staff to record their assessments of readiness-for-discharge criteria via an electronic Clinician Reported Outcome (eClinRO) web-based data capture system (see section 7.1.1).

This protocol will use two independent safety Endpoint Adjudication Committees; one committee for ACS events and one committee for severe and/or generalized cutaneous events. The Acute Chest Syndrome Safety Endpoint Adjudication Committee (ACS-SEAC) will consist of a group of external experts with relevant clinical expertise who will independently evaluate all reported cases of ACS, as well as potential cases of ACS, that occur from the time of the subject's first dose of study drug through the subject's last visit. The ACS-SEAC will use pre-defined criteria to determine whether these investigator-reported events meet the definition of ACS. The Cutaneous Manifestations Safety Endpoint Adjudication Committee (CM-SEAC) will consist of external clinical experts in dermatology who will evaluate all reported cases of cutaneous manifestations and acute skin rashes that develop from the time of the subject's first dose of study drug through the subject's last visit. The CM-SEAC will use pre-defined criteria to determine whether certain investigator-reported events meet the definition of severe and/or generalized cutaneous events. In addition, an external Data Monitoring Committee (E-DMC) will be responsible for ongoing safety monitoring of the study and for informing the sponsor of recommendations made based on their reviews (eg, to continue the study or to stop the study).



SCD=sickle cell disease, VOC-vaso-occlusive crisis, ED=emergency department

3.2. Approximate Number of Subjects

At least 300 subjects are planned to be enrolled (ie, randomized) from approximately 60-70 study sites in the United States and Canada. These 300 subjects will be separated into two cohorts: Cohort 1 will include one adult stratum (≥18 years old) and one pediatric stratum (12-17 years old), Cohort 2 will include one pediatric stratum (6-11 years old).

[redacted]

Under the assumptions of the sample size estimation, 300 subjects from Cohort 1 and Cohort 2 combined should provide at least 282 total events, [redacted]

3.3. Approximate Duration of Subject Participation

Subjects who enter the study in crisis will participate in the study for approximately 44 days. This includes 1 day for screening, up to 8 days for the double-blind treatment period, and a post-discharge follow-up period of approximately 35 days. Under certain situations,

complications may occur during the subject's hospitalization and the subject's participation in the study may exceed 44 days.

Subjects who enter the Pre-VOC period of the study while well (ie, not in VOC) will participate in the study for more than 44 days. The duration of the pre-VOC period for these subjects is variable and unpredictable. Once the subject has a VOC requiring hospitalization, affirms informed consent and meets all eligibility criteria, their participation in the double-blind treatment period and follow-up period of the study will be approximately 44 days, as described above.

3.4. Approximate Duration of Study

This study will be completed in approximately 48 months. The end of the study is the date of the last contact with the last subject on the study (ie, Last Subject Last Visit).

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

An eligibility card will be provided to ensure review of all inclusion and exclusion criteria.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. ≥6 years of age.
2. Documented diagnosis of sickle cell disease (HbSS, HbS-βthalassemia [HbSβ^0 and Hb Sβ^+thalassemia], HbSC or HbS-Variant, including HbSD and HbSE).
3. Diagnosis of VOC at the time of enrollment; necessitating admission to the hospital with treatment including IV opioids. This applies to the VOC/Treatment-Ready Screening entry point.
4. Able to commence the first dose of study drug within 24 hours from the administration of the first dose of IV opioids (Subjects treated as an outpatient within the past 48 hours for the same VOC episode may be enrolled if dosing with study drug is expected within 24 hours from the administration of the first dose of IV opioids for this admitting presentation).
5. Evidence of a personally signed and dated informed consent (and assent, where applicable) document indicating that the subject (or a legally acceptable representative/parent(s)/legal guardian) has been informed of all pertinent aspects of the

study. This applies to consent/assent at the time of Pre-VOC/Study Entry Screening or VOC/Treatment-Ready Screening.

6. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
7. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the duration of the active treatment period (starting at VOC/Treatment-Ready Screening) and for at least 28 days after the last dose of assigned treatment.

   Female subjects who are not of childbearing potential (ie, meet at least one of the following criteria):

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;
   - Have medically confirmed ovarian failure;
   - Have achieved post-menopausal status, defined as cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state. If FSH result is not available by the end of the screening period the decision will be based on the investigator's judgment and subject's medical history.

   All other female subjects (including females with tubal ligations and females that do NOT have a documented hysterectomy, bilateral oophorectomy and/or ovarian failure) will be considered to be of childbearing potential.

4.2. Exclusion Criteria

Subjects presenting with any of the following, from the time of VOC/Treatment-Ready Screening up to the time of randomization unless otherwise stated, will not be included in the study:

1. Serious systemic infection, evidenced by clinical signs and symptoms, and/or microbiological investigations, consistent with this diagnosis. Subjects with fever < 39°C (102.2°F) may be considered for enrollment if in the opinion of the investigator there is no evidence of any serious systemic infection. Subjects with fever ≥ 39°C (102.2°F) are excluded.

2. Subjects presenting with the following clinical risk factors of acute chest syndrome:

   - Hypoxia – defined as O_2 saturation of <90% (by pulse oximetry) on room air on 2 separate readings 15 minutes apart, or single value of PaO_2 <60 mmHg on arterial blood gas,

     and/or

   - Hemoglobin <5 gm/dL.

3. Acute chest syndrome, at the time of presentation, as defined by the National Institutes of Health (NIH) treatment guidelines:[24,25]

   New pulmonary infiltrate involving at least one complete lung segment consistent with the presence of alveolar consolidation, (excluding atelectasis) AND one or more of the following:

   - Chest pain;
   - Temperature >38.5^{o} C;
   - Tachypnea;
   - Wheezing or rales;
   - Cough.

4. SCD pain atypical of VOC, including hepatic or splenic sequestration, cholecystitis, or pneumonia.

5. At the time of presentation:

   - acute stroke, or
   - severe avascular necrosis of the hip/shoulder when the presenting pain is only in the affected hip/shoulder.

6. Estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2 (refer to Appendix 1 for calculation).

7. History consistent with rapidly progressive decrease or decrement in renal function, in the opinion of the investigator.

8. Alanine aminotransferase (ALT/SGPT) >3 times the upper limit of normal (X ULN) (based on clinic laboratory normal range).

9. Platelets <50,000/mm^3.

10. Subjects currently receiving transdermal analgesics and/or the expectation that transdermal analgesics may be used during the study for treatment of this episode of VOC (see Section 5.8.2).

11. Recent (within the past 30 days) major surgery (see definition in Section 4.3.2), hospitalization for reasons other than VOC, documented serious infection requiring IV antibiotic treatment, or significant bleeding.

12. Hospitalization for uncomplicated VOC, or treatment with parenteral pain medications in other medical settings such as the emergency department or day hospital for uncomplicated VOC, from 48 hours to 14 days prior to admitting presentation.

    - Subjects may be included if treated as an outpatient within the past 48 hours for the same VOC episode.

13. Recent (within the past 14 days) diagnosis of cerebrovascular accident, or transient ischemic attack.

14. Greater than 5 episodes of hospitalization for VOC in the past 6 months (180 days).

15. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

16. Any condition(s) that compromises the subject's ability to comply with and/or perform study-related activities or that poses a clinical contraindication to study participation (these conditions include, but are not limited to, inadequate medical history to assure study eligibility; inadequate venous access).

17. Subjects previously randomized in the current study.

18. Participation in other studies involving investigational drug(s) (Phases 1-4) within 4 weeks before the current study begins and/or during study participation.

19. Expectation that the subject will not be able to be followed for the duration of the study.

20. Pregnant female subjects or breastfeeding female subjects;

21. Male subjects able to father children and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the active treatment period (starting at VOC/Treatment-Ready Screening) and for at least 28 days after last dose of study drug.

22. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.

23. Active use of illicit drugs and/or alcohol dependence, as determined by the investigator.

4.3. Life Style Guidelines

4.3.1. Contraception

All male subjects who are able to father children and female subjects who are of childbearing potential and in the opinion of the investigator are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period (ie, starting at the time of VOC/Treatment-Ready Screening) and for at least 28 days after the last dose of study drug. The investigator or his/her designee, in consultation with the subject, will confirm the subject has selected an appropriate method of contraception for the individual subject and their partner from the permitted list of contraception methods (see below), and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least one of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the Schedule of Activities (see Table 1) and document such conversation in the subject's chart. In addition, the investigator or his/her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception are allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

5. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

4.3.2. Surgery

Elective Surgery: Elective surgery during the active treatment period (ie, starting at the time of VOC/Treatment-Ready Screening) through Day 35 Post-Discharge Follow-Up visit, should not be scheduled without first consulting with the Pfizer medical monitor.

Non-elective Surgery: Investigators should contact the Pfizer medical monitor regarding subjects who undergo non-elective surgery to discuss their suitability to remain in the study.

As indicated, recent major surgery is an exclusion criterion for this study. For the purposes of this study, major surgical intervention is defined as surgery involving open abdominal, intracranial or complex orthopedic procedures. Retroperitoneal and thoracic procedures are also considered major surgery. For other major surgeries contact the sponsor's medical monitor.

4.4. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the Investigator Site File that is maintained at the study site.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study number, contact information for the investigational (study) site and contact details for a contact center in the event that the study site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by study site staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the study site and the sponsor study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the study site and the sponsor study team for advice on medical questions or problems that may arise during the study (consult the Study Reference Manual for additional details on communication pathways and contact information). The contact number is not intended for use by the subject directly and if a subject calls that number they will be directed back to the study site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Council on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational products are Rivipansel and a phosphate buffered saline Placebo.

Subjects will be randomized at a 1:1 ratio to one of two treatment groups:

- Rivipansel;
- Placebo.

Subjects aged 12 and over who weigh >40 kg, will receive a loading dose of study drug of 1680 mg followed by a maintenance dose of 840 mg every 12 ± 2 hours. Subjects aged 6 to 11 years, or any subject who weighs ≤40 kg, will receive weight-based dosing (mg/kg) administered as a loading dose of 40 mg/kg (maximum of 1680 mg) followed by a maintenance dose of 20 mg/kg (maximum of 840 mg) every 12 ± 2 hours. Study drug will be administered until criterion 1 of the readiness-for-discharge criteria (see Section 7.1.1) has been met, or up to 15 doses of study drug (1 loading dose and a maximum of 14 maintenance doses), whichever comes first.

5.1. Allocation to Treatment

Assignment of subject identification number and study drug, site drug inventory control, and emergency unblinding will be managed by a randomization tool provided by the sponsor. A manual containing complete instructions for web access and use will be provided to each site prior to study start.

Study site staff will contact the randomization system (online) to enter the subject into the system either at the Pre-VOC/Study Entry Screening visit and/or the VOC/Treatment-Ready Screening visit, depending on the subject's point of entry into the study. The site will enter the subject into the system by indicating minimal information sufficient to distinguish one subject from another (eg, date of birth and gender). The system will generate a subject identification number. After it has been determined that all eligibility criteria have been met, the subject will be randomized to study drug via the randomization system.

Subjects will be prospectively stratified by age (6-11, 12-17, and ≥18 years of age) and genotype (category 1: HbSS, HbSβ^0 thalassemia and HbSD; category 2: HbSC, HbSβ^+ thalassemia and HbS-Variant [other than HbSD]), and randomized according to a computer generated pseudo random code using the method of permutated blocks balanced within each randomization strata.

