Clinical Trial Protocol: C1701-202

Amendment 5, 24 July 2019

Study Title:	A Randomized, Placebo-controlled, Phase 2 Study to Evaluate the Safety and Pharmacodynamics of Once-daily Oral IW-1701 in Patients with Stable Sickle Cell Disease
Study Number/Short Title:	C1701-202 / STRONG SCD
Study Phase:	2
Product Name:	Olinciguat (IW-1701 Tablet)
Indication:	Sickle Cell Disease
Investigators:	Multicenter
Sponsor:	Cyclerion Therapeutics, Inc. [redacted]
[redacted]	[redacted]

	Date
Original Protocol:	08 August 2017
Amendment #1:	08 November 2017
Amendment #2:	09 May 2018
Amendment #3:	31 May 2018
Amendment #4:	17 May 2019
Amendment #5:	24 July 2019

KEY STUDY ROLES

Please refer to the Investigator Site File for information regarding key study personnel.

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SYNOPSIS

Sponsor: Cyclerion Therapeutics, Inc.

Name of Finished Product: Olinciguat (IW-1701)

Name of Active Ingredient: Olinciguat (IW-1701)

Study Title

A Randomized, Placebo-controlled, Phase 2 Study to Evaluate the Safety and Pharmacodynamics of Once-daily Oral IW-1701 in Patients with Stable Sickle Cell Disease

Study Number: C1701-202, Amendment 5	**Study Phase:** 2

Study Objective

Primary: To assess the safety and tolerability of oral, once-daily (QD) IW-1701 when administered for approximately 12 weeks to patients aged 16 to 70 years with sickle cell disease (SCD)

Study Design

Note: *Patients randomized prior to Amendment 4 will continue to be treated according to Amendment 3 for the duration of their study participation. Please see Amendment 3 for details.*

Procedural changes made in association with Amendment 4 will apply only to new patients randomized under that amendment and beyond.

This multicenter, randomized, double-blind, placebo-controlled, parallel-group study with a 2-week single-blind Run-in Period will evaluate oral IW-1701 compared with placebo when administered QD for approximately 12 weeks.

At the Screening Visit (Day -43 to Day -17), patients will undergo preliminary procedures to determine their initial eligibility. At the Run-in Visit (Day -17 to -14), eligible patients will begin 14 to 17 days of single-blind placebo dosing and will begin recording their daily and weekly symptom assessments in an eDiary (a handheld personal electronic device). Patients will be required to complete at least 10 days of daily assessments during the final 14 days of the Run-in Period to remain eligible for randomization into the Treatment Period.

On Day 1 of the Treatment Period, patients who continue to be eligible will be randomized to double-blind study drug (QD IW-1701 or placebo; see Study Treatment). Also on Day 1 and for each uptitration visit, patients must remain in the clinic at least 6 hours postdose and will be allowed to leave at the Investigator's discretion.

At all scheduled study visits (see Schedule of Events), patients will undergo safety, efficacy, and PK assessments; and, as applicable, will take the relevant study drug dose and will be issued study drug supply for subsequent at-home QD dosing. Safety assessments at unscheduled visits will be conducted per Investigator discretion. In addition, patients will receive regularly scheduled phone calls in between the scheduled visits to monitor treatment-emergent adverse events (TEAEs) and concomitant medication(s) and procedure(s). Throughout the Treatment Period, patients will continue completing the patient-reported outcome (PRO) questionnaires

each day in their eDiary. They will return to the clinic 28 (-3/+7) days after their last study drug dose for final Follow-up assessments.

Study Treatment

During the Run-in Period, all patients will take single-blind placebo QD for 14 to 17 days.

Dose	Run-in Period ([Day -17 or -14] to Day -1)
Placebo once daily	1×matching placebo tablet

During the Treatment Period, patients will be randomized in a 3:1 ratio to receive double-blind study drug (IW-1701:placebo) for up to 89 days. As shown below, dosing will begin with 6 mg IW-1701 QD and will subsequently be titrated to 12 and then to 18 mg QD, depending upon safety and tolerability (see Section 3.5.4.2).

Randomized Dose	Treatment Period Week (Days)					
	Week 1 (Day 1–Day 7)		Weeks 1 through 3 (Day 8–Day 28)*		Weeks 4 through 12 (Day 29–Day 85)*	
	QD Dose	Dosage	QD Dose	Dosage	QD Dose	Dosage
18 mg IW-1701	6 mg	2×3-mg IW-1701 tablet	12 mg	4×3-mg IW-1701 tablet	18 mg	6×3-mg IW-1701 tablet
Placebo	Placebo	2×matching placebo	Placebo	4×matching placebo	Placebo	6×matching placebo

QD=once daily
* Patients must meet criteria in Section 3.5.4.2 to uptitrate.

Study Population and Planned Number of Patients

The overall study will randomize approximately 88 patients (~40 under Amendment 3 and earlier and ~48 starting with Amendment 4 and beyond) with a confirmed medical history of SCD, including HbSS, HbSC, HbS/β^0-thalassemia, and HbSβ^+-thalassemia, who are 16 to 70 years of age, and who have experienced at least 1 and not more than 10 sickle cell-related pain crises in the past 12 months. Patients taking HU, erythropoietin, L-glutamine, and/or prophylactic antibiotics must have been on a stable regimen (ie, same drug and same dose) for ≥8 weeks before the Randomization Visit.

See Eligibility Criteria for full inclusion and exclusion criteria.

Study Assessments

Safety and baseline: Medical history, demographic information, prior and concomitant medications/supplements, and adverse events (AEs) will be collected. Physical examinations; vital sign measurements, including orthostatic blood pressure and oxygen saturation; clinical laboratory tests; pregnancy tests; and electrocardiograms will be performed. Note: Patients taking HU should be monitored for hematologic toxicities per the current prescribing information.

PROs: Patients will self-administer questionnaires daily (Sickle Cell Disease-Symptom Assessment Form [SCD-SAF] and analgesic use), weekly (Patient Global Impression of Severity), and at study visits (work and school absences due to SCD, Patient-reported Outcomes Measurement Information System [PROMIS] Fatigue Short Form 7a, Adult Sickle Cell Quality of Life Measurement Information System [ASCQ-Me], Patient Global Impression of Change, EuroQol-5D-5L [EQ-5D-5L], and Short Form Health Survey 12v2 [SF-12v2]). Patients who

provide specific consent may also be contacted by a third-party vendor after ending their treatment period to participate in a 1-time telephone interview regarding the SCD-SAF and the PRO eDiary device.

Pharmacodynamic: Blood and urine will be collected for biomarker determinations.

Pharmacokinetic: Blood will be collected to determine plasma concentrations of IW-1701.

Dose Adjustments

It is recommended that the patient is evaluated in the clinic prior to any dose modification.

According to his/her medical judgement, an Investigator may adjust a patient's dose as outlined below. Adjustments should be made, if possible, in consultation with the Medical Monitor.

- Patients who do not tolerate the initial 6-mg QD dose during Week 1 of the Treatment Period should be reduced to a 3-mg QD dose (ie, reduction by 1 tablet), with escalation to 6 mg QD considered at the Week 4 visit if they meet uptitration criteria (Section 3.5.4.2). Subsequent titration to 12 mg or higher will not be permitted for those patients.
- Patients who do not tolerate an uptitration to 12 or 18 mg should be reduced to their prior tolerated dose level (ie, 6 or 12 mg, respectively). Subsequent titration to a higher dose will not be permitted for those patients.
- If a patient develops any of the following **study drug-related TEAEs**, his/her dose will be reduced to his/her prior tolerated dose level (or to 3 mg QD if receiving the initial 6 mg dose) and will not be titrated to a higher dose:
  - 1 episode of Grade 3 vomiting (assessed per Common Terminology Criteria for Adverse Events [CTCAE] v4.03) lasting >48 hours and not responsive to antiemetic therapy
  - 1 episode of Grade ≥3 syncope
  - 2 episodes of Grade 2 presyncope without orthostatic hypotension

Investigators should notify the Medical Monitor of all decisions to reduce dose or to discontinue dosing on a per-patient basis.

With the exception of the lead-in dose during the first week, once a patient down-titrates, titration to a higher dose will not be permitted.

Note: Patients taking hydroxyurea (HU) should be monitored for hematologic toxicities per the current prescribing information.

Removal of Individual Patients from Dosing

On an individual basis, a patient will be discontinued from study drug if any of the following are reported: pregnancy, hemorrhage of Grade ≥2, pulmonary edema, and/or a QT interval corrected using Fridericia's formula of >500 msec or is an increase of >60 msec from baseline. See Section 3.4.2 for additional details.

Data Monitoring Committee (DMC)

An independent DMC will review trial safety data both periodically and on an ad hoc basis. After each periodic or ad hoc review of safety data, the DMC will recommend trial continuation, continuation with modification, or termination. Details will be provided in a DMC charter, which will be developed in collaboration with the DMC members.

Statistical Methods

Sample Size Determination

For this Phase 2 study, an overall sample size of approximately 88 patients is planned. Of these patients, approximately 40 are expected to be randomized under Protocol Amendment 3 or earlier. Starting with Amendment 4, approximately 48 patients are anticipated to be randomized in a 3:1 ratio to receive 18 mg of IW-1701 or placebo, respectively (see Study Treatment). The sample size starting with Amendment 4 was determined outside of statistical considerations and is considered reasonable based on precedent set by prior studies of similar nature and design.

Statistical Analysis

Continuous variables will be summarized using descriptive statistics. Categorical variables will be summarized using the number and percent of patients in each category. Unless otherwise specified, all confidence intervals will be 2-sided with a confidence level of 95%. No adjustments will be made for multiplicity.

Final Date: 24 July 2019

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

Patients must meet all of the following criteria to be eligible for enrollment in this study:

1. Patient has provided written consent before any study-specific procedures are performed; for patients <18 years of age, parental permission and child assent will be obtained.
2. Patient is ambulatory male or female 16 to 70 years of age at the Screening Visit.
3. Patient has sickle cell disease (SCD), including HbSS, HbSC, HbSβ0-thalassemia, or HbSβ+-thalassemia, documented in their medical history by hemoglobin electrophoresis or genotyping.
4. If receiving hydroxyurea (HU), erythropoietin, L-glutamine, or prophylactic oral antibiotics, patient has had no change in regimen(s) (ie, drug and dose) for at least 8 weeks before the Randomization Visit and has no plans to change regimen(s) during the study. If receiving HU, patient must have been prescribed HU for at least 6 months prior to the Randomization Visit. (Note: Patient is not required to be taking medication[s] for SCD.)
   Should the patient begin any new chronic treatment/therapy for SCD during the study or alter any current treatment/therapy for SCD during the study, the Sponsor Medical Monitor must be informed.
5. If receiving chronic medication(s) for hypertension, patient has had no change in regimen(s) (ie, drug and dose) for at least 8 weeks before the Randomization Visit and has no plans to change regimen(s) during the study.
6. Per medical history and/or patient recall, patient has had at least 1 and no more than 10 sickle cell-related pain crises in the 12 months before the Screening Visit and none occurring in the 4 weeks before the Randomization Visit.
   For assessing study eligibility, an SCD-related pain crisis is defined as an acute episode of new-onset pain that lasts ≥2 hours with no medically determined cause other than a vaso-occlusive event and requires presentation to a medical facility (eg, acute care setting, Emergency Department, urgent care clinic) and treatment with oral or parenteral opioids, parenteral nonsteroidal anti-inflammatory drugs, or other analgesics, prescribed by a healthcare provider.
7. Patient has clinically acceptable (per Investigator discretion) electrocardiogram (ECG) with QT interval corrected using Fridericia's formula (QTcF interval) <500 ms at the Screening Visit.
8. Patient has seated systolic blood pressure (BP) from 90 to 160 mmHg at the Screening Visit. (Note: BP for eligibility will be the average of 3 measurements obtained with an

appropriately sized cuff at 2-minute intervals after the patient has been sitting quietly for ≥5 minutes.)

9. Female patient must be postmenopausal (no menses for ≥12 consecutive months) or surgically sterile (ie, bilateral oophorectomy, hysterectomy, or tubal sterilization [tie, clip, band, or burn]); must agree to completely abstain from heterosexual intercourse; or, if heterosexually active, must agree to use 1 of the following methods of birth control from the date she signs the informed consent form (ICF) until 90 days after the final dose of study drug:
   - Progesterone implant and/or an intrauterine device (IUD)
   - Combination of 2 highly effective birth control methods (eg, diaphragm with spermicide plus a condom, condom with spermicide plus a diaphragm or cervical cap, hormonal contraceptive [eg, oral and transdermal patch] plus a barrier method, or partner with vasectomy [conducted ≥60 days before the Screening Visit or confirmed via sperm analysis] plus a hormone or barrier method).
10. Male patient must be surgically sterile by vasectomy (conducted ≥60 days before the Screening Visit or confirmed via sperm analysis), must agree to completely abstain from heterosexual intercourse, or, if heterosexually active, must agree to use a combination of 2 highly effective birth control methods (eg, partner use of progesterone implant and/or IUD, condom with spermicide plus a partner diaphragm or cervical cap, partner hormonal contraceptive [including progesterone implant] plus a barrier method, or postmenopausal partner [for ≥1 year] plus barrier method) from the Screening Visit through 90 days after the final dose of study drug.
11. Patient is fluent in the language of the local ICF (eg, English, Spanish, Arabic, French).
12. Patient completes daily eDiary entries for at least 10 days during the last 14 days of the Run-in Period as assessed at the Randomization Visit. (Note: To enter the Run-in Period, patient must meet all eligibility criteria applicable to the Screening Visit.)

