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Statistical Analysis Plan for Interventional Studies

Sponsor Name: Cyclerion Therapeutics, Inc.

Protocol Number: C1701-202

Protocol 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

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Amendment #1: 08-Nov-2017
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Notice of Confidential and Proprietary Information:

Revision History

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0.1	17-Mar-2020	[redacted]	Initial Release Version
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0.3	11-May-2020	[redacted]	Final SAP, updated based on comments from Cyclerion
1.0	22-May-2020	[redacted]	Finalized SAP

I confirm that I have reviewed this document and agree with the content.

Approvals

[redacted]

Name, Title	Signature	Date (DD-Mmm-YYYY)
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Cyclerion Therapeutics, Inc. Approval

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[redacted] Sponsor Contact	[redacted]	26 may 2020

Table of Contents

1. Glossary of Abbreviations

Abbreviation	Description
AE	Adverse Event
ANCOVA	Analysis of Covariance
ASCQ-Me	Adult Sickle Cell Quality of Life Measurement Information System
ATC	Anatomical Therapeutic Chemical
BLQ	Below Assay's Limit of Quantification
BMI	Body Mass index
BP	Blood Pressure
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EOT	End of Treatment
EQ-5D-5L	Euro QOL 5-Dimension 5-Level
F/U	Follow UP
HU	Hydroxyurea
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IQR	Interquartile Range
ITT	Intent to Treat
IW-1701	olinciguat
LSM	Least-Squares Mean
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numerical Rating Scale
olinciguat	IW-1701

Abbreviation	Description
PCS	Physical Component Summary
PD	Pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
PRO	Patient-Reported Outcome
PROMIS	Patient-reported Outcomes Measurement Information System
PT	Preferred Term
QD	Once Daily
QTcF	QT Interval Corrected for Heart Rate using Fridericia's Formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCD	Sickle Cell Disease
SCD-SAF	Sickle Cell Disease – Symptom Assessment Form
SD	Standard Deviation
SEM	Standard Error of Mean
SF-12v2	Short-Form Health Survey 12, Version 2
SI	Standard International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures and Listings
VAS	Visual Analog Scale
VOC	Vaso-occlusive Crisis
WHO	World Health Organization

2. Purpose

This statistical analysis plan (SAP) describes the planned analysis of the safety, tolerability, efficacy and PK data from Study C1701-202, a randomized, placebo-controlled, Phase 2 study to evaluate the safety and pharmacodynamics of once-daily (QD) oral olinciguat (IW-1701) in participants with stable sickle cell disease (SCD). A detailed description of the planned tables, figures, and listings (TFLs) to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

Note: Throughout this SAP, reference to "IW-1701" is replaced by its international nonproprietary name (olinciguat), where possible.

The intent of this document is to provide additional detailed guidance for the planned statistical analyses of the safety, tolerability, efficacy and PK data as defined in the study protocol. Any changes to the protocol planned analyses must be agreed upon between Cyclerion [redacted] and documented under Section 11 (Changes from Analysis Planned in Protocol).

This SAP must be finalized prior to locking of the clinical database for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for the analyses presented in this study's CSR, along with the final version of the protocol, as applicable. This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between Cyclerion [redacted] and identified in the CSR.

2.1. Responsibilities

[redacted] perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings; the full population pharmacokinetic (PK) analysis will be provided in a separate PK analysis report which will be provided by a different vendor; only the PK plasma concentrations (see Section 9) will be summarized under this SAP.

2.2. Timings of Analyses

The final analyses of safety and pharmacodynamics is planned after all participants have either completed the final study visit or terminated early from the study and the data processing has been completed, and the study database has been locked.

3. Study Objectives

3.1. Study Objectives and Endpoints

Table 1 provides the study objectives and the corresponding endpoint(s) that will be summarized and analyzed to determine if the objective is met.

Table 1: Study objectives and corresponding endpoints

Objective	***Endpoint***
	Primary
The primary objective is to assess **the safety and tolerability** of oral, once-daily (QD) olinciguat when administered for approximately 12 weeks to participants aged 16 to 70 years with sickle cell disease (SCD).	Incidence (number and percentage of patients) and frequency (number of events) of treatment-emergent adverse events (TEAEs)
	Incidence of TEAEs by severity
	Incidence of study drug-related TEAEs
Exploratory Patient-reported Outcomes	
To evaluate the effect of oral, once-daily olinciguat on **symptoms of SCD, health-related quality of life,** and biomarkers when administered for approximately 12 weeks to participants aged 16 to 70 years with SCD	Change from baseline in Sickle Cell Disease – Symptom Assessment Form (SCD-SAF) total score at Weeks 4, 8, 12, and End of Treatment (EOT)
	Pain as measured on the 11-point numerical rating scale (NRS) by week and for the overall Treatment Period
	Percent change from baseline in 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
	Change from baseline in fatigue as measured on the 11-point NRS by week and for the overall Treatment Period
	Change from baseline ASCQ-Me pain impact score
Exploratory Pharmacodynamics	
To evaluate the effect of oral, once-daily olinciguat on symptoms of SCD, health-related quality of life, and **biomarkers** when administered for approximately 12 weeks to participants aged 16 to 70 years with SCD	Change from baseline in hemoglobin at Weeks 4, 8 and 12
	Proportion of patients with change from baseline in hemoglobin ≥1 g/dL at end of treatment
	Change from baseline in fetal hemoglobin at Weeks 4, 8 and 12
Exploratory Pharmacokinetics	
To evaluate the **pharmacokinetics (PK)** of oral, once-daily olinciguat when administered for approximately 12 weeks to participants aged 16 to 70 with SCD	Plasma concentrations of olinciguat at assessed timepoints

Note: Bolded parameters associate directly with corresponding endpoint(s).