Subjects will be randomized into one of the two treatment groups, either rivipansel every 12 hours or placebo every 12 hours with an allocation ratio of 1:1. This is according to a randomization schedule generated by the sponsor, and to which sponsor personnel directly involved in the study conduct are blinded. [redacted]

During a successful randomization, the randomization system will give the investigative site a code which corresponds to study drug that has been previously shipped to the site and is in the site's inventory ready to be dispensed. This code corresponds to study drug of that treatment group to which the subject has just been randomized. [redacted]

[redacted]

5.2. Breaking the Blind

The subject, sponsor, alliance partner (Parexel), and all other site staff and study personnel in direct contact with the study subjects will be blinded to treatment allocation. The research pharmacist (or designee) will be unblinded and will prepare and label all study drug/placebo in a blinded manner to maintain the blind for all other personnel.

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be an electronic process. Blinding codes should only be broken in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator should contact Pfizer or a designee (eg, Pfizer Medical Monitor, Pfizer clinician, Pfizer Study Manager, Parexel site monitor, or Parexel Clinical Operations Lead) before breaking the blind. If unable to consult with the sponsor study team, the investigator or sub-investigator may break the blind for a given subject experiencing an SAE or other medical emergency. The investigator accesses the appropriate randomization code for the given subject through the centralized randomization system. Any blinded individual who unexpectedly comes into possession of a subject's treatment assignment must immediately notify Pfizer or a designee (eg, Pfizer Medical Monitor, Pfizer clinician, Pfizer Study Manager, Parexel site monitor, or Parexel Clinical Operations Lead) without communicating the subject's treatment assignment. When the blinded code is broken, the reason must be fully documented on the case report form.

Subjects whose code is broken will be discontinued from study drug and will continue to be followed as per the procedures outlined in the Schedule of Activities (see Table 1), up to the Day 35 Post-Discharge Follow-Up visit (Visit 4).

Any broken blinds will be documented in the study report.

[redacted]

5.3. Subject Compliance

All doses of study drug will be administered by the appropriately designated staff at the investigational site. The site monitor will review all dosing records to ensure study drug was infused according to the protocol. Deviations will be documented.

5.4. Drug Supplies

5.4.1. Dosage Form(s) and Packaging

Rivipansel (as the sodium salt) will be supplied by the sponsor. Vials will contain rivipansel as a 30 mg/mL solution and the concentration of the solution is based on the active moiety. Rivipansel is presented as a sterile, colorless to pale brown solution for single use administration in a 30 mL clear glass vial sealed with a grey stopper and aluminum over-seal for administration by intravenous infusion. The content of the rivipansel vials should be

clear, but a fine swirl or haze of particulate matter may be observed on agitation of the solution.

A phosphate buffered saline (PBS) placebo, clear, colorless solution will also be supplied by the sponsor. The placebo will be supplied as a sterile solution for single use administration in a 30 mL clear glass vial sealed with a grey stopper and aluminum over-seal for administration by intravenous infusion.

Vials will be packaged in individual cartons and identified with a unique identification (ID) number for subsequent unit dose preparation according to the Investigational Product (IP) Handling Manual.

Each packaged lot of blinded drug supplies will look visually identical up to the carton containing the vials being opened. Therefore when the drug supplies are received at the site no special procedures are required to maintain the blind (ie, both the active and placebo vial cartons should be handled and stored the same). However, to avoid unblinding due to potential color difference between the active and placebo solutions, only unblinded study site staff should open the cartons containing the vials.

Vial adapters and syringe filters will be supplied by the sponsor for dose preparation.

For further details regarding the composition of the drug product and the placebo, please refer to the Investigator Brochure for Pfizer compound PF-06460031 (GMI-1070, rivipansel).

5.4.2. Preparation and Dispensing

The randomization system will identify the specific vials to be used to prepare the dose for each subject according to the randomization list.

Subjects aged 12 and over who weigh >40 kg, will receive a loading dose of 1680 mg followed by a maintenance dose of 840 mg every 12 ± 2 hours. Two vials will be assigned by the randomization system for the loading dose and a single vial for each of the subsequent maintenance doses.

Subjects aged 6 to 11 years, or any subject who weighs ≤40 kg, will receive a loading dose of 40 mg/kg (maximum of 1680 mg) followed by a maintenance dose of 20 mg/kg (maximum of 840 mg) every 12 ± 2 hours. The weight measured as part of the VOC/Treatment-Ready screening procedures will be used to determine the appropriate dose to be administered during the study.

Study drug will be administered until criterion 1 of the readiness-for-discharge criteria (see Section 7.1.1) has been met, or up to 15 doses of study drug (1 loading dose and a maximum of 14 maintenance doses), whichever comes first.

Active or placebo sterile solution for intravenous infusion will be prepared and stored according to details specified in the IP Handling Manual.

The unblinded pharmacist (or designee) will prepare the study drug and, as described in the IP Handling Manual, this will include the requirement for the study drug to be filtered upon transfer to the infusion bag or syringe through a 0.22 micron syringe filter. A second unblinded person on the study site staff must verify the correct dose was prepared prior to dispensing.

To avoid unblinding due to a potential color difference between the active and placebo solutions, only unblinded study site staff should open the vial cartons and prepare the dose.

The unblinded pharmacist (or designee) will prepare the study drug in a manner that will conceal any potential color difference between the active and placebo solutions, as described in the IP Handling Manual. For infusions administered with a syringe pump, the sponsor will provide sites with tinted translucent tape to cover the syringe and the in-line filter in the IV line. For infusions administered via infusion bag, sponsor-provided covers will be placed over the bag and tinted translucent tape will be used to cover the drip chamber and the in-line filter in the IV line. The unblinded pharmacist (or designee) will label the study drug in a manner that does not identify the contents. Blinded site staff will receive the study drug in a blinded manner from the pharmacy.

5.5. Administration

Dosing of eligible subjects will be initiated as early as possible, but no later than 24 hours from the administration of the first dose of IV opioids. Study treatment will be administered every 12 ± 2 hours until criterion 1 of the readiness-for-discharge criteria (see Section 7.1.1) has been met, or up to 15 doses of study drug (1 loading dose and a maximum of 14 maintenance doses), whichever comes first.

Prior to initiation of study drug infusion, the IV access should be flushed with normal saline to prevent any potential incompatibilities with residual solutions in the access line. Rivipansel or placebo solution will be infused intravenously over a period of 20 minutes (up to 40 minutes is allowable) from the start of the study drug IV infusion using an administration set that includes a 0.2 or 0.22 micron in-line filter, or an extension set with a 0.2 or 0.22 micron in-line filter. The dosing IV line must be flushed with normal saline to ensure complete administration of the study drug.

Details of the IV infusion will be described in the IP Handling Manual and the Study Drug Administration Guidance Document.

The planned schedule for dosing every 12 ± 2 hours should remain as *planned,* irrespective of adjustments for timing based on the 2 hour window for dosing. Dosing schedule should not be adjusted for actual dosing times. See example in Table 2 below.

Table 2. Sample Dosing Schedule (example of acceptable dosing schedule)

Dose	Planned Start Time	Actual Start Time
First dose/Loading dose (am)	9 am	9 am
Second dose (pm)	9 pm	10 pm
Third dose (am)	9 am	8:30 am
Fourth dose (pm)	9 pm	10:30 pm

Rivipansel sterile solution has been shown to be compatible with 5% Dextrose in Water (D5W), Normal Saline (0.9% sodium chloride, [NS]), or any combinations of the two; for example, 5% Dextrose in 0.9% sodium chloride (D5/NS), 5% Dextrose in 0.45% sodium chloride (D5/ ½ NS), and 5% Dextrose in 0.225% sodium chloride (D5/ ¼ NS). Any of these solutions may be co-administered alone or in combination with up to 20 mEq/L KCl. Co-administration with any other IV medications or fluids administered through the same IV line is not permitted.

5.6. Drug Storage

Vials of rivipansel and placebo solutions are required to be stored in their original container and in accordance with the study drug label.

The investigator, or an approved representative, eg, pharmacist, will ensure that all study drug, including placebo, are stored in a secured area with controlled access under recommended storage conditions and in accordance with applicable regulatory requirements.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of study drug receipt throughout the study. Even for continuous monitoring systems, a log or site procedure which ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no temperature excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to labeled storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the study drug must be quarantined and not used until Pfizer provides documentation of permission to use the study drug. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the product(s) are briefly out of labeled temperature range are not considered excursions. More specific details will be provided to the sites separately. Refer to the Investigational Product manual for additional details regarding excursion reporting requirements for the sites.

5.7. Drug Accountability

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies. Study drug inventory and accountability forms will be maintained by the unblinded pharmacist or designee, and examined and reconciled by the unblinded monitor.

The sponsor, or designee, will provide guidance on the destruction of unused study drug (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer and all destruction must be adequately documented.

5.8. Concomitant Treatment(s)

5.8.1. Prohibited Prior to Study Entry

Subjects receiving transdermal analgesics at the time of study entry will be excluded from enrolling into the study.

Active use of illicit drugs at the time of study entry is prohibited. The term "illicit drugs" includes, but is not limited to, cocaine, heroin, ecstasy, and phencyclidine (commonly known as 'PCP'). Investigators are encouraged not to enroll subjects for whom inappropriate use of prescribed opioids may interfere with interpretation of study endpoints.

5.8.2. Prohibited During the Study

Use of transdermal analgesics (including, but not limited to fentanyl or lidocaine patches) is not allowed for treatment of the qualifying episode of VOC during the study. The following are not considered transdermal analgesics: Transcutaneous Electrical Nerve Stimulation (TENS) units; skin patches that only deliver heat therapy such as a ThermaCare® patch, topical anesthetic creams, gels, or ointments (such as Lidocaine cream), or topical anesthetic sprays, provided they are not being administered to treat the episode of VOC.

Systemic steroid therapy used specifically for the treatment of an uncomplicated VOC is not permitted during the study. However, systemic steroid use for other indications (eg, severe reactive airway disease) is allowed.

5.8.3. Permitted During the Study

Treatments intended for other indications may be administered as usual. The use of inhaled or topical steroids, hydroxyurea, and nonsteroidal anti-inflammatory drugs (NSAIDs)will be allowed. The use of medical marijuana is not excluded for the purposes of this study.

All concomitant treatments taken during the study (1 week prior to signing or affirming VOC/Treatment-Ready informed assent/consent and through the last post-dose follow-up assessment) should be recorded in the source document and Case Report Form (CRF). All concomitant treatments should be confirmed and reviewed by the investigator or his/her designee prior to each dose for the duration of the study.

5.8.4. Pain Management

Pain management should follow the usual standard of care considering the institution's usual procedures and determined by the sickle cell disease clinical team which may include the hematologist, emergency medicine staff, pain specialist, hospitalist and nurse coordinator. Specific medications, dosing and infusion parameters should be individualized according to the subject's acute pain characteristics taking into account past medical history, concomitant medications, concurrent clinical concerns, and protocol restrictions as noted in Section 5.8.2.. The following suggestions are offered to standardize management:

- Recommended IV pain medications include, but are not limited to, morphine, hydromorphone, ketorolac, or fentanyl, used in accordance with standard clinical practice. Study site staff should contact Pfizer's medical monitor when considering medications not included in this list;
- Initial treatment should aim to achieve pain control; pain control is defined as pain that does not require further escalation of pain medication OR subject reports pain is controlled;
- Ongoing treatment should aim to maintain pain control; consider weaning IV opioids once pain is controlled;
- Patient-controlled analgesia (PCA) use (basal and bolus dosing) is encouraged for all subjects, per hospital procedure;
- In addition to IV pain medications, subjects should receive other supportive care and treatments according to standard of care. These may include, but are not limited to, the following:
    - adequate hydration per routine procedure;
    - incentive spirometry at regular intervals and/or other respiratory therapies (which are highly encouraged);
    - supplemental oxygen
    - adjunctive mechanical treatments such as massage, application of heat packs, etc.