EXCLUSION CRITERIA

Patients who meet any of the following criteria will not be eligible to participate in the study:

1. Patient requires a program of prescheduled, regularly administered chronic blood transfusion therapy, has received a transfusion in the 8 weeks before the Randomization Visit, and/or is scheduled to receive a transfusion during the study.
2. Patient has been hospitalized for an SCD-related complication in the 4 weeks before the Randomization Visit.
3. Patient is planning to undergo major surgery during the trial or has undergone surgery within 4 weeks of the Screening Visit, other than minor dermatologic procedures.

4. Patient has used oral or parenteral corticosteroids in the 8 weeks before the Randomization Visit. Note: Transient use for ≤2 days may be acceptable; consult the Medical Monitor for confirmation.
5. Patient has taken opioid(s) >200 morphine mg equivalent/day within the 4 weeks before the Randomization Visit.
6. Patient is taking aspirin ≥325 mg daily, any P2Y12 inhibitor, any anticoagulant medication, specific inhibitors of phosphodiesterase 5 (PDE5), nonspecific inhibitors of PDE5 (including dipyridamole and theophylline), any supplements for the treatment of erectile dysfunction, riociguat, or nitrates or nitric oxide donors in any form. These medications are prohibited from the Run-in Visit (which may occur from Day -14 to Day -17) through the duration of the study.

[redacted]

8. Patient has any of the following clinical laboratory values at the Screening Visit:
   a. Hemoglobin ≤6 g/dL
   b. Platelets $\leq 100 \times 10^9$/L
   c. Absolute neutrophils $\leq 1.5 \times 10^9$/L
   d. Alanine aminotransferase >1.5×the upper limit of normal (ULN) as defined by laboratory
   e. Direct bilirubin >3×ULN as defined by laboratory
   f. Creatinine clearance <30 mL/minute/1.73 m^2 by the Modification of Diet in Renal Disease equation (1):

      $$GFR\ (mL/minute/1.73\ m^2) = 175 \times S_{cr}^{-1.154} \times Age^{-0.203} \times 0.742\ (\text{if female}) \times 1.212\ (\text{if black})$$

      where S_{cr} is serum creatinine
   g. Prothrombin time and/or activated partial thromboplastin time (aPTT) >1.5×ULN and considered clinically significant by the Investigator, and/or international normalized ratio (INR) >1.5
8. Patient has oxygen saturation ≤90% by pulse oximetry on room air at the Screening Visit and/or at the Randomization Visit.
9. Patient has had inpatient hospitalization for alcoholism or drug addiction in the 12 months before the Screening Visit or is positive for any the following at the Screening Visit unless legally prescribed:

Amphetamines	Benzodiazepines	Opiates	Propoxyphene
Barbiturates	Cocaine	Phencyclidine	

10. Patient has major concurrent illness or medical condition that in the opinion of the Investigator would preclude participation in a clinical study, including but not limited to:
    a. Uncontrolled significant cardiovascular disease or clinically significant cardiac arrhythmia as assessed by the Investigator
    b. Serious event such as stroke or transient ischemic attack ≤12 months before Randomization, or deep venous thrombosis or pulmonary embolism ≤6 months before Randomization
    c. History of platelet dysfunction, hemophilia, von Willebrand disease, coagulation disorder, other bleeding diathesis condition(s), or significant, nontraumatic bleeding episodes, such as from a gastrointestinal source, even if patient has normal complete blood count, prothrombin time, and activated partial thromboplastin time at the Screening Visit
    d. Known severe central nervous system vasculopathy (eg, Moyamoya disease, arteriovenous malformations)
    e. Interstitial lung disease requiring continuous oxygen
    f. Known severe pulmonary hypertension (tricuspid regurgitant jet velocity ≥3.0 m/sec on 2D echocardiogram or an estimated pulmonary artery systolic pressure ≥40 mmHg) or any pulmonary hypertension associated with idiopathic interstitial pneumonia(s)
    g. Known cirrhosis of the liver with Child-Pugh score of A, B, or C
11. Patient has a history of cancer, other than basal cell carcinoma, in the last 5 years.
12. Patient has a history of clinically significant hypersensitivity or allergy to any of the ingredients contained in the active or placebo drug products.
13. Female patient who is pregnant or breastfeeding. Breastfeeding is not allowed from Screening until 90 days after the final dose of study drug.
14. Female patient who may wish to become pregnant and/or plans to undergo egg donation or egg harvesting for current or future in vitro fertilization during the study and/or within 90 days after the last dose of study drug.
15. Male patient unwilling to refrain from sperm donation during the study and for at least 90 days after the last dose of study drug.
16. Patient has previously received IW-1701 in a study, has received any other investigational drug during the 30 days or 5 half-lives of that investigational drug (whichever is longer) before the Screening Visit, is planning to receive another investigational drug at any time during the study, has an active investigational medical device currently implanted, and/or is planning to have an investigational medical device implanted at any time during the study.
17. Patient will not be able to adhere to the trial assessment schedule, or, in the clinical judgement of the Investigator, the patient is otherwise not suitable for the trial.

Note: Screening Visit assessments may take place over more than 1 day. Patients may be rescreened per Investigator judgement after consultation with the Medical Monitor. Laboratory assessments may be repeated if an error is suspected. In certain circumstances local laboratory values may be acceptable.

SCHEDULE OF EVENTS

Study Period	**Screening**		**Treatment**									**F/U**	
Contact Type	**Visit**	**Visit**	**Visit**	**Call**	**Visit**	**Calls**	**Visit**	**Calls**		**Visit**	**Call**	**Visit**	**Visit**
Visit Name	**Screening**	**Run-in** [a]	**Random-ization**	**-**	**Week 1**	**-**	**Week 4**	**-**	**-**	**Week 8**	**-**	**Week 12/EOT**	**F/U/ EOS**
Day (D)→ Procedure ↓	**Day -43 to -15**	**Day -17 to -14**	**Day 1**	**Day 2**	**Day 8 ±1**	**Wk1 V+1D, D15±2, D22±2**	**Day 29 ±3**	**Wk4 V +1D**	**D43 ±2**	**Day 57 ±7**	**D71 ±2**	**Day 85 -7/+4**	**Day 113 -3/+7**
ICF signed	X												
I/E confirmation	X	predose	predose										
Demographics	X												
Medical/SCD history	X												
Prior & concomitant meds & procedures	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam [b]	X	predose	predose		predose		predose			predose		predose	X
Weight & height	W, H	W	W		W		W			W		W	W
12-lead ECG [c]	X		predose pd: 4h (±15m)		predose pd: 4h (±15m)							X	
AE evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug screen [d]	X												
Pregnancy test [e]	X	predose	predose		predose		predose			predose		predose	X
Urinalysis sample	X		predose		predose		predose			predose		predose	X
Oral temperature & RR	X		predose pd:1h (±15m)		predose		predose			predose		predose	X
O_2 saturation	X	predose	predose		predose		predose			predose		predose	X
Seated BP, pulse [f]	X		pd: 6h (±15m)		predose pd: 6h (±15m)								
Seated-to-standing BP/pulse [g]	X	X	predose pd: 1,3,6 (±15m)		predose pd:1,3,6 (±15m)		predose pd:1h (±15m)			predose pd:1h (±15m)		predose pd:1h (±15m)	X

Study Period	**Screening**		**Treatment**									**F/U**	
Contact Type	**Visit**	**Visit**	**Visit**	**Call**	**Visit**	**Calls**	**Visit**	**Calls**		**Visit**	**Call**	**Visit**	**Visit**
Visit Name	**Screening**	**Run-in** [a]	**Random-ization**	**-**	**Week 1**	**-**	**Week 4**	**-**	**-**	**Week 8**	**-**	**Week 12/EOT**	**F/U/ EOS**
Day (D)→ Procedure ↓	**Day -43 to -15**	**Day -17 to -14**	**Day 1**	**Day 2**	**Day 8 ±1**	**Wk1 V+1D, D15±2, D22±2**	**Day 29 ±3**	**Wk4 V +1D**	**D43 ±2**	**Day 57 ±7**	**D71 ±2**	**Day 85 -7/+4**	**Day 113 -3/+7**
Clinical laboratory blood samples	X		predose		predose		predose			predose		predose	X
Genotyping blood sample (w/patient consent)			predose										
PK blood sample			predose pd: EOV		predose pd: EOV		predose pd: EOV			predose pd: EOV		predose pd: EOV	X
Urine samples for UACR		predose	predose				predose					predose	X
Blood sample for biomarkers			predose		predose		predose					predose	X
Blood samples for platelet biomarkers [h]			predose pd: 5h(±15m)				predose					predose	
eDiary registration /training		predose											
eDiary device check			predose										
PROMIS Fatigue; Absences		predose	predose		pd: ≤1h		pd: ≤1h			pd: ≤1h		pd: ≤1h	
ASCQ-Me		predose			pd: ≤1h		pd: ≤1h			pd: ≤1h		pd: ≤1h	
PGIC												pd: ≤1h	
EQ-5D-5L & SF-12v2		predose	predose									pd: ≤1h	X
Randomization			X										
Study drug supply/return [i]		X	X		X		X			X		Return only	
In-clinic study drug dosing [j]		X	X		X		X			X		X	
eDiary return												X	
Transfer: Cognitive debrief. patient contact info [k]												X	

Study Period	Screening		Treatment									F/U	
Contact Type	Visit	Visit	Visit	Call	Visit	Calls	Visit	Calls		Visit	Call	Visit	Visit
Visit Name	Screening	Run-in [a]	Random-ization	-	Week 1	-	Week 4	-	-	Week 8	-	Week 12/EOT	F/U/ EOS
Day (D)→ Procedure ↓	Day -43 to -15	Day -17 to -14	Day 1	Day 2	Day 8 ±1	Wk1 V+1D, D15±2, D22±2	Day 29 ±3	Wk4 V +1D	D43 ±2	Day 57 ±7	D71 ±2	Day 85 -7/+4	Day 113 -3/+7
Study completion													X

AE=adverse event; ASCQ-Me=Adult Sickle Cell Quality of Life Measurement Information System; BP=blood pressure; debrief.=debriefing; D=Day(s); ECG=electrocardiogram; eDiary=electronic diary; EOS=end of study; EOT=end of treatment; EOV=end of visit; EQ-5D-5L=EuroQOL 5-dimension questionnaire; F/U=follow-up; h=hour(s); H=height; ICF=informed consent form; I/E=inclusion/exclusion; m=minute(s); O_2=oxygen; pd=postdose; PGIC=Patient Global Impression of Change; PK=pharmacokinetic(s); pre=predose; PROMIS=Patient-reported Outcomes Measurement Information System; RR=respiratory rate; SF12v2=Short Form Health Survey Version 2; temp=temperatures; UACR=urine albumin-to-creatinine ratio; V=Visit; W=weight; Wk=Week

a. The Run-in Visit must occur at least 3 calendar days after the Screening Visit. The Run-in dosing period will continue for 14 to 17 days; see Section 3.1.
b. For Treatment Period visits, physical exam may be symptom directed but must include the cardiovascular and respiratory systems.
c. Patient must be supine for ≥5 m before the ECG recording. If QTc result is outside of normal range, perform in triplicate and calculate the average. If ECG result is clinically abnormal, repeat. If repeated ECG is also clinically abnormal, site should follow standard institutional procedures until resolved. If concerns remain, issue should be escalated to Medical Monitor.
d. Urine screen for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and propoxyphene.
e. For women of reproductive potential, a negative pregnancy test by urine dipstick must be documented at all study visits; negative results must be confirmed before each in-clinic dosing. If urine test is positive, see Section 3.8.7.2. All patients should be reminded of birth control requirements.
f. Seated BP at the Screening Visit, 6 hours postdose at the Randomization Visit, and at predose and 6 hours postdose at the Week 1 Visit will be the average of 3 measurements obtained at 2-m intervals after patient has been sitting quietly for ≥5 m. Other BP and all pulse measurements may be single measurements obtained after the patient has been sitting quietly for ≥5 m.
g. *Orthostatic measurements:* Patient must sit quietly for approximately ≥5 m before seated BP and pulse measurements are taken, and then assume standing position for 2 m (±1 m) before standing BP and pulse measurements are taken. Vital signs (including BP) must be measured before blood sampling when applicable.
h. Not collected at sites located in Lebanon
i. Starting with the Run-in Visit and throughout the Treatment Period, patients will be instructed to bring all study drug bottles to each clinic visit for confirmation of at-home dosing compliance via tablet count. Study drug will be resupplied as applicable.
j. Study drug will be administered in the clinic on study visit days after predose assessments. Patients should take study drug 1 hour before or 2 hours after food, with water, and may swallow 2 tablets together, when applicable. Study drug may be taken with concomitant medications. Coffee or juice may be allowed if the patient feels faint. During the Treatment Period, dose levels will be titrated as indicated in Table 2 for patients meeting criteria in Section 3.5.4.2. See Section 3.5.4.3 for dose adjustment instructions. Instructions for temporary dosing interruptions are in Section 3.5.4.4.
k. *For patients participating in the cognitive debriefing interview study*: Prior to EOT Visit (including early terminations ≥4 weeks post randomization), study staff will transfer the patient's contact information (name, subject ID, phone number, email address) and EOT visit date to Adelphi Values with notification that the patient has scheduled their EOT Visit. See Section 3.8.9.4.