3.2. Brief Description

This Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study with a 2-week single-blind Run-in Period will evaluate the safety and pharmacodynamics (PD) of oral olinciguat compared with placebo when administered QD for approximately 12 weeks in participants with SCD.

At the Screening Visit, participants will undergo preliminary procedures to determine their initial eligibility. At the Run-in Visit (which will occur at least 3 calendar days after the Screening Visit), eligible participants will then begin 14 to 17 days of single-blind placebo dosing and will begin recording their daily and weekly symptom assessments in an electronic diary (eDiary).

On Day 1 of the Treatment Period, participants who continue to be eligible will be randomized to double-blind study drug (QD olinciguat or placebo). Note that participants enrolled under protocol Amendment 3 or earlier were randomized differently than those randomized under Amendment 4 and later, as described below.

- Under Amendment 3 or earlier: Participants were randomly assigned in a 1:1:1:1 ratio to placebo, 2 mg olinciguat, 4 mg olinciguat, or 6 mg olinciguat (see Table 3)
- Under Amendment 4 and later: Participants were randomly assigned in a 3:1 ratio to 18 mg olinciguat or placebo (see Table 4)

On Day 1 and for each up-titration visit, participants must remain in the clinic at least 6 hours postdose and will be allowed to leave thereafter at the Investigator's discretion.

At all scheduled study visits, participants 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. In addition, participants will receive scheduled phone calls in between the scheduled visits to monitor TEAEs and concomitant medications and procedures. Throughout the Treatment Period, participants will continue completing the patient-reported outcome (PRO) questionnaires each day in their eDiary.

Beginning in March 2020, remote visits via phone call have been allowed to accommodate the impact of COVID-19 on study visits and participants' safety. The phone visits, when necessary, have been utilized to collect adverse event, concomitant medication, select vital sign timepoints, uptritration eligibility, and other relevant data.

As much as possible, participants will return to the clinic about 28 days after their last study drug dose for final Follow-up assessments.

3.3. Participant Selection

The study will select participants with SCD according to the inclusion/exclusion criteria listed in the relevant version of the protocol.

3.4. Determination of Sample Size

For this Phase 2 study, an overall sample size of approximately 88 participants is planned. Of these participants, approximately 40 are expected to be randomized under Protocol Amendment 3 or earlier and approximately 48 participants are expected to be randomized under Amendment 4 and later (see Section 3.5). The sample size was determined outside of statistical considerations and is considered reasonable based on precedent set by prior studies of similar nature and design.

3.5. Treatment Assignment

During the Run-in Period, all participants will receive placebo in a single-blind manner (Table 2).

Table 2. 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

The Treatment Period is double blind and placebo controlled. Participants will be randomized through central randomization based on the protocol applicable at the time. The computer-generated randomization schedule will be prepared by an independent statistician not otherwise associated with the conduct of the study.

Under Protocol Amendment 3 or earlier, eligible participants will be stratified by hydroxyurea (HU) use and randomly assigned in a 1:1:1:1 ratio to 6 mg olinciguat, 4 mg olinciguat, 2 mg olinciguat, or placebo at Randomization Visit on Day 1 (Table 3).

Table 3. Dose Regimen by Treatment Period Week for Participants Randomized Under Amendment 3 and Earlier

Randomized Dose Level	Week 1=half dose		Weeks 2 to 12=full dose *	
	Dosage	QD Dose	Dosage	QD Dose
6 mg IW-1701	3 mg IW-1701 daily	1 × 3-mg IW-1701 tablet	6 mg IW-1701 daily	2 × 3-mg IW-1701 tablet
4 mg IW-1701	2 mg IW-1701 daily	1 × 2-mg IW-1701 tablet	4 mg IW-1701 daily	2 × 2-mg IW-1701 tablet
2 mg IW-1701	1 mg IW-1701 daily	1 × 1-mg IW-1701 tablet	2 mg IW-1701 daily	2 × 1-mg IW-1701 tablet
Placebo	Placebo daily	1 × matching placebo tablet	placebo daily	2 × matching placebo tablet

Under Amendment 4 and later, eligible participants will be stratified by HU use and randomly assigned in a 3:1 ratio to 18 mg olinciguat or placebo (Table 4).

Table 4. Dose Regimen by Treatment Period Week for Participants Randomized Under Amendment 4 and Later

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

3.6. Blinding and Unblinding

Unblinding of a participant'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 participant. 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).

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 Data Monitoring Committee (DMC) as well as the Sponsor's Pharmacovigilance group will review summaries of adverse event (AE) data and may request unblinded safety data.

3.7. Administration of Study Medication

Throughout the Run-in and the Treatment Period, participants will be instructed to take study drug QD with water, in the morning, at approximately the same time each day, at least 1 hour before or 2 hours after food. Table 2, Table 3, and Table 4, respectively, summarize the dosing regimens during the Run-in Period (all protocol versions), the Treatment Period under Amendment 3 and earlier, and the Treatment Period under Amendment 4 and later.

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

3.8. Study Procedures and Flowchart

The study schedule from screening through follow-up under Protocol Amendment 3 is presented in Table 5a. (See respective study protocol for minor differences in the Schedule of Events for the original protocol through Amendment 2.) The study schedule under Protocol Amendments 4/5 is show in Table 5b.