5.8.5. Transfusion

In all cases, the medical judgment of the responsible physician will determine the course of treatment. The following suggestions are made for standardized management of transfusions in study subjects:

- Uncomplicated pain episodes generally do not require transfusion for treatment.
- Conditions that may develop during the course of the hospitalization which may require transfusion as determined by the physician might include, but are not limited to the following: acute neurologic event, severe ACS with significant oxygen requirement, unrelenting cases of priapism, severe anemia with cardiac decompensation, and/or symptomatic anemia (such as subjective shortness of breath or postural dizziness), worsening of anemia with an inadequate reticulocyte response, or splenic or hepatic sequestration.

6. STUDY PROCEDURES

NOTE: Due to the young age of some subjects in this study, certain activities, such as receiving follow-up phone calls, will be performed by a subject's proxy and/or caregiver. A proxy or caregiver is a person who provides for and/or oversees the general care of the subject and could be a parent, other family member, or legally acceptable representative. Where applicable in this protocol, the term subject will also refer to proxy and/or caregiver.

[redacted]

Electronic devices (eg, smart phone, tablet, or computer) will be used by the study site staff to record their assessment of specified readiness-for-discharge criteria via an eClinRO web-based data capture system (see section 7.1.1). If the study site staff attempt, but are unable to complete the readiness-for-discharge questionnaire in the eClinRO web-based capture system for an individual assessment and/or confirmation, a back-up data capture method may be utilized as outlined in the Readiness-for-Discharge Assessments guidance document.

[redacted] eClinRO Training

Training materials and user guides will be provided to the study site staff and the subjects. Before being allowed to enter clinical data into the [redacted] eClinRO devices, each user must be trained in use of the system and their responsibilities for data entry. Each subject or proxy allowed to enter clinical data must select a Personal Identification Number (PIN) that must be kept private and must only be used by the subject and/or any proxy/proxies. Similarly, each study site staff personnel allowed to enter clinical data must select a password that must be kept private. Clinical data will not be able to be entered without first entering the PIN or password. The [redacted] eClinRO systems will authenticate the identity of the user. All users must be trained that passwords and PIN codes are not to be shared.

An on-system training module will be employed in which successful completion of the module is a gateway to allowing study site staff and subjects to proceed with using the system unaided.

The study site will allow access to view data on the [redacted] eClinRO systems to authorized regulatory personnel or sponsor auditors in conformance with information in the Investigator Initiation Package.

Site Responsibilities for [redacted] eClinRO

The details of site responsibilities and procedures for [redacted] eClinRO will be covered in more detail in documentation provided to the study site staff.

The investigator must make sure that the delegation of responsibility to study site staff for [redacted] entering data into the [redacted] eClinRO systems are specifically documented using the appropriate forms and are based on documented evidence of adequate training in administration and use of the [redacted] eClinRO systems. Regardless of how the Investigator delegates responsibility for [redacted] entering data into the [redacted] eClinRO device, the investigator remains responsible for providing adequate supervision and oversight of the colleagues, employees, and any third parties per Food and Drug Administration (FDA) regulations and guidelines and Good Clinical Practice.

The details of Site Monitor responsibilities and procedures for [redacted] eClinRO will be covered in more detail in the Study Monitoring Plan.

[redacted] eClinRO Vendor Responsibilities

The [redacted] eClinRO systems will conform to regulations and regulatory guidance concerning data security.

The [redacted] eClinRO vendor will take responsibility for hosting and administration of their database on behalf of the study sites until the study sites have received and accepted the official archive of the clinical data entered into the [redacted] eClinRO system. Clinical data in the [redacted] eClinRO database, including Readiness for Discharge Criteria 1 and 2 [redacted] will be maintained by the vendor during that period will be considered source data. The vendor will not modify the source data except by signed instruction of the relevant principal investigator or study site staff member specifically delegated that duty by the principal investigator, consistent with good clinical practice and provisions of the protocol.

6.1. Screening

6.1.1. Pre-VOC/Study Entry Screening

6.1.1.1. Consent of Subjects

A written, Pfizer and institutional review board (IRB)/ ethics committee (EC)-approved, informed consent/assent (as appropriate) must be obtained before initiating study procedures. See Section 12.3.

Investigators may choose to identify, through chart review, those subjects who may be appropriate for the study before they develop VOC. These subjects may be educated about the study [redacted] when they are well, such as in the office setting, and approached for consent/assent while not experiencing a pain crisis.

After consent, subject information will be entered into the sponsor's randomization system to document the subject has entered into the Pre-VOC/Study Entry Screening period. A subject identification number will be generated. Serious adverse events must be reported to Pfizer from the time of signing Pre-VOC/Study Entry informed consent.

Formal assessment for eligibility will not be performed at this time. No blood samples will be collected for laboratory analysis. The subject will not be enrolled, or randomized to a treatment arm at this time. Subjects who sign consent pre-VOC may discontinue the study at any time. At the time of VOC, the subject will be asked if they want to continue participating in the VOC/Treatment-Ready Screening and if eligible, be randomly assigned to blinded study drug. The subject's affirmation must be documented.

These subjects will have the option of using a transportation service to take them to and from the hospital at the time of their crisis.

6.1.1.2. Monthly Telephone Contacts

Study site staff will be encouraged to contact the subject by telephone every 4 weeks (±7 days). During these phone contacts, the study site staff will ask the subject how they have been feeling, as well as remind the subject about the appropriate procedures to follow when experiencing an acute VOC event necessitating hospitalization (including use of the transportation service provided by the sponsor). If the subject or investigator prefer, the monthly contacts may be a clinic visit.

6.1.2. VOC/Treatment-Ready Screening

6.1.2.1. Visit 1, VOC/Treatment-Ready Screening

In addition to consenting a subject in the office setting, prior to a pain crisis, some subjects may be initially approached for consent when presenting to the emergency room/clinic in VOC. Investigators are encouraged to identify subjects with VOC who are planned or likely to be admitted, and approach them for consent/assent and eligibility criteria early in the process of treatment for VOC.

A written, Pfizer and institutional review board (IRB)/ethics committee (EC)-approved, informed consent/assent (as appropriate) must be obtained before initiating study procedures. See Section 12.3.

For subjects consented while well, it is necessary for the subject to affirm informed consent at the time of VOC.

Following consent/assent or affirmation of informed consent (if applicable) at the time of VOC, all subjects will enter the VOC/Treatment-Ready screening period and undergo the following screening activities to determine if they are eligible for the study. Blood samples for laboratory tests, which are required to determine eligibility, will be drawn at this visit. If the screening tests have exclusionary results that are considered, in the opinion of the investigator, to be due to a laboratory error or a transient condition, these tests may be repeated once during the VOC/Treatment-Ready screening period after discussion with the sponsor's medical monitor.

Results from local laboratory tests conducted, prior to informed consent being obtained for the study, as part of the subject's standard of care can be used as Screening samples (examples include Hematology and Serum Chemistry panels and urinalysis) to determine the subject's eligibility provided the samples were collected within 24 hours prior to the time of VOC/Treatment-Ready informed consent (or affirmation of consent), and, the subject appears clinically unchanged in the opinion of the investigator. This includes pregnancy test results provided the test performed had a sensitivity of at least 25 mIU/mL. Should the investigator believe there is any clinical reason a test result may have changed, then the test should be repeated.

Site staff should perform the activities listed below.

1. For subjects consented at the time of VOC, enter subject information into sponsor's electronic randomization system to document the subject has entered into the VOC/Treatment-Ready screening period. A subject identification number will be generated.

2. Collect vital signs (temperature [°Celsius], respiratory rate, pulse, blood pressure, and pulse oximetry).

3. Measure body weight and height.

[redacted]

[redacted]

5. Conduct a complete physical examination including an assessment of the following body systems: general appearance, skin, head, ears, eyes, nose, mouth, throat, spine, neck, thyroid, chest, respiratory, cardiovascular, abdominal (including liver and kidneys), musculoskeletal, extremities, neurological, genitourinary and lymph nodes. Particular attention will be directed at areas affected by pain as well as to the respiratory system for clinical signs of ACS such as chest wall pain, tachypnea and wheezing or rales on chest auscultation and the genitourinary system for clinical signs of priapism.

6. Collect blood samples for:

   - Hematology panel (see Table 3); local laboratory;
   - Serum Chemistry (see Table 3); local laboratory;
     - eGFR must be calculated as per Appendix 1

   [redacted]

   - Hemoglobin Electrophoresis; central laboratory. Note: Sample will only be collected if subject's diagnosis of SCD (ie, laboratory result by hemoglobin electrophoresis, High Performance Liquid Chromatography [HPLC], or genotype analysis) cannot be source documented. The result of this sample is not needed for determining study eligibility.

7. Collect urine for Urinalysis; to be analyzed at the local laboratory.

8. Perform contraception check (see Section 4.3.1). Confirm that the subject, if female, has not missed a menstrual period or is otherwise at risk for suspected pregnancy (to avoid the situation in which the subject is pregnant but it is too early to result in a positive urine pregnancy test). Female subjects who have missed a menstrual period should not be enrolled until that issue is resolved.

9. Perform pregnancy test on female subjects of childbearing potential. Pregnancy test result is to be available and negative to confirm the subject does not meet Exclusion Criterion #20 and in advance of randomization for study drug dosing assignment.. Study drug should not be administered when the pregnancy test result is indeterminate or positive.

10. Collect demographic information and medical history.

11. Collect Sickle Cell Disease-specific history (eg, SCD genotype, start time of this VOC event, medications used to treat this pain event, frequency of painful crises requiring hospitalization, SCD related complications such as history of ACS, priapism, etc).

12. Record prior and concomitant medication: all medications administered within 1 week of signing the VOC/Treatment-Ready informed assent/consent or affirmation of informed consent (if applicable).

13. Record prior and on-going parenteral opioids administered.

14. Record prior and concomitant non-drug treatments/procedures: all non-drug treatments/procedures administered within 1 week of signing the VOC/Treatment-Ready informed assent/consent or affirmation of informed consent (if applicable).

15. Review and confirm study eligibility criteria.

16. If subject has met all eligibility criteria, enter subject information using sponsor's electronic randomization system to document the subject has been enrolled and obtain randomization information.

If the subject is determined to be a screen failure due to inability to initiate dosing within 24 hours from the administration of the first dose of IV opioids, presence of serious infection, ACS, or other recent clinical events excluding the subject from participating, rescreening will be allowed at the time of the subject's next VOC, pending approval from the sponsor's medical monitor. All screening procedures would have to be repeated, including the consent process, as part of the re-screening process.

6.2. Study Period

6.2.1. Visit 1, Day 1 – Loading Dose

All subjects should be dosed with study drug as early as possible, but the start of study drug dosing should be no later than 24 hours from the administration of the first dose of IV opioids.

At this visit, the following will be performed:

1. Record adverse events.

2. Record concomitant medications, including parenteral opioid use. Record IV opioid use approximately every 4 hours for the first 48 hours from the start time of the study drug loading dose.

3. Record concomitant non-drug treatments/procedures.

[redacted]

5. Administer study drug infusion. Record the date and time (24-hour clock) of the beginning and the end of the infusion.

Dosing with study drug will continue every 12 (±2) hours until the study drug is discontinued. For those subject 6 to 11 years old, or any subject ≤ 40kg, the weight measured as part of the VOC/Treatment-Ready screening procedures will be used to determine the appropriate dose to be administered during the study. Study drug will be administered as described in Section 5, Study Treatments.