1. INTRODUCTION

1.1 SICKLE CELL DISEASE

Sickle cell disease (SCD), a group of genetic blood disorders affecting hemoglobin.(2) The inherited mutation results in a substitution of the amino acid valine for glutamic acid in the 6th position of the beta globin chain causing the formation of hemoglobin S (HbS).(3) When deoxygenated, this hemoglobin polymerizes into rigid chains that deform red blood cells (RBCs) into the characteristic sickle shape. These less-flexible, sickled RBCs cause inefficient blood flow to organs and tissues and are more susceptible to hemolysis, with an average lifespan of approximately 20 days versus 120 days for normal RBCs.(4) Upon hemolysis, hemoglobin released into the plasma scavenges nitric oxide (NO), which reduces NO bioavailability and in turn leads to vasoconstriction, endothelial dysfunction, and systemic inflammation.(5, 6) The combined effects of vasoconstriction, inflammation, and leukocyte adhesion to the endothelium are believed to contribute to many symptoms of SCD, including painful vaso-occlusive crises and chronic pain. SCD is the most common genetic hematological disorder worldwide, with millions affected, including approximately 100,000 Americans.(2) Globally, it is estimated that more than 300,000 children are born with the disease each year.(7-9)

Nonclinical safety data support investigation of IW-1701 in the age range proposed for this study. The progression of SCD varies, but in general, during the first years of life, patients are at risk for complications such as: acute chest syndrome precipitated by infection, infarction, embolism, and pulmonary sequestration; pleuritic pain due to avascular necrosis of ribs or sternum; strokes (median age of onset, 6 years with recurrent strokes in 50%–70%); hypersplenism leading to splenectomy and/or chronic transfusion; and aplastic crisis.(10) In later childhood and early adolescence, patients may experience nocturnal enuresis, bone pain crises, avascular necrosis of the femoral head, chronic leg ulcerations, delayed growth and puberty and, in boys, priapism. In adulthood, the risk for hemorrhagic stroke peaks and the risk for acute chest syndrome continues. In addition, increased pulmonary fibrosis and pulmonary hypertension stress cardiac function, and progressive glomerular fibrosis and associated decrease in glomerular filtration rate often lead to renal failure.(10) Because patients are affected by this congenital disease starting at birth, they may benefit from earlier therapeutic intervention.

Hydroxyurea (HU) is approved by the Food and Drug Administration (FDA) and is indicated to reduce the frequency of painful crises and the need for blood transfusions.(11, 12) Warnings for the use of HU include myelosuppression, secondary malignancies, embryo-fetal toxicity, cutaneous vasculitic toxicities, and macrocytes, and patients on HU require periodic laboratory tests to monitor for cytopenias. The side effects as well as issues with patient compliance with HU therapy and/or lab monitoring have contributed to low overall utilization rates.(13) Hydroxyurea (SIKLOS) was approved by the FDA in 2017 for the treatment of pediatric patients as young as 2 years of age.(14)

L-glutamine (ENDARI) was approved by the FDA in 2017 (15) and is indicated to reduce the acute complications of SCD in adults and in children older than 5 years. Both ENDARI and SIKLOS are the first SCD medicines to be approved for pediatric patients in the US. ENDARI is the first new treatment for adults with SCD in nearly 2 decades.

There remains considerable unmet medical need in SCD, not only for treatments that prevent painful crises and other acute complications, but also for treatments that address the daily symptoms of the disease, including chronic pain.

1.2 RATIONALE FOR USE OF AN SGC STIMULATOR IN SCD

NO is the primary mediator of vasodilation. Endothelial-derived NO activates the signaling enzyme, soluble guanylate cyclase (sGC), to convert guanosine triphosphate to cyclic guanosine-3',-5'-monophosphate (cGMP). In turn, cGMP stimulates protein kinases, which decrease intracellular calcium levels and relax the vascular smooth muscle. The cGMP is then degraded by phosphodiesterase (PDE) enzymes.(16) The NO-sGC-cGMP pathway is the main mechanism by which NO regulates vasodilation. In addition to regulating vascular tone, NO reduces smooth muscle proliferation and produces anti-inflammatory effects by decreasing cytokine-induced expression of adhesion molecules and decreasing the production of proinflammatory cytokines.(17) Because NO bioavailability is reduced in SCD patients, smooth muscle sGC and cGMP activity are also reduced and, consequently, vascular relaxation and vasodilation are inhibited and blood flow is reduced. Therefore, the NO-sGC-cGMP pathway offers a potential therapeutic target for increasing cGMP levels in SCD. Indeed, in mouse models of SCD, PDE9 inhibitors, which block the degradation of cGMP, have been shown to reduce leukocyte

adhesion, vaso-occlusion, and RBC sickling, and to improve survival.(18-22) sGC stimulators, which act directly on sGC to increase cGMP production, may offer another way to modulate the NO-sGC-cGMP pathway to compensate for reduced NO levels in patients with SCD.

1.3 IW-1701 BACKGROUND

The Sponsor is developing olinciguat (IW-1701), an orally administered stimulator of sGC, for the treatment of disorders that may be modulated by the NO-sGC-cGMP signaling pathway.

For a description of the properties of IW-1701 and the results of the nonclinical and clinical studies completed thus far, please refer to the most recent Investigator's Brochure (IB).

1.3.1 Nonclinical Data Supporting the Investigation of IW-1701 as a Potential Therapy for SCD

For a summary of the results of the nonclinical studies, please refer to the most recent IB.

2. STUDY OBJECTIVES

Primary

- To assess the safety and tolerability of oral, once-daily (QD) IW-1701 when administered for approximately 12 weeks to patients aged 16 to 70 years with SCD

Exploratory

- To evaluate the effect of oral, once-daily IW-1701 on symptoms of SCD, health-related quality of life, and biomarkers when administered for approximately 12 weeks to patients aged 16 to 70 years with SCD
- To evaluate the pharmacokinetics (PK) of oral, once-daily IW-1701 when administered for approximately 12 weeks to patients aged 16 to 70 years with SCD

3. INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN

Note: *Patients randomized prior to Amendment 4 will continue to be treated according to Amendment 3 for the duration of their study participation. Please see Amendment 3 for details.*

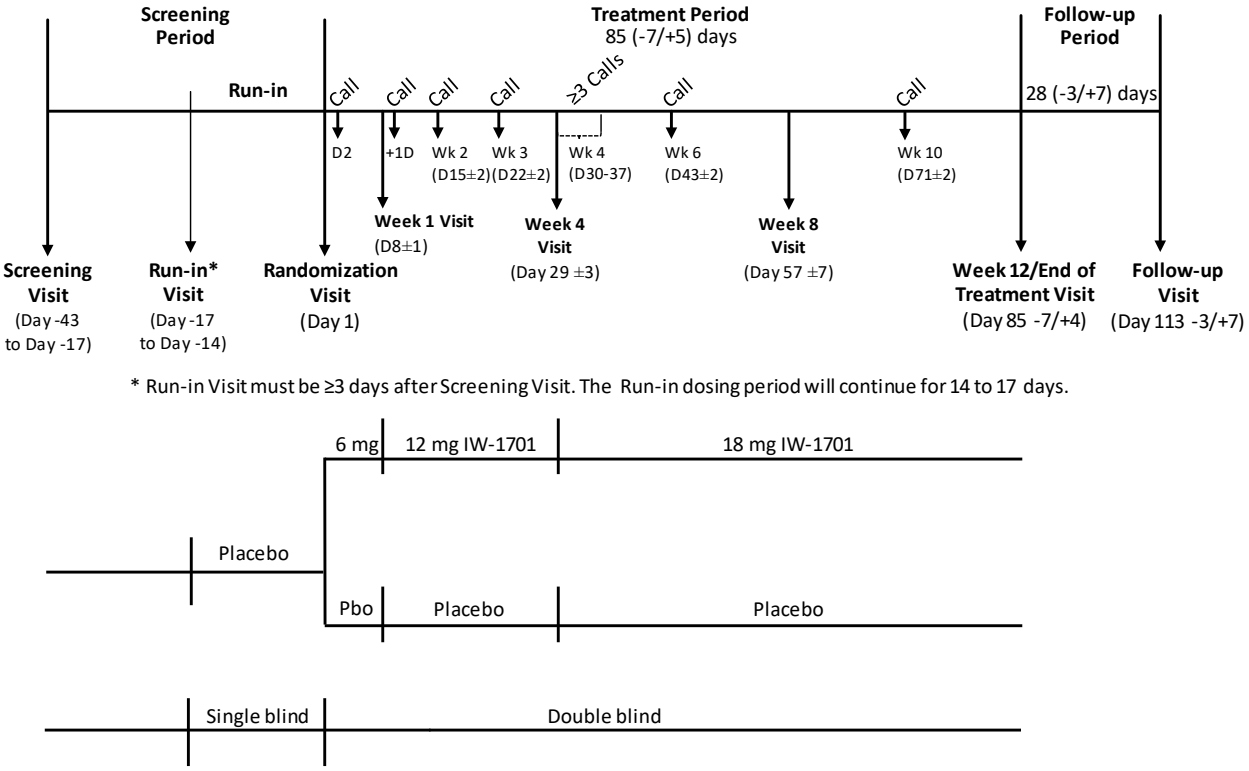
Procedural changes made in association with Amendment 4 will apply only to new patients randomized under that amendment and beyond.

This multicenter, randomized, double-blind, placebo-controlled, parallel-group study with a 2-week single-blind run-in will evaluate oral IW-1701 administered QD for approximately 12 weeks compared with placebo.

The overall study will randomize approximately 88 patients with SCD (~40 patients randomized under Amendment 3 or earlier; ~48 under Amendment 4 and beyond). The patients will be between 16 to 70 years of age and, if taking HU, will be on a stable regimen (refer to Section 3.4.1 for a description of the study population; see Eligibility Criteria for full details). After a 2-week, single-blind, placebo Run-in Period, eligible patients will be stratified by HU use (yes or no) and randomly assigned in a 3:1 ratio to receive 18 mg IW-1701 QD or placebo (see Table 2).

Each patient will progress through 3 study periods: a Screening Period that will include a single-blind placebo Run-in Period, a double-blind Treatment Period, and a Follow-up Period (Figure 1).

Figure 1. Study Schematic for Amendment 4 Onward



PBO=placebo; Wk=week

Screening Period: The Screening Period will begin with the signature of the informed consent form (ICF) at the Screening Visit and may last up to 43 days. At the Screening Visit, patients will undergo preliminary procedures to determine their initial eligibility. The Screening Period will include the Run-in dosing period.

- **Run-in Period**: The single-blind Run-in will begin at least 3 days after the Screening Visit and is defined as the 14 to 17 days before the first dose of double-blind study drug on Day 1. At the Run-in Visit, eligible patients will take their first single-blind (placebo) dose in the clinic, will undergo safety and pharmacodynamic (PD) assessments, and will complete patient-reported outcome (PRO) questionnaires in an eDiary (a handheld personal electronic device) that will be issued for their use. They will continue to take once-daily single-blind placebo at home and will record daily and weekly assessments in their eDiary throughout this period. Patients will be required to complete at least 10 days of daily assessments during the final 14 days of the Run-in Period to remain eligible for randomization into the Treatment Period.

Treatment Period: The double-blind Treatment Period will begin on Day 1 at Randomization (there is no Day 0) and will end after the End-of-Treatment (EOT) Visit on Day 85 (-7/+4).

Eligible patients will take their first dose of double-blind study drug in the clinic on Day 1 and will undergo safety, PRO, PK, and PD assessments at prespecified times according to the Schedule of Events. Patients must remain in the clinic at least 6 hours postdose and thereafter will be allowed to leave at the Investigator's discretion. Starting on Day 2, patients will take their daily double-blind study drug dose at home, per Section 3.5.4.1. Also on Day 2, preferably in the afternoon, patients will receive a phone call for adverse event (AE) and concomitant medication and procedure(s) assessment. Throughout the Treatment Period, patients will continue to record daily assessments in their eDiary.

At their Week 1 (Day 8 [±1]) and Week 4 (Day 29 [±3]) visits, respectively, patients who meet the uptitration criteria (see Section 3.5.4.2) will begin taking the applicable higher dose. At these visits, patients must again stay in the clinic at least 6 hours postdose to undergo safety, PRO, PK, and PD assessments at prespecified times according to the Schedule of Events and thereafter will be allowed to leave at the Investigator's discretion. On the day after these 3 visits, preferably in the afternoon, patients will receive a phone call for assessment of AEs and concomitant medication(s) and procedure(s).