Table 5a Schedule of Events (Amendment 3)

Study Period →	Screening	Run-in	Treatment									F/U
Contact Type →	Visit	Visit	Visit	Call	Visit	Calls	Visit	Call	Visit	Call	Visit	Visit
Visit Name →	Screening	Run-in*	Randomization	-	Week 1	-	Week 4	-	Week 8	-	Week 12/ EOT	F/U
Day (D) → Procedure ↓	Day -43 to -15	Day -17 to -14	Day 1	Day 2	Day 8 ±1	Wk1 V+1D, D15±1, D22±1	Day 29 ±3	D43 ±1	Day 57 ±7	D71 ±1	Day 85 -7/+4	Day 113 -3/+7
ICF signed	X											
I/E confirmation	X	predose	predose									
Demographics	X											
Medical history	X											
Prior & concomitant meds & procedures	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam (a)	X	predose	predose		predose		predose		predose		predose	X
Weight & height	W, H	W	W		W		W		W		W	W
12-lead ECG (b)	X		predose pd: 4h (±15m)		predose pd: 4h (±15m)						X	
AE evaluation	X	X	X	X	X	X	X	X	X	X	X	X
Drug screen (c)	X											
Pregnancy test (d)	X	predose	predose		predose		predose		predose		predose	X
Urinalysis sample	X		predose		predose		predose		predose		predose	X
Oral temperature and 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 (e)	X		pd: 6h (±15m)		predose pd: 6h (±15m)							
Seated-to-standing BP/pulse (f)	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	Run-in	Treatment									F/U
Contact Type →	Visit	Visit	Visit	Call	Visit	Calls	Visit	Call	Visit	Call	Visit	Visit
Visit Name →	Screening	Run-in*	Randomization	-	Week 1	-	Week 4	-	Week 8	-	Week 12/ EOT	F/U
Day (D) → Procedure ↓	Day -43 to -15	Day -17 to -14	Day 1	Day 2	Day 8 ±1	Wk1 V+1D, D15±1, D22±1	Day 29 ±3	D43 ±1	Day 57 ±7	D71 ±1	Day 85 -7/+4	Day 113 -3/+7
Clinical laboratory blood samples	X		predose		predose		predose		predose		predose	X
Genotyping blood sample (w/consent)			predose									
PK blood sample			predose pd: 1,2,4,5h (±15m)		predose pd: 1,2,4,5h (±15m)		predose pd: 2h (±1h)		predose pd: 2h (±1h)		predose pd: 2h (±1h)	X
Blood samples for biomarkers			predose pd: 5h (±15m)		predose						predose	X
Blood samples for platelet biomarkers			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		X	X				X		X			
In-clinic study drug dosing (g)		X	X		X		X		X		X	
Study drug return & MEMScap review			X		X (h)		X		X		X	
eDiary return											X	
Transfer: Cognitive debrief. patient contact info (i)											X	
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; EOT=end of treatment; 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); MEMS=Medication Event Monitoring System; 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; V=Visit; W=weight; Wk=Week

* *The Run-in Visit must occur at least 3 calendar days after the Screening Visit.*

a. For Treatment Period visits, physical exam may be symptom directed but must include the cardiovascular and respiratory systems.
b. 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.
c. Urine screen for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and propoxyphene.
d. For female patients, 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
e. Seated BP at the Screening Visit, 6 hours postdose at the Randomization Visit, and 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 will be single measurements obtained after the patient has been sitting quietly for ≥5 m.
f. 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.
g. 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.
h. At the Week 1 Visit, patients will bring the study drug bottles dispensed on Day 1 to the clinic. MEMScaps will be read and the patient will receive their Day 8 (±1) study drug dose in the clinic from the Day 1 bottles. The subject will continue to dose from the Day 1 bottles until they return for the Week 4 Visit. Patients who qualify will begin taking the up-titrated dose; see Section 3.5.4.2 for up-titration requirements.
i. *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.

Table 5b. Schedule of Events (Amendments 4 and 5)

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.

4. Analysis Populations

The following analysis populations are defined for this study. The different analysis populations will be listed.

4.1. Screened Population

The Screened Population will include all participants who sign the informed consent form and receive a participant identification number.

4.2. Single-blind Run-in Population

The Single-blind Run-in Population will include all participants who enter the single-blind Run-in period and receive 1 dose of single-blind study drug (placebo).

4.3. Safety Population

The Safety Population will include all randomized participants who receive at least 1 dose of double-blind study drug. Participants in this population will be evaluated according to the treatment they actually received.

4.4. Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will include all randomized participants. Participants in this population will be evaluated according to the treatment arm they were assigned at randomization.

4.5. Pharmacokinetic Population

The PK Population will include all randomized participants who receive at least 1 dose of olinciguat and have at least 1 evaluable postdose PK concentration assessment.

4.6. Evaluable Population

The Evaluable Population will include all randomized participants with no major protocol deviations (Section 4.7) who complete at least 6 weeks of double-blind study drug. Participants with unexpected plasma concentration values will be excluded (ie, participant who were randomized to placebo but have consistently measurable plasma concentrations of olinciguat and participants randomized to olinciguat with consistent BLQ concentration values). These participants will be identified by the pharmacokineticist at Cyclerion before database lock and unblinding.

4.7. Protocol Deviations

Protocol deviations and 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, participants 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% (including Single-blind Run-in Period and Double-blind Treatment Period).

In addition, the sub-categories ‘Related to COVID-19’ and ‘Unrelated to COVID-19’ will be collected to assess the impact of COVID-19 on the protocol deviation data.

The number and percentage of participants with major protocol deviations will be summarized by type of deviation and relationship to COVID-19 and by treatment arm for the ITT Population. All protocol deviations will be presented in a data listing.

5. General Aspects for Statistical Analysis

5.1. General Methods

All applicable data will be summarized by randomized treatment arm, unless specified otherwise. For summary tables, unless otherwise noted, participants who were randomized to placebo will be summarized as:

1) PBO1: participants who were randomized to placebo under Protocol Amendment 3 or earlier,

2) PBO2: participants who were randomized to placebo under Protocol Amendment 4 or later, and

3) Overall: participants who were randomized to placebo under any version of the protocol.