6.2.2. Visit 1, Day 1 – First 24 Hours After Loading Dose

During the first 24 hours from the start time of the loading dose the following activities will be performed:

[redacted]

3. Record adverse events.

4. Record concomitant medications, including parenteral opioid use. Record IV opioid use approximately every 4 hours for the first 48 hours from the start time of the study drug loading dose.

5. Record concomitant non-drug treatments/procedures.

[redacted]

8. Evaluate readiness-for-discharge criteria using the eClinRO web-based data capture system every 4 (±1) hours from the start time of the loading dose during "daytime hours" only (defined as 6:01am to 10:00pm). Evaluate and capture data relevant to readiness-for-discharge criteria data in the electronic Case Report Form (eCRF) as per data capture requirements (see Section 7.1.1). Depending on what time the loading dose is

administered, the schedule of readiness-for-discharge assessments may be different for the day the study drug loading dose is administered than for subsequent days (refer to Section 7.1.1 for details on the exact timing of the readiness-for-discharge assessments). If it becomes apparent that the subject has become ready-for-discharge during the "night-time hours" (defined as 10:01pm to 6:00am), an ad hoc assessment should be undertaken.

9. Administer study drug infusion every 12 (±2) hours after loading dose. Record the date and time (24-hour clock) of the beginning and the end of each infusion.

6.2.3. Visit 1, Day 2 through Day 8 (or End of Treatment)

While the subject is hospitalized, the following activities are to be performed on a daily basis, unless otherwise noted, until End of Treatment:

1. Record adverse events.

2. Record concomitant medications, including parenteral opioid use. Record IV opioid use approximately every 4 hours for the first 48 hours from the start time of the study drug loading dose.

3. Record concomitant non-drug treatments/procedures.

4. Collect vital signs (temperature [ºCelsius], respiratory rate, pulse, blood pressure, and pulse oximetry).

[redacted]

7. Conduct a targeted physical exam, daily through 24 hours after last dose (if not discharged first), assessing the following at a minimum: skin, chest, respiratory, cardiovascular, abdominal, and musculoskeletal systems. Particular attention will be directed at areas affected by pain. Additional body systems may be examined at the discretion of the investigator.

8. Evaluate readiness-for-discharge criteria using the eClinRO web-based data capture system every 4 (±1) hours during "daytime hours" only (defined as 6:01am to 10:00pm). Evaluate and capture data relevant to readiness-for-discharge criteria data in the eCRF as per data capture requirements (see Section 7.1.1). Refer to Section 7.1.1 for details on the exact timing of the readiness-for-discharge assessments. [redacted]

9. Administer study drug infusion every 12 (±2) hours until criterion 1 of the readiness-for-discharge criteria (see Section 7.1.1) has been met, or up to 15 doses of study drug, whichever comes first. Record the date and time (24-hour clock) of the beginning and the end of each infusion.

[redacted]

The following End of Treatment procedures are to be performed within 24 hours after the last dose of study drug. This will occur prior to discharge, either on Day 8 or earlier.

1. Conduct a targeted physical exam, assessing the following at a minimum: skin, chest, respiratory, cardiovascular, abdominal and musculoskeletal systems. Particular attention will be directed at areas affected by pain. Additional body systems may be examined at the discretion of the investigator.

2. Collect vital signs (temperature [ºCelsius], respiratory rate, pulse, blood pressure, and pulse oximetry).

3. Collect blood samples for:

   - Hematology panel (see Table 3); local laboratory;
   - Serum Chemistry (see Table 3); local laboratory;

   [redacted]

4. Collect urine for Urinalysis; to be analyzed at the local laboratory.

5. Perform pregnancy test on female subjects of childbearing potential.

[redacted]

8. Evaluate readiness-for-discharge criteria using the eClinRO web-based data capture system every 4 (±1) hours during "daytime hours" only (defined as 6:01am to 10:00pm). Evaluate and capture data relevant to readiness-for-discharge criteria data in the eCRF as per data capture requirements (see Section 7.1.1). Refer to Section 7.1.1 for details on the exact timing of the readiness-for-discharge assessments. [redacted]

9. Record adverse events.

10. Record concomitant medications, including parenteral opioid use.

11. Record concomitant non-drug treatments/procedures.

6.2.4. Visit 1, Post-Treatment Daily Assessments

Subjects who remain hospitalized after their treatment with study drug ends (on Day 8 or earlier) will undergo the following assessments for each additional day of hospitalization:

1. Collect vital signs (temperature [°Celsius], respiratory rate, pulse, blood pressure, and pulse oximetry).

[redacted]

4. Evaluate readiness-for-discharge criteria using the eClinRO web-based data capture system every 4 (±1) hours during "daytime hours" only (defined as 6:01am to 10:00pm). Evaluate and capture relevant readiness-for-discharge criteria data in the eCRF as per data capture requirements (see Section 7.1.1). Refer to Section 7.1.1 for details on the exact timing of the readiness-for-discharge assessments. [redacted]

5. Record adverse events.

6. Record concomitant medications, including parenteral opioid use.

7. Record concomitant non-drug treatments/procedures.

6.2.5. Discharge

At the time the discharge order is written, the following activities are to be performed:

1. Conduct a targeted physical exam assessing the following at a minimum: skin, chest, respiratory, cardiovascular, abdominal and musculoskeletal systems. Particular attention will be directed at areas affected by pain. Additional body systems may be examined at the discretion of the investigator.

2. Record adverse events.

3. Record concomitant medications, including parenteral opioid use.

4. Record concomitant non-drug treatments/procedures.

[redacted]

7. Evaluate readiness-for-discharge using the eClinRO web-based data capture system. Evaluate and capture data relevant to readiness-for-discharge criteria data in the eCRF as per data capture requirements (see Section 7.1.1). Note: Subjects should continue to be followed until leaving the hospital, even if the readiness-for-discharge criteria have been met, to ensure there are no updates needed.

8. Record the date and time of discharge (documented date and time of the hospital discharge order [written or verbal] by a qualified healthcare provider).

[redacted]

11. Educate the subject about the open-label extension study, Study B5201003, as appropriate.

6.3. Post-Discharge Daily Assessments

[redacted]

6.4. Post-Discharge Follow-Up Visits

6.4.1. Visit 2, Day 7 Post-Discharge Follow-Up Phone Call

Approximately 7 (±3) days after discharge, the investigator (or designee) will contact the subject by telephone in order to collect information regarding the occurrence of any AEs, the use of concomitant medications and treatments/procedures, and to remind the subject about using appropriate contraception (if applicable) and the upcoming Day 35 Post-Discharge Follow-Up visit (Note: If the subject or investigator prefer, the Day 7 Post-Discharge contact may be a clinic visit). [redacted]

6.4.2. Visit 3, Day 21 Post-Discharge Follow-Up Phone Call

Approximately 21 (±5) days after discharge, the investigator (or designee) will contact the subject by telephone in order to collect information regarding the occurrence of any AEs, the use of concomitant medications and treatments/procedures, and to remind the subject about using appropriate contraception (if applicable) and the upcoming Day 35 Post-Discharge Follow-Up visit (Note: If the subject or investigator prefer, the Day 21 Post-Discharge contact may be a clinic visit).

6.4.3. Visit 4, Day 35 Post-Discharge Follow-Up/Early Termination

The following activities are to be performed 35 (±5) days after discharge. However, if the subject is experiencing a VOC or other acute SCD-related event, the visit should be delayed until the acute event has resolved. If the subject terminates from the study early, these same procedures are to be performed no sooner than 28 days from the last dose of study drug.

1. Conduct a targeted physical exam assessing the following at a minimum: skin, chest, respiratory, cardiovascular, abdominal and musculoskeletal systems. Particular attention will be directed at areas affected by pain. Additional body systems may be examined at the discretion of the investigator.
2. Record adverse events.
3. Record concomitant medications.
4. Record concomitant non-drug treatments/procedures.
5. Collect vital signs (temperature [°Celsius], respiratory rate, pulse, blood pressure, and pulse oximetry).
6. Collect blood samples for:
   - Hematology panel (see Table 3); local laboratory;
   - Serum Chemistry (see Table 3); local laboratory;
   - [redacted]

7. Collect urine for Urinalysis; to be analyzed at the local laboratory.

8. Perform contraception check, if applicable (see Section 4.3.1). Document discussion with subject.

9. Perform pregnancy test on female subjects of childbearing potential.

[redacted]

11. Obtain informed consent/assent from the subject for participation in the open-label extension study, Study B5201003, as appropriate. Informed consent/assent for Study B5201003 may be obtained from the time of the Day 35 Post-Discharge Follow Up visit up to 180 days after the Day 35 Post-Discharge Follow-Up visit.

6.5. Subject Re-hospitalization

Events resulting in subject re-hospitalization up until the Day 35 Post-Discharge Follow Up visit are to be recorded and reported as serious adverse events according to the definition in Section 8.7. All re-hospitalizations will be recorded on the hospitalization record case report form. If a subject is re-hospitalized the reason for the re-hospitalization (VOC, ACS, priapism, stroke, aplastic crisis, infection, and splenic sequestration, or other) will be recorded as well as any additional AEs, concomitant medications, treatments and procedures on the appropriate case report forms. Local laboratory results should also be reported.

6.6. Subject Withdrawal

Subjects will be withdrawn from drug administration if any of the following occur:

- Subject refuses to continue treatment.
- Severe ACS, as defined in the protocol (see Section 7.2.4.2.1).
- Acute stroke, or other acute central nervous system changes.
- Serious systemic infection (suggestive of sepsis) with fever >39° C (102.2° F).
- Serious systemic infection, evidenced by clinical signs and symptoms, and/or microbiological investigations, consistent with this diagnosis requiring escalation in medical care, such as meningitis, bacteremia, empyema, or osteomyelitis. Simple pneumonia, responding to antibiotics and not requiring intensive care unit (ICU) care or packed RBC transfusion, will not require withdrawal from study drug administration.
- Elevated WBC >50,000/mm^3.
- Unexpected rise in creatinine, or fall in eGFR, consistent with acute renal failure (see Section 7.2.4.1).

- Pregnancy.
- Severe cutaneous manifestation (see Section 7.2.4.3.1).

All randomized subjects who withdraw from drug administration during the double-blind study treatment period, but continue on the study (including subjects who are randomized but not treated), will continue to be followed as per the procedures outlined in the Schedule of Activities (Table 1), up to Day 35 Post-Discharge Follow-Up visit (Visit 4). [redacted] All efforts will be made to obtain safety data and other endpoint data from subjects. [redacted]

A subject may be withdrawn from the study for any of the safety concerns as listed above, in addition to the following reasons:

- Consent is withdrawn.
- Subject refuses procedures/observations.
- Other reasons (eg, significant protocol violations, non-compliance).

All abnormal laboratory events of clinical significance should be followed until the laboratory values have returned to normal or baseline levels.

If a subject has any clinically significant, study related abnormalities at the conclusion of the study, the Pfizer medical monitor (or designated representative) should be notified and every effort should be made to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

Withdrawal of Consent: Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Subjects who withdraw consent at the time of VOC (and were not randomly assigned) should be considered screen fails.