During Week 2, Week 3, Week 4, Week 6, and Week 10, patients will receive a phone call for AE and concomitant medication and procedure(s) assessments.

At Week 12 (EOT Visit), patients will return to the clinic for safety, PRO, PK, and PD assessments and will return their eDiary and any unused study drug.

Follow-up Period: The Follow-up Period will begin immediately after the EOT Visit and will last for 28 (-3/+7) days. On Day 113 (-3/+7), patients will return to the clinic for the Follow-up Visit and final safety, PRO, PK, and PD assessments.

The study schematic (Figure 1) shows all study visits and calls. For a detailed schedule of all study visits and assessments, refer to the Schedule of Events.

3.2 DISCUSSION OF STUDY DESIGN

A double-blind, placebo-controlled, randomized study design was chosen to provide comparable treatment groups and to minimize chance of selection or Investigator bias in accordance with the concepts in ICH E10, Choice of Control Groups and Related Issues in Clinical Trials (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2001). Placebo was chosen as the control so that the rate of spontaneously occurring AEs can be determined and to reduce the potential for bias in the reporting of AEs.

The 2-week Run-in portion of the Screening Period will establish baseline values for daily and weekly patient-reported assessments. Treatment with single-blind placebo during this period will provide data on potential placebo response, and, in addition, will identify patients with low study drug/eDiary adherence who may benefit from retraining efforts.

The 12-week Treatment Period will compare the effects of IW-1701 with those of the placebo control. This length is sufficient to assess safety and tolerability, changes in patient-reported sickle cell-related symptoms, and changes in levels of biomarkers related to the NO-sGC-cGMP pathway.

Patients will be stratified by HU use (yes or no) to ensure equal allocation across treatment arms within stratum, which serves to control any potentially confounding influence (eg, difference in treatment response in patients taking HU).

Data Monitoring Committee (DMC) safety reviews (Section 3.7) will ensure that dosing will stop should a safety signal be detected. Patients will have a Follow-up Visit 28 (-3/+7) days after the final dose of study drug to determine if any AEs have developed and if AEs that were ongoing at the EOT Visit have resolved.

At each scheduled study visit, including the final Follow-up, women of reproductive potential will have a pregnancy test; results will be reviewed and documented prior to each in-clinic study drug administration, as applicable. Patients of both sexes will be instructed to follow the contraception requirements listed in Section 3.6.4.

3.3 STUDY DURATION AND DEFINITION OF STUDY COMPLETION

Patients will take single-blind placebo daily for up to 17 days during the Run-in Period and will take double-blind study drug (IW-1701 or placebo) daily for up to 89 days during the Treatment Period. Total patient participation will be 127 to 163 days, including the Screening, Run-in, Treatment, and Follow-up periods.

Overall study completion is defined by the last subject last visit (LSLV) date and when the clinical event adjudication committee (CEAC) reaches final determination of the vaso-occlusive crisis events; see Section 5.13.

3.4 STUDY POPULATION

3.4.1 Study Population Description

The overall study will randomize approximately 88 patients who have a confirmed medical history of SCD, including HbSS, HbSC, HbSβ^0-thalassemia, HbSβ^+-thalassemia, who are 16 to 70 years of age, and who have experienced at least 1 and not more than 10 sickle cell-related pain crises in the past 12 months. Patients taking HU, erythropoietin, L-glutamine, and/or prophylactic antibiotics must have been on a stable regimen (ie, same drug and same dose) for at least 8 weeks before the Randomization Visit.

Refer to the Eligibility Criteria for full inclusion and exclusion criteria.

3.4.2 Removal of Patients from Therapy or Assessment

A patient will be considered to have completed the study after completing the Follow-up Visit.

A premature discontinuation will occur when a randomized patient ceases participation in the study prior to completing all study visits.

Patients will be informed that they are free to withdraw from the study at any time and for any reason.

The Investigator may remove a patient from the study if, in the Investigator's opinion, it is not in the best interest of the patient to continue the study. Patients may also be discontinued from the study by the Investigator or the Sponsor at any time for any reason, including the following:

- Adverse event(s)
- Protocol violation, including lack of compliance
- Lost to follow-up (an effort will be made to contact the patient, including sending a certified letter)
- Withdrawal of consent or assent by patient and/or parent permission of patient <18 years old (attempts should be made to determine the reason for withdrawal of consent if possible)
- Study termination by the Sponsor
- Other reasons (eg, administrative reasons)

A patient will be discontinued from study drug dosing for any of the following reasons:

- Female patient has a confirmed pregnancy (see Sections 3.8.7.2 and 3.8.8.9).
- Patient has an AE of hemorrhage of Grade ≥2 per Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (see Section 3.8.8.4).
- Patient develops pulmonary edema.
- Patient has QTcF interval (QT interval corrected using Fridericia's formula) of >500 msec or an increase of >60 msec from baseline (ie, severity CTCAE Grade ≥3), based on machine-read calculations and confirmed with repeat ECG. Such QTcF prolongations should be recorded as AEs.
- Patient's treatment assignment becomes unblinded to the patient or the Investigator/site staff involved in the conduct of the study.

The Sponsor will be notified of any premature discontinuation. The date the patient is withdrawn from the study and the reason for discontinuation will be recorded on the study termination form of the electronic case report form (eCRF). Patients who discontinue from the study due to an AE will be followed until resolution of all of their AEs or until the unresolved AEs are judged by the Investigator to have stabilized.

If a patient does not return for a scheduled visit, the study center must make every effort to contact the patient, including sending a certified letter. In every case, the patient outcome, including lost to follow-up information, will be documented.

3.4.3 Early Termination Procedures

Patients who prematurely discontinue study drug for any reason should complete the safety and PRO assessments that are required at the End of Treatment Visit at the time of their discontinuation and should return to complete the Follow-up Visit 28 -3/+7 days after their final dose of study drug. In addition, for patients who discontinue ≥4 weeks post randomization and have specifically consented to participate in a cognitive debriefing interview, the site will notify the third-party vendor of the date of the patient's Early Termination Visit and their contact information; see Section 3.8.9.4.

3.5 STUDY TREATMENTS

3.5.1 Description of Treatments

3.5.1.1 Investigational Product

IW-1701 tablets are 3-mg oral tablets that are white and round.

3.5.1.2 Placebo

Placebo will match IW-1701 tablets in appearance.

3.5.1.3 Packaging and Labeling

IW-1701 and placebo tablets will be provided in 100-cc high-density polyethylene induction-sealed bottles, 35 tablets per bottle, containing 4 to 6 inches of purified polyester coil.

3.5.1.4 Dosing Regimens

Table 1 summarizes the dosing regimen for all patients during the Run-in Period. Patients will be masked to their treatment (single-blind dosing; see Section 3.5.6).

Table 1. Dose Regimen During Single-blind Run-in Period

Dosage	Run-in (Day -17 or -14 to Day -1); QD Dose
placebo daily	1×matching placebo tablet

QD=once daily

On Day 1 of the Treatment Period, patients will be randomized to double-blind study drug in a 3:1 ratio (IW-1701:placebo). Table 2 summarizes the dosing scheme for each treatment arm by Treatment Period week.

Table 2. Dosing Scheme, by Double-blind Treatment Period Week

Initial Dose Level (Day 1–Day 7)		Week 1 through Week 3 (Day 8–Day 28)		Week 4 through Week 12 (Day 29–Day 85)	
QD Dose	**QD Dosage**	**QD Dose**	**QD Dosage**	**QD Dose**	**QD Dosage**
6 mg IW-1701 daily	2×3-mg IW-1701 tablet	12 mg IW-1701 daily	4×3-mg IW-1701 tablet	18 mg IW-1701 daily	6×3-mg IW-1701 tablet
PBO daily	2×matching PBO tablet	PBO daily	4×matching PBO tablet	PBO daily	6×matching PBO tablet

Note: Patients must meet criteria in Section 3.5.4.2 to uptitrate.
PBO=placebo; QD=once daily

3.5.1.5 Storage and Accountability

IW-1701 tablets and the matching placebo tablets must be stored at controlled room temperature (20°–25°C with excursions permitted to 15°–30°C [59°–86°F]). Any deviation from these storage conditions must be reported to the Sponsor and use of the study drug suspended until authorization for its continued use has been provided by the Sponsor.

The Investigator must ensure that the receipt and the use of all study drug is recorded. All study drug must be retained in a locked room that may only be accessed by the pharmacist, Investigator, or other duly designated persons. Study drug must not be used outside the context of this protocol, and under no circumstances should the Investigator or study center personnel allow the supplies to be used other than as directed by this protocol without prior authorization from the Sponsor.

Subjects will be instructed to return all unused study drug to the study center at their EOT visit. All returned and unused study drug must be retained at the site. At the end of the study, a

complete reconciliation of the study drug will be performed (ie, tablets will be counted). A copy of the final Drug Accountability Log will be provided to the Sponsor or designee, or accountability will be completed electronically within the product returns module of an interactive response technology system when available. All unused and reconciled study drug will be returned to the Sponsor or designee or destroyed according to standard institutional policy or per written instruction from the Sponsor should an alternate disposition be requested. No study drug is to be destroyed without prior written permission of the Sponsor. A copy of the Certificate of Destruction or equivalent shall be provided to the Sponsor once available.

3.5.2 Method of Assigning Patients to Treatment Arms

At the Randomization Visit on Day 1 of the Treatment Period, patients who meet all of the inclusion criteria and none of the exclusion criteria will be stratified by HU use and randomly assigned in a 3:1 ratio to IW-1701 or placebo.

Patients will be assigned to treatment through central randomization. The computer-generated randomization schedule will be prepared by an independent statistician not otherwise associated with the conduct of the study.

Patients and Investigators will be blinded to the randomized treatment assignments. See Section 3.5.6 for more details on blinding in this study.

3.5.3 [redacted]

[redacted]

[redacted]

[redacted]

3.5.4 Selection, Timing, and Adjustment of Dose for Each Patient

3.5.4.1 Study Drug Administration

Throughout the Run-in and the Treatment Period, patients will be instructed to take study drug once daily with water, in the morning, at approximately the same time each day, at least 1 hour before or 2 hours after food. Table 1 and Table 2 summarize the dosing regimens during the Run-in and Treatment Periods, respectively.

On study visit days, study drug will be administered in the clinic after predose assessments, to accommodate measurements at trough plasma levels. Study visits should be scheduled in the morning to accommodate patients' regular dosing schedules and fasting requirements.

Concomitant medications should be taken as prescribed, may be taken at the same time as study drug, and do not need to be taken in the clinic on study visit days.

3.5.4.2 Uptitration (Week 1 and Week 4 Visits) during the Treatment Period

At the Week 1 (Day 8 ±1) Visit during the Treatment Period, patients will begin taking the uptitrated doses as noted in Table 2 in the clinic *unless:* their seated systolic BP is <90 mmHg, their standing heart rate is >20 bpm greater than baseline, or they have unresolved AEs that, in the Investigator's opinion, should preclude uptitration.

- If a patient *does* uptitrate at the Week 1 Visit to 12 mg QD, the patient will be considered for uptitration to 18 mg QD at the Week 4 Visit (Day 29 ±3) based on the criteria listed above.
- If a patient does *not* uptitrate at the Week 1 Visit to 12 mg QD, the patient will remain on 6 mg QD and will be re-assessed at Week 4 for titration to 12 mg QD. If he/she is then uptitrated to 12 mg QD at Week 4, he/she will remain on 12 mg QD for the remainder of the study. If the patient does not meet criteria for uptitration to 12 mg QD at Week 4, he/she will remain at the 6-mg dose for the remainder of the study.

On the day after any uptitration or dose adjustment, preferably in the afternoon, the patient will receive a phone call for AE and concomitant medication assessments. Additional phone calls will be conducted per the Schedule of Events.

3.5.4.3 Dose Adjustments

It is recommended that the patient is evaluated in the clinic prior to any dose adjustment. According to his/her medical judgement, an Investigator may reduce a patient's dose as outlined below. Adjustments should be made, if possible, in consultation with the Medical Monitor.

- Patients who do not tolerate the initial 6-mg QD dose during Week 1 of the Treatment Period should be reduced to a 3-mg QD dose (ie, reduction by 1 tablet), with escalation to 6 mg QD considered at the Week 4 visit if they meet uptitration criteria (Section 3.5.4.2). Subsequent titration to 12 mg or higher will not be permitted for those patients.
- Patients who do not tolerate an uptitration to 12 or 18 mg QD should be reduced to their prior tolerated dose level (ie, 6 or 12 mg QD, respectively). Subsequent titration to a higher dose will not be permitted for those patients.
- If a patient develops any of the following **study drug-related TEAEs**, his/her dose will be reduced to his/her prior tolerated dose (or to 3 mg QD if receiving the initial 6 mg QD dose) and will not be retitrated to a higher dose:
  - 1 episode of Grade 3 vomiting (assessed per CTCAE v4.03) lasting >48 hours and not responsive to antiemetic therapy
  - 1 episode of Grade ≥3 syncope
  - 2 episodes of Grade 2 presyncope without orthostatic hypotension

On the day after any dose adjustment or uptitration, preferably in the afternoon, the patient will receive a phone call for AE and concomitant medication assessments. Additional phone calls will be conducted per the Schedule of Events.