The participants who were randomized to olinciguat dosing regimens will be summarized as:

1) 2 mg: participants who were randomized to 2 mg olinciguat dosing regimen under Protocol Amendment 3 or earlier,
2) 4 mg: participants who were randomized to 4 mg olinciguat dosing regimen under Protocol Amendment 3 or earlier,
3) 6 mg: participants who were randomized to 6 mg olinciguat dosing regimen under Protocol Amendment 3 or earlier, and
4) 18 mg: participants who were randomized to 18 mg olinciguat dosing regimen under Protocol Amendment 4 or later

For safety analysis, the data will be summarized by treatment arm actually received.

In addition, data will be summarized by scheduled visit and/or time-point where appropriate. Unscheduled or repeat assessments will not be included in summary tables, but will be included in listings.

Continuous variables will be summarized using descriptive statistics, including the number of observations (n), mean, standard deviation (SD), median, minimum, maximum and interquartile range (IQR). Categorical variables will be summarized using frequencies and percentages. Unless otherwise specified, percentages will be based on the total number of non-missing values.

Unless otherwise specified, all confidence intervals (CIs) will be 2-sided with a confidence level of 95%. No adjustments will be made for multiplicity.

All statistical analyses will be performed using SAS Version 9.4 or later for Windows.

5.2. Key Definitions

5.2.1. Baseline

Unless other stated, baseline is defined as the last non-missing value measured before administration of randomized study drug on Day 1 of the Treatment Period.

5.2.2. Change from Baseline

Change from baseline will be calculated for the post-baseline assessment as:

Change from baseline = post-baseline value – baseline value

5.2.3. Study Day

"Study Day" represents the number of days relative to initiation of randomized study drug administration in the Treatment Period (ie, Day 1). If the assessment date is after the date of Day 1, the study day is calculated as (date of assessment - date of Day 1 + 1). If the assessment date is prior to the date of Day 1, the study day is calculated as (date of assessment – date of Day 1). There is no study day of 0.

5.2.4. TEAE, SAE, On-therapy SAE

TEAEs are defined as AEs with a reported started date/time that is on/after the first dose date/time the participant receives randomized treatment through 7 days after the last dose of study medication.

SAEs are AEs that result in death, are life-threatening, require hospitalization or prolongation of existing hospitalization, are persistent or result in significant disability/incapacity, result in a congenital anomaly/birth defect, or are important medical events (eg, events that may not result in death, are life threatening, or require hospitalization; such events may be considered serious when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent 1 of the outcomes listed in the wider SAE definition).

On-therapy SAEs are those SAEs that start after the participant has received the first dose of randomized study drug and through 28 days after the final study drug dose.

5.2.5. Vaso-occlusive Crisis (VOC)

An on-study sickle cell-related VOC 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.

5.3. Missing Data

For the purposes of assessing treatment emergence for AEs or classifying medications into prior/concomitant, the following algorithms will be used for partially missing dates. However, the assessment times (start date, stop date) without imputation will be presented in the listings.

For start dates of events:

- Only the year is reported: if the participant received the first dose of randomized study drug in the reported year, date of first dose of randomized study drug will be used as the start date; otherwise '1 January' will be used as the start date.

- Only the month and year are reported: if the participant received the first dose of randomized study drug in the reported month and year, the date of first dose of randomized study drug will be used as the start date; otherwise, the first day of the reported month and year will be used as the start date.

For stop dates of events:

- Only the year is reported: if the last visit is in the reported year, the date of last visit will be used as the stop date; otherwise, '31 December' will be used as the stop date.

- Only the month and year are reported: if the last visit is in the reported month and year, the date of last visit will be used as the stop date; otherwise, the last day of the reported month and year will be used as the stop date.

If an AE has the start date completely missing, this AE will be considered as treatment-emergent, unless the stop date is before first dose of randomized study drug.

If a medication has the stop date completely missing, this medication will be considered as ongoing and concomitant.

5.4. Visit Windows

The following algorithms will be used to map the analysis visit for the on-treatment analysis.

Analysis Visit	Mapping Window (Study Day)
Week 1	Day 7 to Day 14
Week 4	Day 15 to Day 36
Week 8	Day 37 to Day 64
Week 12	Day 65 to (last dosing date + 4 days)

End of Treatment (EOT) analysis visit is defined as the last measurement taken that is on-treatment. For all endpoints other than TEAEs, 'on-treatment' is defined as the first dosing date through 4 days after the end of treatment visit (the last dosing date + 4 days).

Last dosing date needs to be considered for all mappings. eg, if participant comes in for Week 8 but is more than 4 days out of last dosing, then that visit will not be mapped to Week 8 for analysis as the participant is not 'on-treatment'.

If multiple measures are mapped to same analysis visit, the last set of records will be included in the analysis. In listings, data will be presented with visit collected, analysis visit mapped, and analysis flag.

5.5. Pooling of Centers

No pooling of study centers is planned.

6. Demographic, Other Baseline Characteristics and Medication

6.1. Participant Disposition and Premature Discontinuations

The number and percent of participants will be summarized by treatment group (if applicable) and overall for:

- The Screened Population
- Reason for Screen Failures
- Single-blind Run-in Population
- Reason for Run-in Failures
- ITT Population
- Safety Population
- PK Population
- Evaluable Population
- Participants who completed the study treatment
- Reasons for the early discontinuation of study treatment
- Participants who completed the study
- Reasons for the early discontinuation of study

The treatment and study completion status as well as reason for any premature discontinuations will be listed. A listing for eligibility will be provided.

6.2. Demographic and Other Baseline Characteristics

Demographic parameters (eg, age, sex, race, ethnicity, weight, height, and body mass index [BMI, defined as weight in kg divided by height in meters squared], SCD genotype) will be summarized by treatment group for the Safety, ITT, and Evaluable Populations. In addition to the above demographic parameters, smoking status will be listed.