The reason for a subject discontinuing from the study will be recorded in the CRF. A discontinuation occurs when a randomized subject ceases participation in the study, regardless of the circumstances, prior to completion of the protocol. The investigator must determine the primary reason for discontinuation. Should a subject withdraw from the study after receiving study drug, but prior to End of Treatment or Discharge, the subject should complete the procedures as per the End of Treatment visit (Visit 1, see Table 1, Schedule of Activities) at the time of the study discontinuation or as soon as possible thereafter. Subjects withdrawn from the study after End of Treatment or Discharge should return for safety evaluation as per Day 35 Post-Discharge Follow-Up visit (Visit 4) no sooner than 28 days from the last dose of study drug. The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up for each such subject, and document the course of the subject's condition.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In accordance with due diligence requirements, if a subject fails to return for scheduled visit(s), the site shall record information concerning attempts to contact the subject in the subject source documents, including method of contact (eg, letter, phone call) and date of each attempted contact. It is recommended that the investigational site makes two phone calls to a subject who missed the visit, documenting each call in the source documents. A third contact attempt should be a certified letter to the subject, and this letter and the response received become part of the source documents. If a site has made at least 3 unsuccessful attempts to contact the subject and 60 days have elapsed since discharge, the subject is considered lost to follow up (LTFU). Subject's status should be designated LTFU in the CRF and in the study monitoring report. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If after all attempts, the subject remains LTFU, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records. If the subject returns to the site beyond 60 days post-discharge after having been determined to be LTFU, Visit 4, Day 35 study procedures do not need to be performed. Any safety events (SAE/AEs) that occurred up to the date when the subject's Visit 4, Day 35 Post Discharge should have occurred are to be recorded in both the medical records and the eCRF. In addition, SAEs (including any SAEs that may have occurred beyond the subject's Visit 4, Day 35 Post Discharge) will be reported as defined in Section 8.2 of the protocol.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be

collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The sponsor study team will be informed of these incidents in a timely fashion.

7.1. Efficacy

Methods of measuring the efficacy of rivipansel in treating subjects hospitalized for acute VOC that will be used throughout the study are described in this section.

7.1.1. Readiness-for-Discharge Criteria

The primary endpoint is time to readiness-for-discharge, where readiness-for-discharge is met when all of the applicable 6 criteria are documented to have occurred – the criteria are to be assessed in relation to treatment for this VOC event and acute complication(s) directly related to this VOC event:

1. Only oral pain medication is required.
2. Acute complications related to VOC (such as ACS, stroke, priapism) have resolved to the extent that management can be in an outpatient setting, if applicable.
3. IV opioids have been discontinued.
4. IV hydration has been discontinued, if applicable.
5. IV antibiotics have been discontinued, if applicable.
6. RBC transfusion is no longer required for the treatment of this VOC, if applicable.

Refer to the current version of the Readiness-for Discharge Assessments guidance document for examples and further information.

All criteria will be assessed by a member of the study site staff who will complete the readiness-for-discharge questionnaire in the eClinRO web-based data capture system, and enter data in the eCRFs (as appropriate). Once criteria 1 and/or 2 are met, they must be confirmed by the Investigator or qualified designee in the eClinRO web-based data capture system. The Investigator or qualified designee should be deemed, according to the institution's standard of care, appropriately qualified to determine discharge readiness and could be a physician, nurse practitioner, physician assistant, or other medical personnel. To

clarify, if criteria 1 and/or 2 are determined to be met by a member of the study site staff other than the Investigator or qualified designee, then the Investigator or qualified designee must confirm that assessment in the eClinRO web-based data capture system prior to the time the next scheduled assessment is to be made, or the time the subject is discharged, whichever comes first. Confirmation in the eClinRO web-based data capture system will also be required if there is a reversal in subsequent assessments of criteria 1 or 2. The Investigator or qualified designee will be notified in real-time via the eClinRO system whenever criteria 3 through 6 are noted to have been met by the assessor in the system. Site-staff will ensure that relevant data corresponding to criteria 3 through 6 are entered into the eCRF in a timely manner based on the subject's medical records.

The readiness-for-discharge criteria will be assessed in all subjects at pre-defined intervals (and ad hoc as necessary) from the start time of the loading dose until discharge. Routine assessments are to be performed during "daytime hours" only (defined as 6:01am to 10:00pm). Assessments are not to be performed during "night-time hours" (defined as 10:01pm to 6:00am), unless it becomes apparent that the subject has become ready-for-discharge during the "night-time hours", in which case an ad hoc assessment should be undertaken. If all readiness-for-discharge criteria are confirmed to be met prior to the discharge order being issued, and there are no reversals of the readiness-for-discharge status, further evaluations are not required to be documented in the eClinRO system following the time of the discharge order. However, all subjects should be followed until they have left the hospital (i.e., even after the discharge order is issued) to ensure there are no subsequent updates required to the readiness-for-discharge evaluation in the eClinRO system.

The schedule of readiness-for-discharge assessments may be different for the day the study drug loading dose is administered than for subsequent days. The details around the difference in these schedules are as follows:

> If a subject receives their loading dose during the "daytime hours", readiness-for-discharge assessments for that day will be performed every 4 (±1) hours from the start time of the loading dose until 10:00pm. At 10:00pm (±1 hour) an assessment will be performed, signaling the end of the "daytime hours" and the start of the "night-time hours". The next routine assessment will then be at 6:01am (±1 hour) the following morning, signaling the start of the "daytime hours" for that day. The schedule will then be reset such that, further assessments will be performed at 4 (±1) hourly intervals until 10:00pm (±1 hour) that night and this schedule of assessments (6:01am, 10:00am, 2:00pm, 6:00pm and 10:00pm, each ±1 hour) will continue for all subsequent days of Visit 1, until the subject is discharged from the hospital.
>
> If a subject receives their loading dose during the "night-time hours" then the first routine assessment of readiness-for-discharge will be at 6:01am (±1 hour) at the end of the "night-time hours" and the start of the "daytime hours". Further assessments will then be performed at 4 (±1) hourly intervals until 10:00pm (±1 hour) that night and this schedule of assessments (6:01am, 10:00am, 2:00pm, 6:00pm and 10:00pm,

each ±1 hour) will continue for all subsequent days of Visit 1, until the subject is discharged from the hospital.

In addition, an assessment should always be made at the time the decision is made to discharge the subject, regardless of the hour.

If the subject is asleep during "daytime hours" and IV opioids have not yet been discontinued, the subject does not have to be woken to perform the assessment as this can be undertaken while the subject remains asleep. However, if IV opioids have been discontinued then it may be necessary to wake the subject to determine the answer to Question 1 (Only oral pain medication is required?).

The study site staff, including the investigator (or qualified designee), will use an electronic device (eg, smart phone, tablet, or computer) to access the eClinRO web -based data capture system to record and confirm responses to the criteria in the readiness-for-discharge questionnaire. Example screen shots of the readiness-for-discharge questionnaire are included in the eClinRO reference document.

If the study site staff attempts, but is unable to complete the readiness-for discharge questionnaire in the eClinRO system, a back-up data capture method will be utilized as outlined in the Readiness-for-Discharge Assessments guidance document.

If a subject did not receive any IV hydration, IV antibiotics or RBC transfusions, or had no acute complications related to VOC, then these criteria will not affect the determination of the primary endpoint (ie, they are not applicable).

The derivation of the primary endpoint of time to readiness-for-discharge makes use of the dates and times when each of the individual criteria are met. In this derivation:

- For criteria 1 , the earliest date and time of "yes" reported by assessor and confirmed by the Investigator or qualified designee after the last "no" response recorded in the eClinRO web-based data capture system will be used.
- For criteria 2 , the earliest date and time of "yes" reported by assessor and confirmed by the Investigator or qualified designee after the last "no" response, or a confirmed "not applicable" response, in the eClinRO web-based data capture system will be used.
- For criteria 3 through 6, the latest stop date and time in the corresponding eCRF will be used.

After the date and time are determined as above for each of the applicable criteria, the date and time of readiness-for-discharge is defined as the latest of the dates and times among the applicable criteria.

The time to readiness-for-discharge is the difference in hours, between the time and date of the initiation of the first infusion of study drug and the time and date of readiness-for-discharge.

If one or more criteria are never met for a subject, before the subject is discharged, then the time to readiness-for-discharge will be considered as censored. Details on censoring rules are provided in the statistical analysis plan (SAP).

[redacted]

7.2. Safety

Safety will be assessed by physical examinations, vital signs, clinical laboratory results and the spontaneous reporting of AEs, in all subjects who sign consent/assent. Unscheduled safety assessments may be performed at any time during the study to assess any perceived safety concerns. Investigators and Pfizer Clinicians will review individual subject data throughout the conduct of the study to ensure subjects' well-being.

7.2.1. Physical Examination

A complete physical examination will be performed at the VOC/Treatment-Ready Screening visit (see Table 1, Schedule of Activities). The following parameters and body systems will be assessed and any abnormalities described: general appearance, skin, head, ears, eyes, nose, mouth, throat, spine, neck, thyroid, chest, respiratory, cardiovascular, abdominal (including liver and kidneys), musculoskeletal, extremities, neurological, genitourinary and lymph nodes. Particular attention will be directed at areas affected by pain as well as to the respiratory system for clinical signs of ACS such as chest wall pain, tachypnea and wheezing or rales on chest auscultation and the genitourinary system for clinical signs of priapism.

A targeted physical examination will be performed daily while the subject is in the hospital through 24 hours after the last dose of study drug (if not discharged first), at discharge, and at Day 35 Post-Discharge Follow-Up visit (Visit 4) (see Table 1 Schedule of Activities) assessing the following at a minimum: skin, chest, respiratory, cardiovascular, abdominal and musculoskeletal examinations. Particular attention will be directed at areas affected by pain. Additional body systems may be assessed at the discretion of the investigator.

7.2.2. Vital Signs

Temperature, respiratory rate, pulse, blood pressure, and pulse oximetry will be collected throughout the study at the VOC/Treatment-Ready Screening visit, daily while the subject is in the hospital, and at Day 35 Post-Discharge Follow-Up visit (Visit 4) (see Table 1 Schedule of Activities).

Temperature will be collected as oral, tympanic, temporal, or axillary temperature measured in degrees Celsius. Sites are encouraged to use the same method throughout the study.

Blood pressure should be measured in the subject's dominant arm and recorded to the nearest mmHg. Sites are encouraged to use the same arm throughout the study. All blood pressure should be measured consistently throughout the study with the subject in a supine position or in a sitting position, depending on the subject's clinical status.

The use of automated devices for measuring blood pressure and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained first.

Weight is to be measured in kilograms.

Height is to be measured in centimeters and recorded to one decimal place using a stadiometer, if available. The height should be measured with the subject not wearing shoes. If necessary, height can be measured while subject is lying down.

Pulse oximetry will be measured with a pulse oximeter and reported as a percent (use of oxygen supplementation will also be recorded).

7.2.3. Clinical Laboratory Evaluation

Blood and urine samples will be collected at each specified study visit (see Table 1, Schedule of Activities). Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns or in accordance with the guidelines for subject safety monitoring and discontinuation. Clinically significant abnormal findings should be recorded as AEs per Section 8.5.

The following laboratory tests will be performed locally during the study at the VOC/Treatment-Ready Screening visit, End of Treatment, and the Day 35 Post-Discharge Follow-Up visit:

Table 3. Clinical Laboratory Evaluations – Local Laboratory

Hematology	
Hemoglobin	Reticulocyte count
Hematocrit	Platelet count
Red blood cell (RBC) count	WBC count with differential
Serum Chemistry	
Blood urea nitrogen (BUN)	Alanine aminotransferase (ALT/SGPT)
Creatinine	Aspartate aminotransferase (AST/SGOT)
Electrolytes (Sodium, Potassium, Chloride and Bicarbonate) with glucose	Fractionated bilirubin
Lactate dehydrogenase (LDH)	
Urinalysis	
Protein	Blood
Glucose	Nitrite
Ketones	Leukocyte esterase
Estimated Glomerular Filtration Rate (eGFR) at VOC/Treatment-Ready Screening visit (calculated using age appropriate formula in Appendix 1)	

Note: A hemoglobin electrophoresis sample will be collected at the VOC/Treatment-Ready Screening visit and analyzed at the central laboratory only if the subject's diagnosis (ie, laboratory result by hemoglobin electrophoresis, HPLC, or genotype analysis) cannot be source documented.