As noted above, with the exception of the lead-in dose during the first week, once a patient down-titrates, titration to a higher dose will not be permitted.

Investigators should notify the Medical Monitor of all decisions to reduce dose or to discontinue dosing on a per-patient basis.

See Section 3.4.2 for criteria triggering removal of individual patients from study drug dosing.

Note: Patients taking HU should be monitored for hematologic toxicities per the current prescribing information.

3.5.4.4 Temporary Discontinuation/Interruption

If a patient temporarily discontinues study drug for more than 7 contiguous days, he/she may restart study drug, pending evaluation in the clinic by the Investigator and in consultation with the Sponsor's Medical Monitor.

3.5.5 Treatment Compliance

The appropriate amount of study drug will be dispensed to patients in prelabeled bottles. Patients will be asked to return all bottles (including unused tablets) at each subsequent study visit until the end of the Treatment Period.

Treatment compliance will be based on tablet counts during the Treatment Period.

3.5.6 Blinding

The Run-in Period is single blind with all patients receiving placebo; the patients will be blinded and the Sponsor and Investigator will be unblinded.

The Treatment Period is double blind and placebo controlled; the patients, Investigator, and Sponsor personnel involved in the conduct of the trial (ie, study medical monitor, study

statistician, study data manager, and all clinical operations study personnel) will be blinded to treatment assignments. The investigational product and placebo will match in appearance.

Unblinding of a patient's randomized treatment assignment to the Investigator or Sponsor personnel involved in study conduct is restricted to emergency situations in which knowledge of the treatment is necessary for the proper handling of the patient. Except in a medical emergency, the Investigator and study center staff will remain blinded during the conduct of the study and until, at a minimum, all discrepancies in the clinical database are resolved (ie, at the time of the database lock). Individual patient treatment assignment unblinding is available to the Investigator through the interactive web response system in the event of an emergency. The Investigator should make all reasonable efforts to notify and discuss the circumstances requiring unblinding with the Medical Monitor or designee in advance of breaking the blind. If the treatment blind is broken, the reason and the date should be recorded and signed by the Investigator, and information regarding the unblinding should be submitted as soon as possible to the Sponsor. If the Investigator is unblinded to the treatment assignment of a patient, the patient will be immediately withdrawn from study drug dosing (Section 3.4.2) and early termination procedures should be followed (Section 3.4.3).

The Sponsor may also break the blind if necessary for mandatory Regulatory Reporting to the Health Authorities.

To allow for ongoing safety monitoring during the study, members of an external DMC (see Section 5.12) as well as the Sponsor Pharmacovigilance group will review summaries of AE data and may request unblinded safety data.

3.6 RESTRICTIONS

3.6.1 Prohibited Medicines and Supplements

The following medicines and supplements are prohibited starting from the Run-in Visit (which may occur from Day -14 to Day -17) through the duration of the trial:

- Aspirin (>325 mg/day)
- P2Y12 inhibitors (including prasugrel and clopidigrel)
- Any anticoagulant medication
- Specific inhibitors of phosphodiesterase 5 (PDE5) (including sildenafil and tadalafil)
- Nonspecific inhibitors of PDE5 (including dipyridamole and theophylline)
- Any supplements for the treatment of erectile dysfunction
- Riociguat, or any other sGC stimulator
- Nitrates or NO donors in any form

[redacted]

See Appendix 1 for a more complete list of prohibited medicines, supplements, and foods.

[redacted]

[redacted]

3.6.3 Fluid and Food Restrictions

Patients should fast for at least 2 hours before all study visits except the Screening Visit and Run-in, and will continue fasting until at least 1 hour postdose.

Grapefruit juice and other grapefruit products are prohibited from the Run-in Visit (which may occur from Day -14 to Day -17) through the duration of the trial.

3.6.4 Sexual Activity and Birth Control

Female patients who are not postmenopausal (no menses for at least 12 consecutive months) or surgically sterile (ie, bilateral oophorectomy, hysterectomy, or tubal sterilization [tie, clip, band, or burn]) must agree to completely abstain from heterosexual intercourse or, if heterosexually active, must agree to use 1 of the following methods of birth control from the date they sign the ICF until 90 days after the final dose of study drug:

- Progesterone implant or an intrauterine device (IUD)
- Combination of 2 highly effective birth control methods (eg, diaphragm with spermicide plus a condom, condom with spermicide plus a diaphragm or cervical cap, hormonal contraceptive [eg, oral and transdermal patch] plus a barrier method, or partner with vasectomy [conducted ≥60 days before the Screening Visit or confirmed via sperm analysis] plus a hormone or barrier method).

Female patients must wait at least 90 days after the final dose of study drug to try to become pregnant and/or to undergo egg donation or egg harvesting for current or future in vitro fertilization.

Male patients who are not surgically sterile by vasectomy (conducted ≥60 days before the Screening Visit or confirmed via sperm analysis) must agree to completely abstain from heterosexual intercourse, or, if heterosexually active, must agree to use a combination of 2 highly effective birth control methods (eg, partner use of progesterone implant and/or partner IUD, condom with spermicide plus a partner diaphragm or cervical cap, partner hormonal contraceptive [including progesterone implant] plus a barrier method, postmenopausal partner [for ≥1 year] plus barrier method) from the Screening Visit through 90 days after the final dose of study drug.

Male patients must refrain from sperm donation during the study through at least 90 days after the final dose of study drug.

3.6.5 Breastfeeding

Breastfeeding is not allowed from the Screening Visit through 90 days after the final dose of study drug.

3.7 DATA MONITORING COMMITTEE REVIEWS

An independent DMC will review trial safety data both periodically and on an ad hoc basis. An ad hoc DMC review will be triggered if events of a given category are reported at the incidence indicated in Table 3 and are judged to be both study drug related and an SAE (per causality and SAE definitions in Section 3.8.8) by the Investigator and the Sponsor. The inclusion of these AEs is based on the clinical experience with IW-1701, the prescribing information for riociguat,(23, 24) and the patient population for this study.

After each periodic or ad hoc review of safety data, the DMC will recommend trial continuation, continuation with modification, or termination. Refer to Section 5.12 for details regarding the DMC, the scheduled and ad hoc reviews, the data that will be provided for review, and Sponsor decision-making.

Table 3. Categories of SAEs Triggering DMC Review

Treatment-emergent study drug-related SAE category	Number of patients to trigger DMC review
Symptomatic hypotension-related events (eg, syncope)	2
Spontaneous bleeding events (eg, hemoptysis, subarachnoid or subdural hemorrhage, hematemesis, hematochezia)	2

DMC=Data Monitoring Committee; SAE=serious adverse event

3.8 STUDY PROCEDURES AND ASSESSMENTS

The following procedures and assessments will be performed according to the Schedule of Events. During any unscheduled visit, safety assessments will be conducted per Investigator discretion.

3.8.1 Informed Consent

Before a potential study participant undergoes any study-specific evaluations or procedures, he or she must provide written, informed consent. For patients under 18 years of age, both parental permission and child assent will be obtained. See Section 6.2 for more information regarding informed consent.

3.8.2 Medical History and Demographic Characteristics

Demographic characteristics and a complete medical history (including disease-specific history, past procedures, history of migraines, history of smoking, and, for females, date of last menstrual cycle) will be recorded at the Screening Visit.

3.8.3 Prior and Concomitant Medications/Supplements and Procedures

At the Screening Visit, the following information will be recorded for each patient:

- All medications/supplements (including name, dosage, and schedule) the patient is taking on an ongoing basis
- All prior medications/supplements (including name, dosage, and schedule) taken during the 30 days before the Screening Visit
- All relevant prior and current procedures/surgeries

Beginning at the Screening Visit, any medication/supplements or change in medication or supplements taken by a patient during the study and any medical procedure or surgery that the patient undergoes during the study will be documented in the source documents and the eCRF along with the start and stop dates and the reason(s).

3.8.4 Physical Examination, Weight, and Height

Physical examinations will be performed. For Treatment Period visits, the physical examination may be symptom directed but must include the cardiovascular and respiratory systems; all other physical examinations will be complete. A complete physical examination should include examination and assessment of the following:

General appearance	Head, eyes, ears, nose, and throat
Cardiovascular system	Neck
Respiratory system	Musculoskeletal system
Abdomen/liver/spleen	Nervous system
Lymph nodes	Skin
Neurologic status	Mental status

Breast, genitourinary, and rectal examinations are optional and may be performed at the discretion of the Investigator. Any new, clinically significant abnormal findings from the physical examination will be reported as an AE.

Each patient's weight will be recorded at each study visit; height will only be recorded at the Screening Visit.

3.8.5 Electrocardiograms

ECGs must be obtained after the patient has been supine for at least 5 minutes. If a QTc result is outside of the normal range, the ECG should be repeated twice and the average of the 3 should be calculated. Any ECG showing a clinically abnormal result will be repeated. If repeated ECG is also clinically abnormal, site should follow standard institutional procedures until resolved. If concerns remain, issue should be escalated to Medical Monitor.

3.8.6 Vital Signs

3.8.6.1 Respiratory Rate and Temperature

Respiratory rate and oral temperature (°C) should be measured after the patient has been seated for at least 5 minutes.

3.8.6.2 Blood Pressure, Pulse, and Oxygen Saturation

Seated BP at the Screening Visit, at 6 hours postdose at the Randomization Visit (last BP of the visit), and at predose and 6 hours postdose at the Week 1 Visit will be the average of 3 measurements obtained with an appropriately sized cuff at 2-minute intervals after the patient has been sitting quietly for at least 5 minutes. Other seated BP measurements and all pulse measurements may be single measurements obtained after the patient has been sitting quietly for at least 5 minutes.

For seated-to-standing BP and pulse measurements, patients should sit quietly for at least 5 minutes before seated measurements are taken, then assume a standing position for 2 minutes (±1 m) before standing measurements are taken. Values from these measurements will be used for calculation of orthostatic BP and pulse.

Oxygen saturation measurements should be taken by pulse oximeter on room air.

> **NOTE:** If oxygen saturation declines below 85% or if decreasing oxygen saturation (decreasing values across 2 sequential visits), the patient should be assessed (eg, cardiovascular exam, chest x-ray, as indicated) for pulmonary edema or other causes of decreased oxygen saturation.

When applicable, BP, pulse, and oxygen saturation measurements should be taken before blood draws.

3.8.7 Blood and Urine Sample Collection

3.8.7.1 Drug Screen

A urine screen for the following drugs will be performed at the Screening Visit:

Amphetamines	Cocaine	Propoxyphene
Barbiturates	Opiates	
Benzodiazepines	Phencyclidine	

3.8.7.2 Pregnancy Tests

For female patients of reproductive potential, a negative pregnancy test by urine dipstick must be documented at all study visits; negative results must be confirmed prior to each in-clinic dose

administration. In the event of a positive urine pregnancy test, a serum pregnancy test will be performed. If pregnancy is confirmed, see Section 3.8.8.9.

3.8.7.3 Clinical Laboratory Tests

Blood and urine samples will be collected for clinical laboratory tests (Table 4). Additional samples may be collected during unscheduled visits as needed per Investigator discretion.

If Central laboratory results are not available, local laboratory results for study eligibility at the Screening Visit are acceptable, pending preapproval by the Sponsor. Patients must fast at least 2 hours before predose sample collections and for at least 1 hour postdose during the Treatment Period, and for at least 2 hours before sample collections at the Follow-up Visit; fasting is not required for the Screening Visit.

Table 4. Clinical Laboratory Tests

Serum Chemistry	**Hematology (CBC)**	**Coagulation Panel**
Albumin	Hematocrit	aPTT
Alkaline phosphatase	Hemoglobin	Prothrombin time
ALT	Platelet count (MPV)	INR
AST	RBC count	
Bicarbonate	WBC count	**Urinalysis**
BUN	WBC differential	Color and appearance
C reactive protein	(% and absolute):	pH and specific gravity
Calcium	Basophils	Bilirubin
Chloride	Eosinophils	Glucose
Cholesterol	Lymphocytes	Ketones
Creatinine	Monocytes	Leukocytes
Cystatin C	Neutrophils	Nitrites
GGT	RBC indices	Occult blood
Glucose	MCH	Protein
HDL-c	MCHC	Urobilinogen
LDH	MCV	Microscopic (including bacteria,
LDL-c (calculated)	RDW	RBCs, WBCs per HPF if
Magnesium	Reticulocyte count	dipstick is abnormal)
Phosphorus	(% and absolute)	
Potassium	**Additional blood**	**Additional urine**
Sodium	Hemoglobin F	Urine cotinine
Haptoglobin	Hemoglobin A	Urine albumin & creatinine
Bilirubin	Vitamin D	(for UACR) [a]
Total	Ferritin	

Table 4. Clinical Laboratory Tests

Serum Chemistry	Hematology (CBC)	Coagulation Panel
Direct (conjugated)		
Indirect (unconjugated)		
Protein (total)		
Triglycerides		
Uric acid		

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CBC=complete blood count; GGT=gamma glutamyl transferase; HDL-c=high-density lipoprotein cholesterol; HPF=high power field; INR=international normalized ratio; LDH=lactate dehydrogenase; LDL-c=low-density lipoprotein cholesterol; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; MPV=mean platelet volume; RBC=red blood cell; RDW=red blood cell distribution width; UACR=urine albumin-to-creatine ratio; WBC=white blood cell
a. UACR will be calculated as urine albumin (mg/dL) / urine creatinine (g/dL)

3.8.7.4 Pharmacokinetics

Blood samples for PK assessments will be collected.