6.3. Sickle Cell Disease (SCD) History

SCD history will be listed and summarized by treatment group for the Safety Population. SCD history parameters include the time since SCD diagnosis (years), the type of SCD, number of vaso-occlusive crisis (VOCs) in the 12 months prior to the Screening Visit, the number of events (as defined in Eligibility Inclusion Criterion #6) requiring presentation to acute care clinic, the number of such events resulting in hospitalization, and the duration of current SCD treatment (months).

6.4. Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.0) or later.

The number and percentage of participants with medical histories in each system organ class (SOC) and preferred term (PT) will be summarized by treatment group for the Safety Population. The medical history summary table will be sorted by descending overall total of SOC and PT.

Medical history data will also be listed.

6.5. Medication and Procedure

Prior medications/procedures will be defined as medicines/procedures started or stopped prior to the date of first dose of double-blind study drug. Concomitant medications and procedures will be defined as medications/procedures started, continued, or stopped on or after the date of first dose of double-blind study drug. Any medication/procedure started after the date of last dose of study drug will not be considered concomitant for the purposes of analysis.

Medications will be coded according to Anatomical Therapeutic Chemical (ATC) class using the World Health Organization (WHO) Drug Dictionary, Version 201706 DDE (Enhanced) B2 or newer.

Both prior and concomitant medication use will be summarized separately by the number and percentage of participants receiving medication in each ATC level 4 and PT for each treatment group based on the ITT Population. Multiple medications used by a participant in the same ATC class or PT will only be counted once for each corresponding category. Listings for medications and procedures will also be produced and will include medications and procedures reported through the Follow-up Visit.

6.6. eDiary Compliance

The eDiary compliance will be calculated for each participant in the Safety Population and summarized by treatment group for the baseline (single blind run-in) and double-blind treatment periods, and weekly. A complete eDiary is defined as having responses to each of the daily eDiary questions.

$$eDiary\ Compliance\ = 100\ \times \frac{Number\ of\ Complete\ eDiary\ Days}{Number\ of\ Expected\ eDiary\ Days}$$

The eDiary compliance will be summarized as outlined in Table 6.

Table 6. eDiary Compliance

Parameter	Description	Variable Type
eDiary Compliance Baseline Double-blind Treatment Period --Week 1 --Week 2 --: --: --Week 12 Overall	Percent of completed eDiary days relative to number of days in reporting interval	Continuous
≥80% Compliance	Number of participants with ≥80% of completed eDiary days	Categorical

7. Safety Analysis

All safety analyses will be performed using the Safety Population. Safety will be assessed on the basis of AE, clinical laboratory data, vital signs, ECG, physical examinations.

The safety endpoints utilized to access the primary objective of the study, safety and tolerability, are defined in Section 3.1.

7.1. Study Drug Exposure and Compliance

Exposure to study drug, calculated as the number of days from the first dose taken post-randomization to the date of the last dose taken, inclusive, will be summarized as both categorical variable (based on different lengths) and numeric variable, by treatment group for the Safety Population. Patient years (defined as total treatment duration in days for a specific treatment group divided by 365.25) will be also derived for participants by treatment group.

The total number of tablets taken between specified visits and overall for the entire study will be calculated for each participant. Treatment compliance will be based on the number of tablets expected to be taken.

$$Compliance\ (\%) = 100 \times \frac{Number\ of\ Tablets\ Taken}{Number\ of\ Tablets\ Expected\ to\ be\ Taken}$$

The number of tablets taken will be calculated as (total number dispensed – total number lost – total number returned). If the number of tablets lost is missing or unknown, the number lost will be estimated as zero. Compliance will not be calculated if dispensed number or returned number is missing.

Percent compliance for study drug will be summarized by treatment group for each scheduled visit and overall for the Safety Population. Compliance rates will also be categorized as '<80%', '80%'-120%', and '>120%', and summarized by treatment group.

7.2. Adverse Events

AEs will be coded using the MedDRA Version 20.0 or later and will be classified by MedDRA SOC and PT.

AEs are collected from date of signed informed consent form (ICF) through the last Follow-up Visit. TEAEs, SAEs, and on-therapy SAEs are defined in Section 5.2.4. Pre-treatment AEs during Screening are defined as AEs started on/after Screening Visit and before the first dose of Run-in placebo. Pre-treatment AEs during Single-blind Run-in Period are defined as AEs started on/after the first dose of Run-in placebo and before the first dose of randomized study drug.

The number and percentage of participants who experience at least 1 TEAE as well as those who experience each specific SOC and PT will be presented by treatment group for the Safety Population. For presentation of AE incidence, AEs will be sorted by SOC, and within each SOC, by PT in the decreasing incidence of the last column of summary table, and then the column before it one by one. AEs will also be presented by severity (CTCAE v.4.03; Grade 1–Grade 5). For AEs that change severity ratings, the AE will be included only once in the summaries, under the maximum severity rating assigned by the Investigator. Additionally, TEAEs and SAEs occurring in the first, second, and fifth week of the double-

blind Treatment Period will be listed separately to distinguish among any effects of the initial dose (Week 1), the up-titrated dose (Week 2), and the further up-titrated dose (Week 5).

AEs occurring during Screening and the Single-blind Run-in Period will be summarized and listed separately.

More specifically, the following summary tables will be provided:

1. Overall Summary of TEAEs
2. Incidence of TEAEs by SOC and PT
3. Incidence of TEAEs by SOC, PT, and severity
4. Incidence of TEAEs by SOC, PT and relationship to double-blind study drug
5. Incidence of on-therapy SAEs by PT
6. Incidence of AEs leading to study drug discontinuation by PT
7. Incidence of pre-treatment AEs during Screening by SOC and PT (Screened Population)
8. Incidence of pre-treatment AEs during Single-blind Run-in Period by SOC and PT (Single-blind Run-in Population)
9. Incidence of adverse events of special interest (AESIs) by PT
10. Incidence of TEAEs by SOC, PT, and region (US vs. Lebanon)
11. Incidence of VOCs by PT
12. Summary of VOC events by location (eg, extremity) and outcome (eg, acute chest syndrome)

All AEs will be listed. In addition, list of all TEAEs and TEAEs occurring during the first, second, and fifth week of double-blind treatment period will be provided. Severe TEAEs (Grade ≥3 per CTCAE v.4.03 criteria), study drug-related TEAEs (those that are determined by the Investigator to be related to study treatment), SAEs, TEAEs leading to study drug discontinuation, AEs leading to death (if any), and AESIs will be presented in separate listings.