7.2.4. Triggered Requirements

This section presents specific safety parameters of concern for the study drug that require follow-up action.

Table 4. Triggered Requirements

Condition	Action
Changes in Renal Function	
If the repeat eGFR result is ≤60 mL/min/1.73 m^2	Stop study drug administration
Severe Acute Chest Syndrome (Section 7.2.4.2.1)	Stop study drug administration
Severe Cutaneous Manifestations (Section 7.2.4.3.1)	Stop study drug administration

7.2.4.1. Changes in Renal Function

The identification of deteriorating renal function could be based on rising serum creatinine or blood urea nitrogen (BUN), worsening proteinuria, or other abnormalities on urinalysis (with or without microscopic evaluation), or a change in clinical features (such as changes in urine output or physical findings such as pedal edema). Based on the clinical judgment of the investigator if any of these or other clinical features develop, the eGFR is to be repeated (refer to Appendix 1 for calculation). Given that subjects are eligible to participate in this study if their eGFR is >60 mL/min/1.73 m^2, if the repeat eGFR is ≤60 mL/min/1.73 m^2 treatment is to be stopped.

7.2.4.2. Acute Chest Syndrome Events

For the purposes of this protocol, ACS will be defined by NIH treatment guidelines[24,25] as follows:

- New pulmonary infiltrate involving at least one complete lung segment consistent with the presence of alveolar consolidation, (excluding atelectasis) AND one or more of the following:
    a. Chest pain;
    b. Temperature >38.5° C;
    c. Tachypnea;
    d. Wheezing or rales;
    e. Cough.

Note: the clinical signs and symptoms of ACS were updated in the NIH Evidence-Based Management of Sickle cell Disease: Expert Panel Report (2014), however, for the purposes of this protocol the above definition will continue to be used[29]

Subjects will be monitored for development of ACS throughout the study. The identification of ACS will be made by the study site staff and communicated to Pfizer or designee. Clinical events that might represent ACS may be identified by the Pfizer Study Team or designee during the review of subject data listings or by site monitors during routine monitoring of subject study records. The Pfizer study team will notify the study site staff if they identify a potential ACS event that has not been reported by the site. All reported cases of potential ACS that occur from the time of the subject's first dose of study drug through the subject's last visit will be evaluated by the Acute Chest Syndrome Safety Endpoint Adjudication Committee (ACS-SEAC; see Section 9.7.1).

The Pfizer Study Team or designee will provide a listing of specific documents needed to support ACS event adjudication by the ACS-SEAC. Obtaining the documentation will be the responsibility of the study site staff. ACS event documentation will include, but is not limited to any of the following: daily hospital/clinic notes and physical examination documentation, hospital discharge summaries, operative and procedural reports, chest x-rays,

vital signs including oximetry, laboratory reports and results of other diagnostic tests, autopsy reports and death certificate information.

7.2.4.2.1. Severe ACS (Withdraw from Study Drug Administration)

For the purposes of this protocol, severe acute chest syndrome is defined as an ACS diagnosis as above (Section 7.2.4.2), and the requirement for at least one of the following:

- ICU Transfer;
- Mechanical ventilation;
- Oxygen requirement of >50% FiO_2, or the use of high flow oxygen delivery system, or bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP).

Subjects that develop severe ACS are to be terminated from study drug administration. Subjects that develop mild or moderate cases of ACS may continue to receive treatment with study drug.

7.2.4.3. Cutaneous Manifestations

The identification of cutaneous manifestations and acute skin rashes will be made by the study site staff and communicated to Pfizer or designee. Clinical events of cutaneous manifestations and/or acute skin rashes may also be identified by the Pfizer Study Team or designee during the review of subject data listings or by site monitors during routine monitoring of subject study records. The Pfizer study team will notify the study site staff if they identify a potential event that has not been reported by the study site staff. All cases of cutaneous manifestations and acute skin rashes that develop from the time of the subject's first dose of study drug through the subject's last visit will be independently evaluated by the Cutaneous Manifestations Safety Endpoint Adjudication Committee (CM-SEAC; see Section 9.7.2) to determine if they constitute severe and/or generalized cutaneous events.

A dermatologic evaluation of severe and/or generalized acute skin rashes should be undertaken locally. Evaluation of less severe cases should also be undertaken where feasible. A biopsy should be considered based upon this dermatologic evaluation. For severe and/or generalized cutaneous reactions and any reactions that are considered "unexpected" or unusual, photographs should be obtained per instructions provided in a separate study manual and differential blood count and serum aminotransferase assays performed. Photographs and blood samples are strongly encouraged at the time of the event in cases of mild or transient cutaneous manifestations (eg, mild and transient allergic reactions or exacerbation of pre-existing conditions such as eczema).

The Pfizer Study Team or designee will provide a list of specific documents needed to support rash adjudication by the CM-SEAC. Obtaining the documentation will be the responsibility of the study site staff. Rash event documentation will include, but is not limited to any of the following: photographs, hospital discharge summaries including dermatologic evaluation at the time of rash, operative reports, pathology reports of biopsy (if

done), laboratory reports (including differential blood count and serum aminotransferase), clinic notes, results of other diagnostic tests, autopsy reports and death certificate information.

7.2.4.3.1. Severe Cutaneous Manifestation (Withdraw from Study Drug Administration)

For the purposes of this protocol, a severe cutaneous manifestation that would require study drug discontinuation is defined as the occurrence of any of the following:

- Any skin eruption with mucosal or visceral involvement.
- Any skin eruption that includes blisters, vesicles, pustules or purpura.
- Any skin eruption that involves >50% of the body surface area.

Decisions around withdrawal from study drug administration for cutaneous manifestations not meeting the above criteria will be made on a case-by-case basis by the investigator who, if appropriate, may discuss the case with a local dermatologist, and/or the Sponsor's Medical Monitor, and/or members of the CM-SEAC.

7.3. Pregnancy Testing

For female subjects of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at the VOC/Treatment-Ready Screening visit prior to study drug administration, at the End of Treatment visit, and at the Day 35 Post-Discharge Follow-Up visit. A negative pregnancy test result is required before the subject may receive the study drug. Study drug should not be administered if the pregnancy test is indeterminate or positive. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), and at the end of the study to confirm the subject has not become pregnant during the study. In the case of a confirmed pregnancy, the subject will be withdrawn from study drug but may remain in the study. Pregnancy tests may also be repeated as per request of IRB/ECs or if required by local regulations.

[redacted]

[redacted]

7.6. Stored Specimens

Any remaining plasma and serum [redacted] will be stored for exploratory retrospective analyses associated with trial and program related endpoints (eg, safety, efficacy), the subjects' disease, the drug's mechanism of action, or to support personalized medicine approaches. Retaining the residual plasma and serum specimens for analysis at a

later date makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study.

To protect subjects' confidentiality, the stored specimens and data generated from them will be coded with the subject's study ID number. Samples will be kept in a facility accessible only by badge-swipe. Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the specimens and data generated from them will not have access to the key nor any personally identifying information. Specimens will only be used for the purposes described here and in the informed consent document/patient information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, specimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post-marketing research. Subjects can withdraw their consent for the use of their specimens at any time by making a request to the investigator, in which event any remaining specimen will be destroyed; data already generated from the specimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the specimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Subjects are notified in the informed consent document/patient information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians; nor will they be recorded in the subject's medical record. There is no intention to contact subjects after completion of the clinical trial.

It is possible that the use of these specimens may result in commercially viable products. Subjects will be advised in the informed consent document/patient information sheet that they will not be compensated in this event.

[redacted]

[redacted]

[redacted]

7.7. Total Blood Volume

Table 7. Total Blood Volume in Adults (≥ 18 year of age)

Study Participation	Blood Volume (mL)							
Study Visit/Contact ID	Screen/Pre-Loading Dose	First 24 hours/ Post Loading Dose	Pre Dose 2 or 3	Post Dose 2 or 3	Pre Dose 5 or 6	End of Treatment	Day 35 Post-Discharge Follow-Up visit	Total
Clinical Laboratories	9ml					9ml	9ml	27ml
Hemoglobin Electrophoresis[a]	4ml							4ml
Pregnancy Test[b]	2ml					2ml	2ml	6ml
[redacted]								
[redacted]								
Total								

a. Sample will only be collected if subject does not have a documented diagnosis of SCD.
b. Pregnancy test can be either serum or urine as long as the sensitivity is at least 25 mIU/mL. Sample will only be collected from female subjects of childbearing potential.
[redacted]

Table 8. Total Blood Volume in Pediatrics 12-17 years of age

Study Participation	Blood Volume (mL)							
Study Visit/Contact ID	Screen/Pre-Loading Dose	First 24 hours/ Post Loading dose	Pre Dose 2 or 3	Post Dose 2 or 3	Pre Dose 5 or 6	End of Treatment	Day 35 Post-Discharge Follow-Up visit	Total
Clinical Laboratories	4.5ml					4.5ml	4.5ml	13.5ml
Hemoglobin Electrophoresis[a]	4ml							4ml
Pregnancy Test[b]	2ml					2ml	2ml	6ml
[redacted]								
[redacted]								
Total								

a. Sample will only be collected if subject does not have a documented diagnosis of SCD.
b. Pregnancy test can be either serum or urine as long as the sensitivity is at least 25 mIU/mL. Sample will only be collected from female subjects of childbearing potential.
[redacted]

Table 9. Total Blood Volume in Pediatrics 6-11 years of age

Study Participation	Blood Volume (mL)							
Study Visit/Contact ID	Screen/Pre-Loading Dose	First 24 hours/ Post Loading Dose	Pre Dose 2 or 3	Post Dose 2 or 3	Pre Dose 5 or 6	End of Treatment	Day 35 Post-Discharge Follow-Up visit	Total
Clinical Laboratories	4.5ml					4.5ml	4.5ml	13.5ml
Hemoglobin Electrophoresis[a]	4ml							4ml
Pregnancy Test[b]	2ml					2ml	2ml	6ml
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a. Sample will only be collected if subject does not have a documented diagnosis of SCD.
b. Pregnancy test can be either serum or urine as long as the sensitivity is at least 25 mIU/mL. Sample will only be collected from female subjects of childbearing potential.

[redacted]

[redacted]

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the study drug will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a

serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject or subject's parent(s)/legal guardian/legally acceptable representative provides informed consent/assent (either Pre-VOC/Study Entry consent or VOC/Treatment-Ready consent depending on the subject's entry point into the study), which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving study drug, through and including the subject's last visit or 28 calendar days after the last administration of the study drug, whichever is longer. Serious adverse events occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

AEs (serious and non-serious) should be recorded on the CRF from the time the subject has taken at least one dose of study drug through the subject's last visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

Medication errors may result, in this study, from:

- Incorrect route of administration;
- Administration of expired study drug;
- Administration of the wrong product;
- Administration to the wrong subject;
- Administration at the wrong time;
- Administration at the wrong dosage strength;
- Administration of incorrect dose of study drug;
- Administration of study drug that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study drug under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error CRF which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the study drug;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated adverse event(s) is captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or the sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

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

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize

the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

Unless the investigator believes that there is a causal relationship between study drug and the event specified below, this event should not be reported by the investigator as an SAE as described in the Serious Adverse Event Reporting Requirements section of this protocol. However, this event should still be captured as an AE in the CRF if it meets reporting requirements detailed in Section 8.2.