3.8.7.5 Biomarkers

Blood and urine samples for assessment of pharmacodynamic effects will be collected per the SoE and assayed per the laboratory manual(s).

3.8.7.6 Genotyping (Optional, per Patient Consent)

A single blood sample for exploratory assessment of genetic factors that may be related to interindividual differences in drug disposition, BP, or other PD responses will be collected from patients who have provided specific written consent for sample collection and storage.

3.8.8 Adverse Events

All patients will be monitored for AEs throughout the study. All AEs will be recorded in accordance with the procedures outlined in this section.

3.8.8.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE, therefore, can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes, but is not limited to, the following:

- Any unfavorable changes in general condition
- Any clinically significant worsening of a preexisting condition
- Any intercurrent diseases and accidents

Note: A procedure is not an AE, but the reason for a procedure may be an AE.

3.8.8.2 Definition of Serious Adverse Events

An SAE is defined as any AE occurring at any dose that results in any of the following:

- Death
- Life-threatening: The patient was at immediate risk of death from the reaction as it occurred (ie, it does not include a reaction that hypothetically might have caused death if it had occurred in a more severe form)
- Hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity: a substantial disruption of a person's ability to conduct normal daily functions
- Congenital anomaly/birth defect
- Important medical events: Events that may not result in death, be life threatening, or require hospitalization. Such an event may be considered serious when, based on appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Emergency room visits that do not result in admission to the hospital should be evaluated for 1 of the other serious outcomes (eg, life-threatening, other serious [medically important] event).

3.8.8.3 Causality Assessment

For all AEs, the Investigator must provide an assessment of causal relationship to study drug. The causality assessment must be recorded in the patient's source documentation and on the AE page of the subject's eCRF. Causal relationship must be assessed according to the following:

Related: An event where there is a reasonable possibility of a causal relationship between the event and the study drug. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the TEAE.

Unrelated: Any other event

3.8.8.4 Severity Assessment

The Investigator will provide an assessment of the severity of each AE by recording a severity rating in the patient's source documentation and on the AE page of the patient's eCRF. *Severity,* which is a description of the intensity of manifestation of the AE, is distinct from *seriousness,* which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality. Severity of AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03.(25)

For AE terms not included in CTCAE v4.03, severity will be reported as CTCAE grades as indicated below.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

Note: A semicolon indicates "or" within the description of the grade.
ADL=activities of daily living; AE=adverse event
* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

3.8.8.5 Adverse Events of Special Interest (AESIs)

Based on the mechanism of action of sGC and anticipated vasodilation effects, the Sponsor will collect AESIs related to symptomatic or Grade ≥2 per NCI-CTCAE hypotensive events and/or tachycardia AEs. In addition, based on the prescribing information for riociguat (23, 24), bleeding events, pulmonary edema, and bone-related events, including fractures, will also be categorized as AESIs. The specific list of terms will be provided in the safety management plan and statistical analysis plan (SAP).

This classification means that although these events might be nonserious, they will be reported to the Sponsor per the timelines of SAEs, along with a causality assessment and an event narrative.

3.8.8.6 Pain Crisis Events

Sickle cell-related pain crisis events will be documented throughout the duration of the trial. Each crisis will be reported to the Sponsor within 24 hours of the Investigator becoming aware of the event.

An on-study sickle cell-related pain crisis is defined as an acute episode of new-onset pain that lasts at least 2 hours with no medically determined cause other than a vaso-occlusive event and that requires treatment with oral or parenteral opioids, or parenteral nonsteroidal anti-inflammatory drugs, or other analgesics prescribed by a healthcare provider in a medical facility or by telephone management documented in medical records. Note that this definition differs slightly from the definition that is to be used to assess study eligibility (see Inclusion #6).

Acute chest syndrome, hepatic sequestration, splenic sequestration, priapism (each requiring a visit to a medical facility or documented telephone management) and death (except that due to suicide, accident, or other event clearly unrelated to the patient's medical condition) will also be considered pain crises, as well as subtypes of pain crises, for analysis purposes.

In the event of a sickle cell-related pain crisis, the following laboratory values, at minimum, should be recorded if part of local practice and available to the study site: hemoglobin, reticulocyte count (% and absolute), C-reactive protein, direct and indirect bilirubin, lactic dehydrogenase, and haptoglobin.

Information regarding the TEAEs related to the underlying disease will remain part of the Sponsor's ongoing internal signal detection process. To ensure consistency, all crisis events will be reviewed by the CEAC (see Section 5.13). Because these events are anticipated in this study population, the Sponsor does not anticipate reporting them as IND safety reports unless evidence suggests a causal relationship between the drug and the events.

3.8.8.7 Recording Adverse Events

AEs will be collected and recorded from the time the patient signs the ICF at the Screening Visit through the last Follow-up Visit. All AEs, regardless of the assumption of a causal relationship with study procedures or study medication, must be recorded in the patient's source documentation and subsequently on the appropriate AE page of the patient's eCRF. This record includes AEs the patient reports spontaneously, those observed by the Investigator, and those elicited by the Investigator in response to open-ended questions during the study, such as "Have you had any health problems since your last visit?"

For every AE, the Investigator must:

- Provide an assessment of the severity, causal relationship to the study medication, and seriousness of the event
- Document all actions taken with regard to the study medication (eg, no action taken, treatment interrupted, or treatment discontinued)
- Detail any other treatment measures taken for the AE, including concomitant medications and/or procedures

Laboratory abnormalities and changes in vital signs, physical examination findings, and 12-lead ECG parameters should be considered AEs and reported on the AE page of the patient's eCRF if the Investigator considers them clinically significant and are not already associated with an AE.

Any medical condition that is present when a patient is screened and does not worsen in severity and/or frequency should be reported as Medical History and not as an AE. However, if the condition worsens to a clinically significant degree at any time during the study, it should be reported as an AE.

3.8.8.8 Reporting SAEs and AESIs

An AE that meets any of the SAE criteria or qualifies as an AESI (see Section 3.8.8.5) must be reported to Syneos Health Global Safety and Pharmacovigilance (GSPV) within 24 hours from the time site personnel first learn of the event. All initial and follow-up event details must be recorded in the subject's source documentation and on the appropriate AE reporting page of the subject's eCRF, regardless of whether the event is considered causally related to study medication.

Regardless of causality, SAE and AESI events must be reported and recorded from the time the patient signs the ICF at the Screening Visit until the last Follow-up Visit. Any events that occur at any time after the specified follow-up period that the Investigator considers to be related to study medication should also be reported immediately.

All SAE and AESI Report Forms should be emailed to:

safetyreporting@syneoshealth.com

or sent via fax as indicated below.

From study sites in:	Use fax number:
United States	1-877-464-7787
United Kingdom	0-800-680-0612
Lebanon	[please send via email]

If follow-up is obtained or requested by Syneos Health GSPV, the additional information should be sent in a timely manner. Copies of discharge summaries, consultant reports, autopsy reports, and any other relevant documents may also be requested.

Appropriate remedial measures should be taken by the Investigator using his/her best medical judgment to treat the AEs. These measures and the patient's response to these measures should be recorded. All AEs regardless of relationship to study medication, will be followed by the Investigator until satisfactory resolution, until the Investigator deems the AE to be chronic or stable, or until the patient is lost to follow-up.

The Investigator will be responsible for reporting unanticipated events as defined in 21 CFR 312.64 to the institutional review board (IRB) or to the independent ethics committee

(IEC), as applicable. The Sponsor will be responsible for reporting to the regulatory authorities the events that it considers to be serious, unexpected, and related to study drug in accordance with 21 CFR 312.32.

3.8.8.9 Exposure to Study Drug During Pregnancy and Reporting Pregnancy

A female patient who reports pregnancy before randomization to study drug must be withdrawn from the study. The pregnancy will be recorded as a reason for screen failure. Since there will have been no exposure to study drug, there will be no need to notify Syneos Health GSPV of the pregnancy.

A female patient who reports pregnancy after randomization must discontinue study drug at once. The site must notify Syneos Health GSPV within 24 hours from the time that site personnel first learn of the pregnancy. The site should make reasonable efforts to follow the pregnancy to term and notify Syneos Health GSPV of the pregnancy outcome (within 24 hours of being informed) including elective termination. If the pregnancy is associated with an SAE, a separate SAE form must be completed.

All Pregnancy Report Forms should be emailed to:

safetyreporting@syneoshealth.com

or sent via fax as indicated below.

From study sites in:	Use fax number:
United States	1-877-464-7787
United Kingdom	0-800-680-0612
Lebanon	[please send via email]

3.8.9 Patient-reported Questionnaires

3.8.9.1 Daily Questionnaires via eDiary

Patients will complete the following questionnaires daily using a study-specific eDiary.

3.8.9.1.1 SCD-SAF

The Sickle Cell Disease-Symptom Assessment Form (SCD-SAF) will assess sickle cell-related symptoms, including an assessment of pain on an 11-point numerical rating scale (NRS).

3.8.9.1.2 Analgesic Use

Patients will be asked to record use of pain medication (name[s] of medication[s]).

3.8.9.2 Weekly Questionnaires via eDiary

Patients will complete the following questionnaires weekly using a study-specific eDiary.

3.8.9.2.1 PGI-S

The Patient Global Impression of Severity (PGI-S) is a single-item questionnaire that assesses impression of disease severity on a 5-point verbal rating scale.

1. Overall, how would you rate your sickle cell disease symptoms over the past 7 days? Please select one option.

1 ☐	None
2 ☐	Mild
3 ☐	Moderate
4 ☐	Severe
5 ☐	Very severe

3.8.9.3 Study Visit Questionnaires

Patients will complete the following questionnaires at specified study visits. Questionnaires should be completed in the order presented below, as applicable to the study visit.

3.8.9.3.1 Work and School Absences

Patients will be asked to record number of days missed from school or work due to SCD symptoms.

3.8.9.3.2 PROMIS© Fatigue—Short Form 7a

The Patient-reported Outcomes Measurement Information System (PROMIS) Fatigue—Short Form 7a is a self-administered questionnaire that assesses the impact and experience of fatigue in the 7 days prior to the administration of the questionnaire.(26) Patients respond using a verbal rating scale.

3.8.9.3.3 ASCQ-Me SM

The Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me) is a PRO measurement system that assesses the physical, social, and mental impact of SCD on adults in the past 7 days, 30 days, or 12 months.(2) The 3 domains of the ASCQ-Me consist of the following subscales: pain impact, pain episodes, sleep impact and stiffness impact (physical health), emotional impact (mental health), and social functioning impact (social health). Patients respond using verbal rating scales. Patient will complete all the subscales except the pain episodes subscale.

3.8.9.3.4 PGIC

The Patient Global Impression of Change (PGIC) is a single-item questionnaire that assesses perception of change in overall health status since the start of the study on a verbal rating scale (very much improved to very much worse).

1. Since the start of the study, how would you describe your overall health status? Please select one option.

1 ☐	Very Much Worse
2 ☐	Much Worse
3 ☐	Minimally Worse
4 ☐	No Change
5 ☐	Minimally Improved
6 ☐	Much Improved
7 ☐	Very Much Improved

3.8.9.3.5 EQ-5D-5L

The EuroQol 5-Dimension 5-Level (EQ-5D-5L) questionnaire is a generic self-administered measure of health status.(21) The first component consists of 5 questions assessing the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses to the 5 questions define a health state for which a utility index can be derived from published algorithms.(22) The second component of the EQ-5D is a visual analog scale asking

patients to rate their health from 0 to 100 (0 represents worst imaginable health state and 100 represents best imaginable health state).

3.8.9.3.6 SF-12v2®

Short Form Health Survey (SF-12v2) is a widely used generic self-administered measure of health-related quality of life and measures 8 concepts of health: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional problems, and mental health (psychological distress and psychological well-being). These 8 scales are aggregated into 2 summary measures: the physical component and mental component summary scores.(23)

3.8.9.4 SCD-SAF Cognitive Debriefing Interview

For patients who provide specific consent, cognitive debriefing interviews will be conducted to support the SCD-SAF as fit for purpose in the context of a clinical trial. When a participating patient's Week 12/End of Treatment Visit (or an early termination ≥4 weeks post randomization) has been scheduled, the study site will transfer the patient's contact information and visit date to the third-party vendor conducting the interview. Telephone interviews will be conducted within 1 week of the Week 12/End of Treatment Visit. During this 1-time interview, patients will be asked open-ended questions that are intended to assess the validity of the SCD-SAF content and the usability of the PRO eDiary device. Details are provided in the Cognitive Debriefing Interview study manual.