7.3. Laboratory Evaluations

Clinical laboratory parameters (chemistry, hematology, urinalysis) will be summarized as outlined in Table 7. Baseline is defined as the last non-missing measurement before administration of study treatment on Day 1 of the Double-blind Treatment Period. If there is more than 1 measurement for a laboratory parameter at a post-baseline time point, only the last measurement will be used. A listing of clinically significant clinical laboratory abnormalities will be presented. All lab data will be listed.

Table 7. Clinical Laboratory Summaries

Endpoint	Description	Timing	Summary Method
CTCAE v4.03 grading for laboratory values (Grades ≥3)	Summarized by laboratory parameter and CTCAE grade	First dose of study drug through last laboratory measure	Categorical summary
Descriptive	Summary of laboratory parameter (SI Units) at each timepoint measured plus change from baseline	Baseline, Week 1, Week 4, 8, 12 (EOT)	Continuous summary

CTCAE=Common Terminology Criteria for Adverse Events; SI=international system [of]; EOT=end of treatment.

7.4. Vital Signs

Vital signs (oxygen saturation, systolic and diastolic BP, orthostatic systolic and diastolic BP, pulse rate, orthostatic pulse rate, respiratory rate, and oral temperature) will be summarized as outlined in Table 9. Based on the criteria in Table 8, the number and percentage of participants who had observed values and changes from baseline of clinical interest in vital sign parameters will be presented by treatment group.

Table 8. Criteria for Values of Clinical Interest in Vital Signs

Parameter	Flag	Criteria[a]	
		Observed Value	Change From Baseline[b]
Seated systolic blood pressure, mmHg	High	≥180	Increase of ≥10%, ≥20%
	Low	≤90	Decrease of ≥10%, ≥20%
Seated diastolic blood pressure, mmHg	High	≥105	Increase of ≥10%, ≥20%
	Low	≤50	Decrease of ≥10%, ≥20%
Seated pulse rate, bpm	High	≥110	Increase of ≥10%, ≥20%
	Low	≤50	Decrease of ≥10%, ≥20%
Seated O_2 saturation, %	High	NA	NA
	Low	<85%	NA
Oral temperature, Cº	High	38º	NA
	Low	36º	NA
Respiratory rate, breaths per minute	High	18	NA
	Low	8	NA

NA=not applicable.
[a] A post baseline value is considered as clinical interest if it meets both the observed-value and the change-from-baseline criteria.
[b] Baseline is defined as the last non-missing measurement before administration of study treatment on Day 1 of the Double-blind Treatment Period

Table 9. Vital Signs Summaries

Endpoint	Description	Timing	Summary Method
Values of Clinical Interest Findings	Summarized by Vital Signs Measure. See Table 8. (Participants meeting observed value criteria at Baseline are excluded.)[1]	First dose of study drug through last Vital Signs measure	Categorical summary
Descriptive	• Summary Vital Sign measures at each timepoint measured • Change from baseline in trough measurements • Change from predose to each postdose measurement at each visit (where applicable)	Day 1, Week 1, Week 4, 8, 12 (EOT), F/U Visit	Continuous summary

EOT=end of treatment; F/U=follow-up
[1] Applies to Seated O_2 saturation, oral temperature, and respiratory rate only.

Orthostatic changes in systolic BP, diastolic BP, and pulse will be summarized for each treatment group. An orthostatic measurement is obtained by subtracting the seated measurement from the standing measurement.

The number and percentage of participants who meet the following criteria for changes of clinical interest at any postdose time point (including unscheduled assessments) will also be summarized by treatment group:

1. Orthostatic decrease in systolic BP of >20 mmHg from seated to standing
2. Orthostatic decrease in systolic BP of 10% and 20% from seated to standing
3. Orthostatic decrease in diastolic BP of >10 mmHg from seated to standing
4. Orthostatic decrease in diastolic BP of 10% and 20% from seated to standing
5. Orthostatic increase in pulse of >30 bpm from seated to standing
6. Orthostatic decrease in pulse of 10% and 20% from seated to standing

All vital sign data will be listed, including the flag for values of clinical interest.

7.5. ECG 12-Lead Electrocardiogram (ECG)

12-lead ECG measurements will be performed at the scheduled time points, including the heart rate (HR), QT interval, RR interval, PR interval, or QTcF – Fridericia's Correction Formula. ECG overall result will also be collected on the electronic case report form (eCRF). If QTc result is outside of normal range, perform in triplicate and calculate the average. If ECG result is clinically abnormal, repeat.

Descriptive statistics for ECG parameters and changes from the baseline (Day 1) values at Week 1 and the end of treatment (EOT) visit will be presented by treatment group for the Safety Population. Change from predose to postdose for ECG parameters will also be calculated for the Day 1, Week 1, and EOT visits and summarized by treatment group. For ECG triplicates, the mean will be presented as the participant's value at a given visit.

The number and percentage of participants with absolute QTcF intervals in the following categories will be tabulated by treatment group: 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 Week 1 and EOT.

The number and percentage of participants with absolute HR in the following categories will be tabulated by treatment group: <=50 bpm, 50 bpm< HR <110 bpm, and HR >=110 bpm. Shift tables will be presented comparing values between baseline and Week 1 and EOT.