The protocol-specified event that will not normally be reported in an expedited manner:

- The initial, uncomplicated VOC prompting entry into Treatment- Ready Screening. Note: If a subject signs Pre-VOC consent and has a VOC requiring hospitalization, but does not enter into Treatment-Ready Screening, the VOC is to be reported as an SAE. In addition, for all subjects, any re-hospitalization for VOC occurring during the safety follow-up period is to be reported as an SAE.

Should an aggregate analysis indicate that these prespecified events occur more frequently than expected based on the expectation of frequency of the event(s) in question in the population for comparison, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analysis of safety data will be performed on a regular basis per internal standard operating procedures.

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 × ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

  - For subjects with pre-existing 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).

  Concurrent with:

  - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

The subject should return to the investigational 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, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;

- Hospice facilities;

- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with

subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the study drug caused the event, then the event will be handled as "related to study drug" for reporting purposes, as defined by the Sponsor (see the Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to study drug", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the study drug; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the study drug;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the study drug prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the study drug, the investigator must submit this information to the Pfizer Drug Safety Unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information

submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

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 Pfizer of the outcome as a follow up to the initial EDP supplemental form. 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).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [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 as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to the study drug.

Additional information regarding the EDP may be requested by the investigator. 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 study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the Investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF, however a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also the Section on Subject Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject/parent(s)/legal guardian/legally acceptable representative. In addition, each study subject/parent(s)/legal guardian/legally acceptable representative will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

As noted in the Protocol-Specified Serious Adverse Events section, should an investigator judge the identified protocol-specified SAE to have a causal relationship with the study drug the investigator must report the event to the sponsor within 24 hours of investigator awareness, even if that event is a component of the endpoint.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Statistical methodology for summary and analyses of the data collected in this study are given here and further detailed in a statistical analysis plan (SAP) for this study, which will be maintained by Pfizer.

The analysis plan may modify what is outlined in the protocol; however, any major modifications of the endpoint definitions or their analyses will also be reflected in a protocol amendment.

The SAP will describe methods for the assessment of the effects of missing data and sensitivity analyses for the efficacy endpoints.

9.1. Sample Size Determination

This study includes two cohorts: Cohort 1 includes one adult stratum (≥18 years old) and one pediatric stratum (12-17 years old), Cohort 2 includes one pediatric stratum (6-11 years old). The Primary Analysis Population for the study will consist of subjects in both Cohort 1 and Cohort 2.

For the Primary Analysis Population, to allow for the possibility of an efficacy interim analysis, the sample size calculations were based on the following assumptions:

- Distribution of time to readiness-for-discharge is exponential.
- Median times to event are 156 and 106 hours, for the placebo and rivipansel groups, respectively (based on observed data in the Phase 2 trial).
- The stratified log-rank test is used to test the statistical hypothesis in the primary analysis, in support of the primary objective of the study.
- Alpha =0.05, two-sided, Power =0.90.

Based on these assumptions, a total of at least 300 subjects should be enrolled into Cohort 1 and Cohort 2 combined and at least 282 events observed, in order to have at least 90% power for the log-rank test.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The calculation method used above is from Allan Hackshaw's book, *A Concise Guide to Clinical Trials*, published online on April 29, 2009 in the Wiley Online Library.

9.2. Efficacy Analysis

Complete details (including censoring rules for the time-to-event endpoints) on the efficacy analyses are provided in the SAP. The statistical analysis methods will be used for the Primary Analysis Population with Cohort 1 and Cohort 2 combined. In addition, the same analyses will be conducted separately for the two cohorts. A gate-keeping approach will be used for analyses of Cohort 1 and Cohort 2 combined to control overall type I error for the primary and key secondary endpoints. Analyses for Cohort 1 and Cohort 2 combined would provide the basis for initial regulatory approval of rivipansel for the indication of treatment of VOC in SCD subjects.

The efficacy analysis will be performed for the full analysis set, an intent-to-treat (ITT) population which will include all randomized subjects in the study.

9.2.1. Analysis of Primary Endpoint

The primary endpoint is time to readiness-for-discharge from the hospital. Time to readiness-for-discharge is defined as the difference between the readiness-for-discharge date and time (see Section 7.1.1 for detail) and the start date and time of the first infusion of study drug in hours.

Below are examples of scenarios where subjects receive an infusion of study drug but do not meet the primary endpoint criteria:

- If one or more applicable criteria are not met for a subject before the subject is discharged or are missing, then the time to readiness-for-discharge will be treated as censored. If a subject dies in the hospital before all criteria are met, then the time to readiness-for-discharge will be treated as censored.

- If a subject is not hospitalized and prematurely terminates from the study before all criteria are met, the time to readiness-for-discharge will be treated as censored.If a subject is randomized but not infused with study drug, the time to readiness-for-discharge will be defined as the time from randomization to the time of the subject's termination and will be treated as censored.

Details on censoring rules for the time to readiness-for-discharge are provided in the SAP.

The primary analysis will be performed using the Cohort 1 and Cohort 2 populations combined, as well as Cohort 1 and Cohort 2 populations separately. The primary analysis to test the difference between the rivipansel and placebo groups will utilize a stratified log-rank test where the stratifications are age group (Cohort 1 and Cohort 2 combined or Cohort 1 only) and genotype, For Cohort 2, a log-rank test stratified by genotype will be performed.

A Cox regression model with age group (Cohort 1 and Cohort 2 combined or Cohort 1 only) and genotype as stratification variables will be used to estimate the treatment group hazard ratio and the corresponding two-sided 95% confidence interval. Median Time to readiness-for-discharge will be estimated using the Kaplan-Meier product limit method.

The number and percent of subjects who are documented to have achieved the event of readiness-for-discharge, as well as the number and percent of subject who were censored will be reported for each of the treatment groups.

Multiple sensitivity analyses will be conducted and will be fully described in the SAP.

9.2.2. Analysis of Key Secondary Endpoints

Time to discharge from the hospital and time to discontinuation of IV opioids will be analyzed in the same way as the primary endpoint.

Cumulative IV opioid consumption from the time of the loading dose of study drug to discharge, standardized using morphine equivalents, is expected to be non-normal and heteroscedastic. Therefore it will be analyzed using an analysis of covariance (ANCOVA) model on the ranks of the observed data with treatment, age group (Cohort 1 and Cohort 2 combined or Cohort 1 only), and genotype group as factors. Descriptive statistics summaries will also be presented for raw data.

A fixed-sequence approach will be used to control overall type I error for multiple endpoints (1 primary and 3 key secondary endpoints) based on the Cohort 1 and Cohort 2 combined population. This implies that a given endpoint only achieves significance if the prior endpoint in the sequence is statistically significant. The order for testing against placebo is as follows:

1. Time to readiness-for-discharge;
2. Time to discharge;
3. Cumulative IV opioid consumption from the time of the loading dose of study drug to discharge, standardized using morphine equivalents;
4. Time to discontinuation of IV opioids.

[redacted]

[redacted]

9.2.4. Analysis of Other Secondary Endpoints

Cumulative IV opioid consumption within the first 24 hours post-loading dose of study drug, standardized using morphine equivalents, will be analyzed in the same way as cumulative IV opioid consumption from the start time of the loading dose of study drug to discharge.

Percent of subjects re-hospitalized for VOC within 3 days of discharge will be analyzed using exact methods.

[redacted]

9.4. Safety Analysis

The safety data (eg, AEs, SAEs, physical exams, laboratory tests, vital signs) will be summarized in accordance with the Clinical Data Interchange Standards Consortium (CDISC) and Pfizer Standards (CaPS). Safety data that will be specifically summarized include:

- Adverse events according to CaPS;
- Safety laboratory tests according to CaPS;
- Physical exams and vital signs assessments according to CaPS;
- Incidence of adjudicated ACS and incidence of adjudicated severe and/or generalized cutaneous manifestations analyzed using exact methods.
- Percent of subjects re-hospitalized for VOC within 7, 14 and 30 days of discharge analyzed using exact methods.

The safety analysis set will be all subjects who receive at least one infusion of study drug.

9.5. Interim Analysis

An E-DMC will review unblinded safety data on a regular basis. In addition, the study was designed to have a possible interim futility analysis for Cohort 1 after 150 subjects in Cohort 1 had completed the study. No interim analysis was planned for Cohort 2. The conditional power would have been used for the futility decision-making to maintain the overall nominal significance level for the final efficacy analysis at 0.05 (2-sided test).

If an interim analysis for futility were conducted, the details of the objectives, decision criteria and method of maintaining the study blind as per Pfizer's SOPs would have been documented and approved in an E-DMC charter and the detailed analysis plan documented and approved in a SAP.

9.6. Data Monitoring Committee

This study will use an External Data Monitoring Committee (E-DMC). The E-DMC will be responsible for ongoing monitoring of safety of subjects in the study according to the Charter. The E-DMC will include members, external to the Sponsor, with expertise in the clinical management of adult and pediatric SCD patients, statistics, or clinical pharmacology. The E-DMC will receive safety summaries and subject listings presented by masked treatment groups but will have the option to review fully unblinded safety data and/or efficacy data if necessary.

The E-DMC will review accumulating data from this study on a regular basis, at least every 6 months and particular focus will be placed upon evaluation of the pediatric safety data. The initial data review meeting will occur after the first 6 pediatric subjects (6-11 years of age) have completed the study, or approximately 6 months after first subject first visit (FSFV), whichever comes first. An additional review of subjects 6-11 years of age will occur after 12 of these subjects have completed the study. The sponsor and the E-DMC can

request additional data reviews as they see fit and ad hoc meetings will be arranged to accommodate these reviews. During meetings, the E-DMC will review safety data as defined above. [redacted]

Based on these reviews, the E-DMC will have the capacity to make recommendations to the Sponsor that might impact the future conduct of the study. These may include amending safety monitoring procedures, modifying the protocol or consent, modifying the dosing of the pediatric subjects (6-11 years of age), terminating the study, or continuing the study as designed. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate.

In addition to the ongoing review of the safety data in general, the E-DMC will participate in the interim analysis, if performed, to assess futility.

The details around the conduct and responsibilities and roles of the E-DMC will be provided in the E-DMC Charter.

9.7. Safety Endpoint Adjudication Committees

9.7.1. Acute Chest Syndrome Safety Endpoint Adjudication Committee

To help assess the safety endpoint of ACS events in this and the open-label extension study (B5201003), an Acute Chest Syndrome Safety Endpoint Adjudication Committee (ACS-SEAC), consisting of external clinical experts in the relevant clinical areas, will be set up to harmonize and standardize endpoint assessment. The frequency of committee meetings will be dependent on the volume of cases, urgency of review for specific cases, and the preferences of the committee members and the needs of the Sponsor. In order to allow for an unbiased endpoint assessment, members of this committee will be blinded to treatment assignment. The committee will use a-priori defined criteria in tandem with expert clinical judgment to adjudicate the events. Further information about the ACS-SEAC can be found in the respective charter, including a specific description of the scope of responsibilities, a plan where communication timelines are defined, and the exact process and definitions used by the committee to adjudicate the safety events.