4. STUDY ENDPOINTS

4.1 PRIMARY ENDPOINTS

4.1.1 Safety

- Incidence, frequency, and severity of TEAEs and study drug-related TEAEs in IW-1701-treated patients compared with placebo-treated patients over the study

4.2 EXPLORATORY ENDPOINTS

4.2.1 Pharmacodynamic Parameters

4.2.1.1 Hemodynamic Parameters

- Change from Day 1 baseline in seated systolic and diastolic BPs and pulse to predose at Weeks 1, 4, 8, and 12
- Change from Day 1 baseline in orthostatic systolic and diastolic BPs and pulse to predose at Weeks 1, 4, 8, and 12
- For each study visit, change from predose to each postdose timepoint

4.2.1.2 Pain Crisis Parameters

- Time to first pain crisis experienced during the Treatment Period (full definition and subsets defined by visit to medical facility or telephone management)
- Proportion of patients experiencing ≥1 pain crisis during the Treatment Period (full definition and subsets defined by visit to medical facility or telephone management)
- Frequency of pain crises (full definition and subsets defined by visit to medical facility or telephone management)

4.2.1.3 Biomarkers

- Change from baseline in biomarker concentrations at assessed timepoints

4.2.2 Pharmacokinetic

- Plasma concentrations of IW-1701 at assessed timepoints

4.2.3 Patient-reported Outcomes

- Change from baseline in SCD-SAF score at Weeks 4, 8, and 12
- Pain as measured on the 11-point NRS by week and for the overall Treatment Period
- Change from baseline in pain as measured on the 11-point NRS by week and for the overall Treatment Period
- Daily pain response defined as achieving at least a 30% reduction in average daily pain at Week 12
- Change from baseline in ASCQ-Me subscale scores at Week 1, 4, 8, and 12
- PROMIS fatigue score at Week 1, 4, 8, and 12
- Number and proportion of days with analgesic use at Week 4, 8, and 12
- Number and proportion of days of work/school missed due to SCD symptoms at Weeks 4, 8, and 12
- EQ-5D-5L at Week 12
- Change from baseline in SF-12v2 at Week 12

5. STATISTICAL METHODS

5.1 GENERAL CONSIDERATIONS

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation [SD], median, quartiles, range, and interquartile range). Categorical variables will be summarized using the number and percent of patients in each category. Unless otherwise specified, all confidence intervals will be 2-sided with a confidence level of 95%. No adjustments will be made for multiplicity. Details of the data handling methods will be specified in the SAP, to be finalized before unblinding of the study. If not otherwise specified, the baseline value is defined as the last nonmissing value measured before administration of randomized study drug on Day 1. All statistical analyses will be performed using SAS® Version 9.4 (or later) for Windows.

5.1.1 Continuous Endpoints

For continuous endpoints (eg, absolute change from baseline and percent change from baseline), an analysis of covariance model will be fitted with treatment arm and stratification factors (HU use) as categorical variables and the corresponding baseline value as a covariate. Pairwise contrasts will be used to compare each IW-1701 arm with the placebo arm. Least-squares means (LSMs) for each treatment arm, LSM differences between each IW-1701 arm and the placebo arm, their corresponding confidence intervals, and p-values will be presented.

5.1.2 Dichotomous Endpoints

For dichotomous endpoints, the proportions for each IW-1701 treatment arm and the corresponding placebo arm will be compared using a Cochran-Mantel-Haenszel (CMH) test controlling for stratification factors (HU use). The difference in the proportions between each IW-1701 arm and the placebo arm as well as the CMH estimates of odds ratio and p-values will be presented, along with the corresponding confidence intervals.

Additional details regarding the statistical methods will be provided in the SAP, to be finalized before unblinding of the study.

5.1.3 Time-to-event Endpoints

For each treatment arm, Kaplan-Meier estimates will be used to estimate the survival function for time to first pain crisis. The median survival time for each treatment, as well as the Kaplan-Meier curves will be presented.

5.2 DETERMINATION OF SAMPLE SIZE

The sample size was determined outside of statistical considerations and is based on precedent set by prior studies of similar nature and design.

5.3 ANALYSIS POPULATIONS

The following populations will be defined for this study:

- **Screened Population:** All patients who sign the informed consent form and receive a patient identification number
- **Single-blind Run-in Population:** All patients who enter the single-blind Run-in period
- **Safety Population**: All randomized patients who receive at least 1 dose of study drug. Patients in this population will be evaluated according to the treatment they actually received.
- **Intent-to-Treat (ITT) Population**: All randomized patients. Patients in this population will be evaluated according to the treatment arm they were assigned to at randomization
- **PK Population**: All randomized patients who receive at least 1 dose of IW-1701 and have at least 1 evaluable postdose PK parameter assessment
- **Evaluable Population:** All randomized patients with no major protocol deviations who complete at least 8 weeks of treatment (a blinded data review will determine if a more stringent criterion, eg, 10 weeks, is appropriate)

5.4 PATIENT DISPOSITION

The total number of screened patients and the number of patients who are screen failures will be tabulated. The number and percentage of patients randomized and included in each population (Screened, Single-blind Run-in, Safety, ITT, PK, Evaluable) will be presented by treatment arm and IW-1701 overall. The number and percentage of patients who completed the study or discontinued early, as well as the reasons for discontinuation will be presented by treatment arm.

5.5 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic parameters (eg, age, sex, race, ethnicity, weight, height, body mass index [BMI]) and other baseline characteristics will be summarized by treatment arm for the Safety, ITT, and Evaluable Populations.

The number and percentage of patients with abnormalities in medical and surgical histories in each system organ class (SOC) and preferred term (PT) will be summarized by treatment arm for the Safety Population.

5.6 DRUG EXPOSURE AND COMPLIANCE

Exposure to double-blind study drug, calculated as the number of days from the first dose taken to the date of the last dose taken, inclusive, will be summarized by treatment arm for the Safety Population. The total number of doses taken between specified visits and overall for the entire study will be calculated for each subject. Compliance will be based on the number of doses expected to be taken. Percent compliance for double-blind study medication will be summarized by treatment arm and overall for each scheduled visit and overall for the ITT Population. Compliance rates will also be categorized as missing, <80%, ≥80% and ≤120%, and >120% and summarized by treatment arm.

5.7 PRIOR AND CONCOMITANT MEDICATIONS AND PROCEDURES

Prior medications and procedures are defined as those that were initiated and/or completed before the date of first dose of study drug.

Concomitant medications and procedures are defined as any medication or procedure initiated on or after the date of first dose of study drug. Any that are initiated after the date of last dose of study drug will not be considered concomitant.

Both prior and concomitant medication use will be summarized by the number and percentage of patients in each treatment arm receiving each medication within each therapeutic class for the ITT Population. Multiple medications used by a patient in the same category (based on Anatomical-Therapeutic-Chemical classification) will only be counted once.

5.8 MAJOR PROTOCOL DEVIATIONS

Major protocol deviations will be identified and documented based on a review of protocol deviations before database lock and treatment unblinding, and will be used to define the Evaluable Population. The categories of major protocol deviations to be reviewed include, but are not limited to, patients who:

- Did not meet key inclusion/exclusion criteria in the judgement of the evaluability committee
- Received disallowed concomitant medication that could meaningfully impact results
- Had overall treatment compliance rate <80% or >120%

The number and percentage of subjects with major protocol deviations will be summarized by type of deviation and by treatment arm for the ITT Population. All major protocol deviations will be presented in a data listing.

5.9 SAFETY ANALYSES

All safety parameters will be analyzed descriptively for the Safety Population.

TEAEs will be summarized by treatment arm with PT under SOC. Listings will be provided for screening (pretreatment), run-in, and treatment period TEAEs; severe TEAEs, study drug-related TEAEs, SAEs, and TEAEs leading to study discontinuation. Descriptive statistics will be provided for all safety parameters (ECGs, vital signs, and clinical laboratory tests).

ECGs, vital signs, and clinical laboratory tests will be summarized at each timepoint and listings will be provided for patients with abnormal values.

5.9.1 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in standard units) and changes from the baseline values at each assessment timepoint will be presented by treatment arm for each clinical laboratory parameter.

5.9.2 Vital Signs

Descriptive statistics for vital signs (ie, oxygen saturation, pulse rate, systolic and diastolic BP, orthostatic pulse rate, orthostatic systolic and diastolic BP, respiratory rate, temperature and body

weight) and changes from baseline values at each visit will be presented by treatment arm for the Safety Population.

5.9.3 ECGs

Descriptive statistics for ECG parameters and changes from the baseline values at the end of treatment visit will be presented by treatment arm for the Safety Population.

The number and percentage of patients with ECG abnormalities will be tabulated by treatment arm. Shift tables will be presented comparing values between baseline and end of study. A listing of all AEs for patients with ECG abnormalities will also be provided.

The number and percentage of patients with absolute QTcF intervals in the following categories will be examined: QTcF≤450 ms, 450 ms<QTcF≤480 ms, 480 ms<QTcF≤500 ms, and QTcF>500 ms. Shift tables will be presented comparing values between baseline and end of study.

Additionally, the number and percentage of patients with a change from baseline in QTcF interval according to the following categories will be examined: QTcF interval increases by more than 30 ms, but not more than 60 ms, and QTcF interval increases by more than 60 ms. Shift tables will be presented comparing values between baseline and end of study.

5.10 PHARMACODYNAMIC ANALYSES

All PD analyses except the PRO analyses will be based on the Safety and Evaluable Populations.

5.10.1 Controlling for Multiplicity

Due to the exploratory nature of this study, no adjustments will be made for multiple comparisons.

5.10.2 Patient-Reported Outcomes Analyses

Health outcomes analyses will be based on the ITT and Evaluable Populations.

5.10.2.1 SCD-SAF

Descriptive analyses and change from baseline responses will be computed by treatment arm. Full data handling and analyses will be outlined in the SAP.

5.10.2.2 Analgesic use

Descriptive statistics will be computed for days with and without pain medication use by treatment arm.

5.10.2.3 PGI-S

Each response option will be assigned a numerical value to produce the PGI-S score. Descriptive statistics will be presented for the PGI-S and for change from baseline by treatment arm.

5.10.2.4 Work and School Absences

Descriptive statistics will be computed for days missed from work and school.

5.10.2.5 PROMIS Fatigue Short Form 7a

Descriptive analysis and change from baseline will be computed for the PROMIS Fatigue Short Form 7a by treatment arm. The HealthMeasures scoring service can be used to score the questionnaire using the response pattern scoring method. Alternatively, a total raw score can be derived if there are no missing data. All questions must be answered to produce a valid score. If a question is skipped, the HealthMeasures scoring service should be used to create a final score.

A higher PROMIS T-score represents more of the concept being measured. A T-score of 60 is one SD worse than the average United States (US) general population and a T-score of 40 is one SD better than average.

5.10.2.6 ASCQ-Me

Descriptive analysis and change from baseline will be computed for each subscale by treatment arm. A higher score represents better self-reported health for the emotional, pain, sleep, social, and stiffness impact domains. For example, a score of 60 on the emotional impact measure is 1 SD higher than the average US general population, indicating better health.

5.10.2.7 PGIC

Each response option will be assigned a numerical value to produce the PGIC score. Patient responses will be categorized as disease deterioration (0–3 points), stable disease (4 points) or disease improvement (5–7 points) since the initial baseline visit. Descriptive statistics will be presented for the PGIC by treatment arm.

5.10.2.8 EQ-5D-5L

Patient responses to the descriptive system (ie, health state) will be converted to the corresponding utility score and descriptive statistics will be presented for utility score by treatment arm. The same statistics will be calculated for the analog scale reflecting the patient's preference for their health state and presented by treatment arm.

5.10.2.9 SF-12v2

Patient responses will be aggregated into 2 summary measures, the Physical Component Summary and Mental Component Summary scores. Descriptive statistics will be presented for the Physical Component Summary and Mental Component Summary scores of the SF-12v2 and for change from baseline by treatment arm.

5.11 PHARMACOKINETIC ANALYSIS

All PK analyses will be based on the PK Population. Descriptive statistics will be calculated for plasma concentration of IW-1701 at each assessed timepoint by IW-1701 dose level.

The population PK approach based on sparse PK data will be used to determine exposure and oral clearance of IW-1701. Influence of patient demographics (eg, age, race) and effects of concomitant medications on IW-1701 PK exposure will be evaluated. In addition, exposure-effect (such as hemodynamic, biomarkers, efficacy, and safety parameters) relationships will also be explored. The results of these analyses may be reported separately.

5.12 DATA MONITORING COMMITTEE

An independent DMC will be given the responsibility to review trial safety and provide guidance consistent with the objectives of the study and appropriate ethical requirements.

The DMC will comprise physicians who have experience in clinical studies in SCD and 1 biostatistician who has experience in analysis of clinical trials. For DMC members, their only role in this study will be as a member of the DMC, thus ensuring their independent review of safety data.

Two safety review meetings will be scheduled: the first after approximately 29 patients have completed 4 weeks of the Treatment Period and the second after approximately 1/3 (~16) patients enrolled under Amendment 4 or beyond have completed at least 8 weeks of the Treatment Period.

For these periodic reviews, the DMC will be provided with summaries of TEAE data by treatment arms randomly masked. An independent statistician will be responsible for summarizing and submitting these safety data to members of the DMC. All data presentations for the DMC will be performed using the Safety Population. All data that are available at the time of each analysis will be presented utilizing a specified cutoff date prior to the planned DMC session. If a safety/tolerability signal or concerning TEAE imbalance is identified at a review, the committee can request unblinding of the masked treatment and may request additional safety data (eg, vital signs, concomitant medications). At each meeting, the DMC will review accumulated TEAE data and recommend trial continuation, modification, or termination.