The number and percentage of participants 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.

Additionally, the number and percentages of participants with a change from baseline in HR according to the following categories will be examined: HR increases by more than 10 bpm but not more than 30 bpm, and HR increases by more than 30 bpm. Additionally, the number and percent of participants with a change from baseline in HR corresponding to a 20% increase or more will be calculated.

All ECG data will be listed. In addition, a listing of all AEs for participants with a QTcF increase of more than 30 ms or an HR increase of more than 30 bpm will be provided.

7.6. Physical Examination and Weight

The physical examination data will be listed.

For weight, the number and percentage of participants with changes from baseline (defined as Table 10) of clinical interest will be summarized by treatment group for the Safety Population.

Table 10. Changes of Clinical Interest Criteria for Body Weight

Parameter	Flag	Change from Baseline
Weight, kg	High	Increase of ≥10%
	Low	Decrease of ≥10%

8. Pharmacodynamic (PD) Analyses

All PD analyses except the PRO analyses will be based on the Safety and Evaluable Populations. PRO analyses will be based on the ITT and Evaluable Populations. Listings will be provided for all PD-related data.

For the treatment comparisons by statistical modeling:

- comparisons between 18 mg olinciguat group vs. the matched placebo group (PBO2) enrolled under Protocol Amendments 4 and later
- comparisons between each olinciguat group (2 mg, 4 mg, 6 mg, and 18 mg) vs. the overall placebo group combined from all protocols

8.1. Hemodynamics

The hemodynamic parameters are listed here:

- Change from Day 1 baseline in seated systolic and diastolic blood pressures (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 (Day 1, Weeks 1, 4, 8, 12), change from predose to each postdose time point of the same visit for seated systolic BP, diastolic BP and pulse.

Details about BPs and pulse assessment are included in Section 7.4. An orthostatic measurement is derived by subtracting the seated measurement from the standing measurement.

Descriptive statistics will be tabulated for each hemodynamic parameter by treatment group. In addition, an analysis of covariance (ANCOVA) model will be fitted with change from baseline as dependent variable, treatment group, and stratification factor (HU use) as fixed effects, and corresponding baseline value as covariate, at each visit/time point. Pairwise contrasts will be used to compare each olinciguat group with the placebo group. Least-squares means (LSMs) for each treatment group, LSM differences between each olinciguat group and the placebo group, their corresponding 2-sided 95% CIs, and p-values will be presented. Example SAS code for ANCOVA model is shown below:

```
Proc mixed data = analysis_data;
  class stratum trt;
  model chg = base stratum trt;
  lsmeans trt/ cl diff;
run;
```

8.2. Vaso-occlusive Crisis (VOC)

8.2.1. Primary Analysis of Exploratory VOC Parameters

Sickle cell-related pain crisis events will be documented as ‘vaso-occlusive crises’ (VOCs) on the AE eCRF page throughout the duration of the trial and adjudicated by an independent adjudicator. Only

adjudicated events that are deemed VOCs will be utilized in the endpoints defined below. An on-study sickle cell-related VOC is defined in Section 5.2.5.

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 participant's medical condition) will also be considered VOCs, as well as subtypes of VOCs, for analysis purposes.

The exploratory VOC parameters are listed here:

- Time to first VOCs experienced during the Treatment Period, defined as (start date of VOC – the date of first dose of double-blind study drug + 1)
- Proportion of participants experiencing ≥1 VOC during the Treatment Period
- Annualized VOC rate during the Treatment Period, defined as 365* total number of events/ (last dose date – first dose date of double-blind study drug +1)

All 3 VOC parameters will be summarized by descriptive statistics by treatment group.

The time to first VOC will be summarized using Kaplan Meier method; the median event time (if appropriate) and 2-sided 95% CI for the median will be provided; 25% and 75% percentiles will also be presented. Additionally, the Kaplan Meier plots will be generated. For comparison between each olinciguat group and the corresponding placebo group, P-value will be generated from log-rank test.

Example SAS code for Kaplan Meier method is shown below:

```
Proc lifetest data=analysis_data;
  Time AVAL*CNSR(1);
  Strata trt;
Run;
```

For the proportion of participants experiencing ≥1 VOC (dichotomous endpoint), the proportions for each olinciguat treatment group and the corresponding placebo group will be compared using a Cochran-Mantel-Haenszel (CMH) test controlling for stratification factors (HU use). The difference in the proportions between each olinciguat group and the placebo group as well as the CMH estimates of odds ratio, risk difference, and p-values will be presented, along with the corresponding 2-sided 95% CIs.

Example SAS code for CMH model is listed as below:

```
Proc freq data=analysis_data;
    Tables stratum*trt*resp/ cmh alpha=0.05;
Run;
```

The annualized VOC rate will be analyzed using a stratified Wilcoxon rank sum test with HU use as the stratifying factor. The associated P-value will be reported.

8.2.2. Sensitivity Analysis of Annualized VOC Rate

In addition, the following sensitivity analysis will be conducted for annualized VOC rate, using Safety Population.

- Summary using descriptive statistics for participants enrolled under Protocol Amendment 4 or later, with PBO2, and 18 mg olinciguat (split into 6 mg, 12 mg, 18 mg groups based on the participant's last up-titration).

8.3. Biomarkers

8.3.1. Primary Analysis of Exploratory Biomarkers

Biomarker endpoints include the following:

- Change from baseline in hemoglobin (Hb) at Weeks 4, 8 and 12
- Proportion of patients with change from baseline in Hb >1 g/dL at end of treatment
- Change from baseline in fetal hemoglobin (HbF) at Weeks 4, 8 and 12

Blood and urine samples for assessments of PD effects will be collected according to the applicable event schedule in Table 5a and 5b.

For each available biomarker, the observed value and the change from baseline (if applicable) will be summarized using descriptive statistics by treatment group and applicable time point.