9.7.2. Cutaneous Manifestations Safety Endpoint Adjudication Committee

To help assess the safety endpoint of severe and/or generalized cutaneous events in this and the open-label extension study (B5201003), a Cutaneous Manifestations Safety Endpoint Adjudication Committee (CM-SEAC), consisting of external clinical experts in dermatology, will be set up to harmonize and standardize endpoint assessment. The frequency of committee meetings will be dependent on the volume of cases, urgency of review for specific cases, and the preferences of the committee members and the needs of the Sponsor. To ensure accuracy of adjudication, the committee will be blinded to treatment assignment. The committee will use a-priori defined criteria in tandem with expert clinical judgment to

adjudicate the events. Further information about the adjudication process can be found in the CM-SEAC charter, including a specific description of the scope of responsibilities, a plan where communication timelines are defined, and the exact process and definitions used by the committee to adjudicate the safety events.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Ethics Committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

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

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site as well as at Pfizer and clearly

identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

Electronic devices (eg, smart phones, tablets, or computers) will be utilized in this study by study site staff to record their assessment of readiness-for-discharge criteria via an eClinRO web-based data capture system (eClinRO data) [redacted] Screen shots are included in the eClinRO reference document. [redacted] ccess to the mechanism for entry of data on the eClinRO device must be restricted to the study site staff, by use of a username and password known only to the individual user. The [redacted] vendor is responsible for controlling access to [redacted] eClinRO source data and reports on the vendor's database on behalf of the sites. Access controls that conform to relevant regulatory regulations and guidance will be documented by the [redacted] eClinRO vendor and approved by the sponsor study team. Access to source data or reports via the [redacted] eClinRO vendor's web portal and to other study data on the [redacted] eClinRO vendor's server must be strictly controlled by use of security features that include individual logons, assignment of logons to appropriate security groups, and private passwords known only to the individual user.

[redacted] The [redacted] eClinRO vendor is responsible for safeguarding the source data on behalf of the sites. The Investigator Initiation Package will provide details of site data handling responsibilities. The Study Monitoring Plan will provide details of the Site Monitor's responsibilities for monitoring subject and study site staff compliance, checking on the site's efforts to monitor subject compliance, and comparing source data kept at the site with comparable data in the [redacted] eClinRO vendor's database.

The [redacted] eClinRO vendor will transfer [redacted] eClinRO data to Pfizer (or its designated representative) at regular intervals. The Clinical Data Management team at Pfizer (or its designated representative) will review the data to identify inconsistencies and request clarifications from the [redacted] eClinRO vendor or the study site. All requests for changes and deletions of clinical data must be approved by the investigator (or designee). Before any approved change or deletion may be carried out by the vendor, it must also be reviewed by the sponsor study team to verify that it conforms to Good Clinical Practice.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be

retained by the investigator according to International Council for Harmonisation (ICH), according to local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

Study sites will retain [redacted] eClinRO records as required under their contracts with Pfizer and the Investigator Initiation Package. These records will include archives of clinical data and study documentation to be sent to them by the [redacted] eClinRO vendor. The study sites will review the contents of [redacted] eClinRO archives when they are first provided by the [redacted] eClinRO vendor. Once the sites have determined that the archived data is complete and accurate, they will send signed acknowledgement forms to the Pfizer study team.

Pfizer will retain records of the design, development, testing, rollout, maintenance and close out of [redacted] eClinRO and store such records per the relevant SOPs. Pfizer will also retain the acknowledgement forms sent by the study sites regarding their archives per the relevant SOPs.

12. ETHICS

12.1. Institutional Review Board (IRB)/Ethics Committee (EC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the Investigator File. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws, or as requested by government agencies including the Centers for Medicare and Medicaid Services.

With the exception of [redacted] data requested by government agencies including the Centers for Medicare and Medicaid Services, when study data [redacted] are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study linking their numerical code to the subject's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data consistent with applicable privacy laws, and requirements of government agencies including the Centers for Medicare and Medicaid Services.

The informed consent/assent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process must be reviewed by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or his/her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Prior to any screening procedures, at the Pre-VOC/Study Entry Screening and/or VOC/Treatment-Ready Screening, the study will be thoroughly explained to the subject's parent/legally acceptable representative and/or the subject. If the subject wishes to participate in the study and, if appropriate, the parent/legally acceptable representative also desires the subject to participate in the study, an IRB/EC-approved informed consent will be signed and dated by the subject or the legally acceptable representative, before any screening procedures are performed that are specific to the study.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, then the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his/her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing

the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse) and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents. The signed documents will be retained at the site and the investigator must document in the source documents that informed consent and assent were obtained.

The Investigator will need to make the determination as to whether or not the potential subject receiving IV opioids is capable of understanding the information in the consent document. If not, the subject will need a legally acceptable representative to consent on the subject's behalf. The determination of capacity to consent should be documented in the source records.

In determining which potential subjects are capable of providing assent, the Investigator and/or IRB/EC should take into account the age, maturity, and psychological state of the potential subjects. The American Academy of Pediatrics advises that assent usually should be obtained from all subjects with an intellectual age of 7 years or more.

If a subject signed assent for a study, consent must be signed once the subject turns legal age, based on local requirements. If the minor subject reaches the age of majority during the study, as recognized under local law, they must be re-consented as adults to remain in the study. If the enrollment of 'emancipated minors' is permitted by the study, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s) or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

12.4. Subject Recruitment

Advertisements and patient-centric engagement tools and activities approved by ethics committees and investigator databases may be used as recruitment procedures. To facilitate possible logistical burdens for subjects, transportation services will be made available to subjects to and from study visits.

12.5. 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 Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the study drug, Pfizer should be informed immediately.

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in all Participating Countries

End of Trial in all participating countries is defined as the Last Subject Last Visit.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of rivipansel at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 1 week. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

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

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigators of any information collected or generated by Investigators, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigators will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigators will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigators agree to delay the disclosure for a period not to exceed an additional 60 days.

Investigators will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-center study, Investigators agree that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigators are free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institutions will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

1. Centers for Disease Control and Prevention Sickle Cell Disease homepage. Available at: http://www.cdc.gov/ncbddd/sicklecell/data.html. Accessed February 12, 2014.

2. Davis H, Roscoe M, Moore J, et al. Cost of hospitalizations associated with sickle cell disease in the US. Public Health Rep. 1997;112:40-3.

3. Stuart MJ, Nagel RL. Sickle-cell disease. Lancet. 2004;364:1343-60.

4. Frenette PS, Atweh GF. Sickle cell disease: old discoveries, new concepts, and future promise. J Clin Invest. 2007;117:850-8.

5. Platt OS, Thorington BD, Brambilla DJ, et al. Pain in sickle cell disease: rates and risk factors. N Engl J Med. 1991;325:11-6.

6. Steinberg MH. Management of sickle cell disease. N Engl J Med. 1999;340:1021-30.

7. American Academy of Pediatrics, Section on Hematology/Oncology and Committee on Genetics. Health supervision for children with sickle cell disease. Pediatrics. 2002;109:526-35.

8. Ballas SK. Pain management of sickle cell disease. Hematol Oncol Clin North Am. 2005;19:785-802.

9. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease -- Life expectancy and risk factors for early death. N Engl J Med. 1994;330(23):1639-44.

10. Smith WR, Penberthy LT, Bovbjerg VE, et al. Daily assessment of pain in adults with sickle cell disease. Ann Intern Med. 2008;148(2):94-101.

11. Bunn HF. Pathogenesis and treatment of sickle cell disease. N Engl J Med. 1997;337:762-9.

12. Okpala I. Leukocyte adhesion and the pathophysiology of sickle cell disease. Curr Opin Hematol. 2006;13:40-4.

13. Blum A, Yeganeh S, Peleg A, et al. Endothelial function in patients with sickle cell anemia during and after sickle cell crises. J Thromb Thrombolysis. 2005;19(2):83-6.

14. Kato GJ, Martyr S, Blackwelder WC, et al. Levels of soluble endothelium-derived adhesion molecules in patients with sickle cell disease are associated with pulmonary hypertension, organ dysfunction, and mortality. Br J Haematol. 2005;130:943-53.

15. Turhan A, Weiss LA, Mohandas N, et al. Primary role for adherent leukocytes in sickle cell vascular occlusion: A new paradigm. Proc Natl Acad Sci. 2002;99:3047-51.

16. Kaul DK, Hebbel RP. Hypoxia/reoxygenation causes inflammatory response in transgenic sickle mice but not in normal mice. J Clin Invest. 2000;106(3):411-20.

17. Tedder TF, Steeber DA, Chen A, et al. The selectins: vascular adhesion molecules. Br J Rheumatol. 1995;34:1101-4.

18. Ebnet K, Vestweber D. Molecular mechanisms that control leukocyte extravasation: The selectins and chemokines. Histochem Cell Biol. 1999;112:1-23.

19. Chen S, Springer TA. Selectin receptor-ligand bonds: Formation limited by shear rate and dissociation governed by the Bell model. Proc Natl Acad Sci. 2001;98:950-5.

20. Blann AD, Nadar SK, Lip GYH. The adhesion molecule P-selectin and cardiovascular disease. Eur Heart J. 2003;24:2166-79.

21. Kansas GS. Selectins and their Ligands: Current concepts and controversies. Blood. 1996;88: 3259-87.

22. Embury SH, Matsui NM, Ramanujam S, et al. The contribution of endothelial cell P-selectin to the microvascular flow of mouse sickle erythrocytes in vivo. Blood. 2004;104(10):3378-85.

23. Chang J, Patton JT, Sarkar A, et al. GMI-1070, a novel pan-selectin antagonist, reverses acute vascular occlusions in sickle cell mice. Blood. 2010; 116: 1779-1786.

24. Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. N Engl J Med. 2000;342:1855-1865.

25. National Institutes of Health; Division of Blood Diseases and Resources. The management of sickle cell disease. 4th ed. NIH Publication No. 02-2117. Bethesda, MD: US Department of Health and Human Services; 2002.

26. Farrar JT, Young JP Jr, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001 Nov;94(2):149-58.

27. Wong-Baker Faces Foundation homepage. Available at: http://wongbakerfaces.org/. Accessed February 25, 2015.

28. Cleeland CS. Pain assessment in cancer. In: Osaba D(ed). Effect of Cancer on Quality of Life, Chapter 21. CRC Press, Boca Raton FL, 1991.

29. National Institutes of Health. Evidence-Based Management of Sickle Cell Disease: Expert Panel Report. Bethesda, MD: US Department of Health and Human Services; 2014. Available at: www.nhlbi.nih.gov/guidelines.

30. Hackshaw A: A Concise Guide to Clinical Trials, 29 APR 2009; Wiley Online Library. Available at: http://onlinelibrary.wiley.com.proxy1.athensams.net/doi/10.1002/9781444311723.oth2/pdf

31. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12

32. Schwartz GJ, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009; 20: 629-637.

33. Schwartz GJ and Work DF. Measurement and estimation of GFR in children and adolescents. Clin J Am Soc Nephrol. 2009; 4 (11): 1832-43.

Appendix 1. Estimated Glomerular Filtration Rate (eGFR) Calculations

Calculation for subjects ≥18 years of age:

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation estimates glomerular filtration rate (GFR) from serum creatinine, age, sex, and race for adults aged ≥ 18 years.[31]

CKD-EPI Equation

$$GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018[\text{if female}] \times 1.159[\text{if black}]$$

$\kappa = 0.7$ if female
$\kappa = 0.9$ if male

$\alpha = -0.329$ if female
$\alpha = -0.411$ if male

min = The minimum of Scr/κ or 1
max = The maximum of Scr/κ or 1

Scr = serum creatinine (mg/dL)

A CKD-EPI Calculator for investigator and/or site staff is provided via the study-specific Firecrest web-portal.

Calculation for subjects < 18 years of age:

Bedside Schwartz Equation[32, 33]

eGFR = 0.413 x (Height in cm) / (Serum Creatinine in mg/dl)

A Bedside Schwartz Calculator for investigator and/or site staff is provided via the study-specific Firecrest web-portal.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]