The DMC will also be required to perform an ad hoc review should the SAE criteria in Section 3.7 be met. In this circumstance, the committee will be provided with narrative descriptions and all relevant clinical supporting documentation related to the SAEs under review. Upon request, the relevant subjects' unblinded treatment and dose level information will be provided to the committee.

In addition, the DMC will review unblinded safety data from the first 12 randomized patients who are taking an established daily prophylactic aspirin regimen; 1 review will be conducted after the first 6 of these patients are randomized and have completed the Week 1 (Day 8) Visit, and the subsequent review will be conducted after the next 6 of these patients have completed the Week 1 Visit. All available safety data from these patients, including post-Week 1 Visit data, will be included in the review.

In addition to the periodic and ad hoc reviews, during the trial, committee members will be provided with blinded reports on all SAEs.

The DMC or the Sponsor may request ad hoc meetings at any time and at their discretion.

There are no predefined stopping rules for the trial. (See Section 3.4.2 for criteria triggering removal of individual patients from study drug dosing.) However, the DMC will be reviewing safety data as described above. The Sponsor, upon the recommendation of the DMC, may put the study on hold pending regulatory consultation or stop the study at any time for significant safety concerns. If the DMC recommends stopping or modifying the trial, a senior review team from the Sponsor will have the opportunity to review the blinded data and discuss study findings with the DMC. The senior review team will be separate from the clinical study team involved with conduct of the study. The Sponsor may also seek input from relevant regulatory authorities. The Sponsor will make the final decision on the recommendation and will relay its decision to the DMC and relevant regulatory authorities. Additional details will be provided in the DMC charter, which will be developed in collaboration with the DMC members before the first patient is randomized.

5.13 CLINICAL EVENT ADJUDICATION COMMITTEE (CEAC) FOR VASO-OCCLUSIVE CRISES

To ensure consistency across all sites, all SCD-related pain crisis events and vaso-occlusive crises identified by Investigators and reported post-randomization will be reviewed by independent, blinded hematologists specializing in the treatment of SCD who will serve as a CEAC. No sponsor representative will serve as a CEAC member or participate in the adjudication of the events. The CEAC will be blinded to the treatment assignment. If, for any reason, the study blind is broken and revealed to the clinical study team, steps will be taken to ensure that the CEAC members remain blinded. The CEAC Charter, full definitions, and list of required data for review will be developed and finalized in collaboration with the adjudicators before initiation of the first review.

5.14 INTERIM ANALYSES

One or 2 interim analyses may be conducted for business purposes and/or to assist with the planning of future studies. The first may be conducted after all patients enrolled under

Amendment 3 or earlier have completed their end-of-study visit or are lost to follow-up. A second may be conducted after a minimum of one-third of the patients planned for enrollment under Amendment 4 or beyond have completed at least 8 weeks of randomized treatment.

If performed, details regarding the interim analyses will be included in the SAP, along with updates to the data management plan as necessary. An independent statistician not otherwise associated with the study will perform the interim analyses. Select sponsor representatives as identified in the SAP and not otherwise associated with study conduct may become unblinded. Review of the interim analyses for planning purposes will operate independently of the study DMC and CEAC.

5.15 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Any amendment to this protocol will be provided to the Investigator in writing by the Sponsor or its designee. Before implementation, any protocol amendment regarding reportable deviations (as defined by the IRB/IEC) must be approved by the IRB/IEC and the signature page must be signed by the Investigator and received by the Sponsor or its designee, with the following exception: If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB/IEC review and approval. However, the IRB/IEC must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

Deviating from the protocol is permitted only if absolutely necessary for the safety of the patients and must immediately be reported to the Sponsor or its designee.

6. ETHICAL CONSIDERATIONS

6.1 INSTITUTIONAL REVIEW BOARD

Before study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to a patient or patient's legal guardian must be approved by the IRB/IEC.

All IRB/IEC approvals must be dated and signed by the IRB/IEC Chairperson or his or her designee and must identify the IRB/IEC by name and address, the clinical protocol by title and/or protocol number, and the date upon which approval or favorable opinion was granted for the clinical research. Copies of IRB/IEC approvals should be forwarded to the Sponsor. All correspondence with the IRB/IEC should be maintained in the Investigator File.

No drug will be released to the site to dose a patient until written IRB/IEC approval has been received by the Sponsor.

The Investigator is responsible for obtaining continuing review of the clinical research at least annually or more often if specified by the IRB/IEC. The Investigator must supply the Sponsor with written documentation of the approval of the continued clinical research.

The IRB/IEC must be constituted in accordance with Federal and ICH Good Clinical Practice (GCP) guidelines and any relevant and applicable local regulations.

Major changes in this research activity, except those to remove an apparent immediate hazard to the patient, must be reviewed and approved by the Sponsor and by the IRB/IEC that approved the study. Amendments to the protocol must be submitted in writing to the Investigator's IRB/IEC for approval before patients being enrolled into the amended protocol.

6.2 PATIENT INFORMATION AND INFORMED CONSENT

Informed consent procedures will comply with the Code of Federal Regulations (CFR) 21, Parts 50 and 312, and ICH E6(R2) guidelines.

The written ICF must be approved by the IRB/IEC for the purposes of obtaining and documenting consent.

Before entry into the study, each patient and, if the patient is under 18 years of age, the patient's parent, will be provided with a written explanation of the study. For patients who require a parent or legal guardian's permission to participate, 2 consent documents will be used: 1 for obtaining the parent or guardian's permission; and 1, which will outline the study in simplified language, for obtaining the assent of the patient. Combined ICFs may be used if allowed by the site IRB/IEC.

It is the responsibility of the Investigator or appropriately trained health professional to give each patient/parent full and adequate information regarding the objectives and procedures of the study and the possible risks involved. Patients and parent/guardian, if applicable, will then be given the opportunity to ask questions and the Investigator will be available to answer questions as needed. Patients will be informed of their right to withdraw from the study at any time without prejudice. After this explanation and before entering the study, the patient and parent/guardian, if applicable, will voluntarily sign the study-specific ICF.

The patient and parent/guardian, if applicable, will receive a copy of the signed and dated documents. The Investigator must retain each patient's and parent's, if applicable, original signed ICF.

If new information becomes available that may be relevant to the patient's consent and willingness to participate in the study, the ICF will be revised and the patient and parent/guardian, if applicable, will be reconsented. The revised ICF must be submitted to the IRB/IEC for review and approval before its use.

7. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at multiple study sites. The Investigator at each study site will be responsible for ensuring that the study is conducted according to the signed Clinical Trial Agreement, the protocol, IRB/IEC requirements, and ICH GCP guidelines.

The Investigator will be responsible for the oversight of the site's conduct of the study, which will consist of completing all protocol assessments, maintaining the study file and the patient records, drug accountability, corresponding with the IRB/IEC, and completing the eCRF.

7.1 GENERATION OF STUDY RECORDS

Before activating each site, the Sponsor or its designated representative will verify the qualifications of each Investigator, inspect study site facilities, and inform the Investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. All information recorded in the eCRFs for this study must be consistent with the patient's source documentation.

During the course of the study, the Clinical Site Monitor will make study site visits to review protocol compliance, compare eCRFs and individual patient's medical records, assess drug accountability (in a blinded manner), and ensure that the study is being conducted according to pertinent regulatory requirements. All eCRFs will be verified with source documentation. The review of medical records will be performed in a manner that ensures patient confidentiality is maintained.

The Clinical Site Monitor will discuss instances of missing or uninterpretable data with the Investigator for resolution. Any changes to the study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

7.2 DATA QUALITY ASSURANCE

The Sponsor performs quality control and assurance checks on all of its clinical studies. Section 7.4 provides details regarding study monitoring procedures.

The study may be subject to audit by the Sponsor, its representatives, or regulatory authorities. In the event of an audit, the Investigator must agree to allow the Sponsor, representatives of the Sponsor, or the FDA or other regulatory agencies access to all study records.

7.3 ELECTRONIC CASE REPORT FORMS AND DATA MANAGEMENT

Study data will be recorded in the patient's source documentation and entered in eCRF in the Sponsor or designee's electronic data capture (EDC) system. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, all observations, and patient status. The Investigator is responsible for verifying that all data entries on the eCRFs are accurate and correct and ensuring that all data are entered in a timely manner, as soon as possible after the information is collected. An explanation should be provided for any missing data. The Investigator must provide through the EDC system his or her formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for each patient.

The Sponsor will retain the final eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disc or other electronic media will be placed in the Investigator's study file.

A record of screen failures and pretreatment failures will be maintained for patients who do not qualify for enrollment, including the reason for the failure.

7.4 STUDY MONITORING

The Sponsor performs quality control and assurance checks on all of its clinical studies. Before any patients are enrolled in the study, a representative of the Sponsor or its authorized designee will meet with the Investigator and his/her staff to review relevant and important study-related information including, but not limited to, the protocol, the Investigator's Brochure, the eCRFs and instructions for their completion using the EDC system, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs.

A Sponsor representative, the Clinical Site Monitor, will monitor the progress and conduct of the study by periodically conducting monitoring visits and by frequent communications (telephone, e-mail, letter, and fax) with the study sites. The site monitor will ensure that the study is conducted according to the protocol and regulatory requirements. During monitoring visits, the information recorded on the eCRFs will be verified against source documents. Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the Investigator should make all requested study-related records available for direct access.

All aspects of the study will be carefully monitored by the Sponsor or its designee for compliance with applicable government regulations with respect to GCP and current standard operating procedures.

8. STUDY SPONSORSHIP

8.1 INVESTIGATOR AND STUDY TERMINATION

The Sponsor may terminate Investigator participation at any institution for any reason. If participation is ended at the site by either the Sponsor or the Investigator, the Investigator must:

- Return all study medications and any study materials to the Sponsor
- In cases where the Investigator opts to self-terminate, provide a written statement describing why the study was terminated prematurely

The Sponsor may terminate the study in its entirety or at a specific center at any time for any reason, including but not limited to the following:

- Failure to enroll patients
- Protocol violations
- Inaccurate or incomplete data
- Unsafe or unethical practice
- Questionable safety of the study medication
- Suspected lack of efficacy of the study medication
- Administrative decision

8.2 REPORTING AND PUBLICATION

All data generated in this study will be the property of the Sponsor. Study report(s) will be prepared at the completion of the study.

Publication of the results by the Investigator will be subject to agreement between the Investigator and the Sponsor.

9. INVESTIGATOR OBLIGATIONS

9.1 PERFORMANCE

The Investigator must demonstrate reasonable efforts to obtain qualified patients for the study. The Sponsor may terminate the study with any Investigator for Investigator nonperformance or Investigator noncompliance.

9.2 USE OF INVESTIGATIONAL MATERIALS

The Investigator will acknowledge that the drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Investigator or subinvestigators. Study medication must be stored in a safe and secure temperature-monitored location. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. The study site must record the date the study medication was received and maintain a dispensing record in which to record each patient's use. A complete reconciliation of study medication will be performed at the site close-out visit with a final accountability report provided to the Sponsor as part of the site close-out report. Written instructions for return of all unused and reconciled study medication to an appropriate waste handler will be provided before the end of the study. No study medication may be destroyed by study site without prior written permission of the Sponsor.

9.3 RETENTION AND REVIEW OF RECORDS

Records and documents pertaining to the conduct of this study, including eCRFs, source documents, ICFs, laboratory test results, and medication inventory records, must be retained by the Investigator in accordance with locally applicable regulatory requirements; and, in any event, for a minimum period of 5 years and in accordance with the clinical site's contract for this study.

No study records shall be destroyed without notifying Sponsor and giving Sponsor the opportunity to take such study records or authorizing in writing the destruction of records after the required retention period.

If the Investigator retires, relocates, or otherwise withdraws from the responsibility of keeping the study records, custody must be transferred to another person (the Sponsor, IRB/IEC, or other

Investigator) who will accept the responsibility. The Sponsor must be notified of and agree to the change.

9.4 PATIENT CONFIDENTIALITY

All data collected in the context of this study will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations adopted by local jurisdictions applying to confidentiality of data. All patient records will be identified only by patient identification number. Patient names are not to be transmitted to the Sponsor or its authorized designee. The Investigator will keep a Master Patient List on which the patient identification number and the full name, address, and telephone number of each patient is listed.

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APPENDIX 1 PROHIBITED MEDICATIONS, SUPPLEMENTS, AND FOODS

Prohibited from the Run-in Visit (Day -14 to Day -17) through the duration of the study:

- Specific inhibitors of PDE5 including sildenafil, tadalafil, vardenafil
- All supplements for the treatment of erectile dysfunction
- Nonspecific inhibitors of PDE 5 including dipyridamole, theophylline
- Other sGC stimulators, including riociguat
- Nitrates including nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, sodium nitroprusside, amyl nitrate
- Other NO donors in any form, including beetroot
- P2Y12 inhibitors including prasugrel, clopidigrel
- Aspirin ≥325 mg/day
- Any anticoagulant medication
- [redacted]

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