The biomarkers of interest include LDH, reticulocyte count, bilirubin, Hb, HbF, haptoglobin, cystatin-C, urinary albumin and creatinine ratio (UACR), soluble E-selectin, soluble P-selectin, L-selectin, platelet monocyte aggregation, VCAM and ICAM.

Specifically, the following key biomarker responders for Hb and HbF will be summarized for each available visit and EOT.

1. Proportion of participants with increase from baseline in Hb >1 g/dL
2. Proportion of participants with change from baseline in HbF >3% points
3. Proportion of participants with increased change from baseline in HbF and HbF >8%

For each of the key biomarkers (Hb and HbF), the observed value and the changes from baseline will be summarized by treatment group and available visit. In addition, ANCOVA model mentioned in Section 8.1 will be fitted to estimate the difference in change from baseline between each olinciguat group and the placebo group, for each available visit.

The proportion of biomarker responders specified above will be summarized by treatment group. In addition, a Cochran-Mantel-Haenszel (CMH) test (mentioned in Section 8.2) will be used to estimate the difference in the proportions for each olinciguat treatment group and the corresponding placebo group.

8.3.2. Sensitivity Analysis of Key Biomarkers

In addition, the following sensitivity analyses will be conducted for changes from baseline of Hb and HbF and proportions of biomarker responders specified above, using the Safety Population.

- Summary using descriptive statistics for participants enrolled under Protocol Amendment 4 or later, with PBO2, and 18 mg olinciguat (split into 6 mg, 12 mg, 18 mg groups based on the last uptitration).
- Mixed-effect model for repeated measures (MMRM) will be fitted with change from baseline as dependent variable, treatment group, visit, the interaction between treatment and visit and

stratification factor (HU use) as categorical variables, and corresponding baseline value as covariate. For each available visit, LSMs for each treatment group, LSM differences between each olinciguat group and the placebo group, their corresponding 2-sided 95% CIs, and p-values will be presented. An unstructured covariance matrix will be used to model the correlation among repeated measurements. MMRM models will use data available from the Weeks 1, 4, 8 and 12 visits.

8.4. Patient-reported Outcomes

8.4.1. Sickle Cell Disease – Symptom Assessment Form (SCD-SAF)

8.4.1.1. Primary Analysis of SCD-SAF

The SCD-SAF endpoints are listed here:

- Changes from baseline in SCD-SAF total score at Weeks 4, 8, 12, and EOT
- Pain as measured on the 11-point numerical rating scale (NRS) by week and for the overall Treatment Period
- Percent change from baseline in 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
- Change from baseline in fatigue as measured on the 11-point NRS by week and for the overall Treatment Period

The SCD-SAF will assess sickle cell-related symptoms, including an assessment of pain on an 11-point numerical rating scale (NRS) (0 [no symptom] to 10 [worst possible symptom]), using a daily eDiary by participants. Depending on the version of SCD-SAF used by the participant, 7 questions (Version 1) or 8 questions (Version 2) about the symptoms over the past 24 hours are asked, including the worst pain, the worst fatigue, the worst swelling, the worst numbness, the worst tingling (Version 2 only), the worst stiffness, shortness of breath, and difficulty concentrating. If 8-question SCD-SAF (Version 2) is used, SCD-SAF total score is the sum of the 8 sub-scores. If the 7-question SCD-SAF (Version 1) is used, SCD-SAF total score is the sum of the 7 sub-scores multiplied by (8/7). If any individual score is missing, the total score is set as missing. Individual scores include pain sub-score, fatigue sub-score, swelling sub-score, numbness sub-score, tingling sub-score, stiffness sub-score, shortness of breath sub-score, difficulty concentrating sub-score.

The baseline NRS will be determined based on the average of available daily NRS data during the 7 days prior to randomization. The weekly NRS scores are calculated as the average of available daily NRS scores for each week postdose (Week 1 = Day 1 to 7, Week 2 = Day 8 to 14…). The EOT NRS score is the last weekly NRS score collected after the first dosing date and through the last dosing date plus 4 days.

For each mean daily NRS score (total score, each individual score, subtotal score of pain + stiffness + fatigue), the observed value,the changes from baseline, and the percentage change from baseline will be summarized by treatment group and visit. In addition, ANCOVA model mentioned in Section 8.1 will be

fitted to estimate the difference in change from baseline/percent change from baseline of total score/sub-score between each olinciguat group and the placebo group, at each visit.

For the proportion of participants with daily pain response (defined as achieving at least a 30% reduction in average daily pain from baseline) at Week 12, the number and percentage of participants will be summarized by treatment group. Besides, a Cochran-Mantel-Haenszel (CMH) test (mentioned in Section 8.2) will be used to estimate the difference in the proportions for each olinciguat treatment group and the corresponding placebo group.

8.4.1.2. Sensitivity Analysis of SCD-SAF

In addition, the following sensitivity analyses will be conducted for SCD-SAF total score, individual scores for pain, stiffness and fatigue, and subtotal score of pain + stiffness + fatigue, using ITT Population.

1. Summary using descriptive statistics for participants enrolled under Protocol Amendment 4 or later, with PBO2, and 18 mg olinciguat (split into 6 mg, 12 mg, 18 mg groups based on the last uptitration)

2. MMRM mentioned in Section 8.3.2 will be fitted to estimate the differences in change from baseline/percent change from baseline of scores between each olinciguat group and the specified placebo group for each visit

8.4.2. Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me)

The ASCQ-Me endpoint is the change from baseline in ASCQ-Me subscale scores at Week 1, 4, 8, and 12.

The ASCQ-Me is a study visit questionnaire to assess the physical, social, and mental impact of SCD on adults in the past 7 days, 30 days, or 12 months. 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). Participants will complete all the subscales except the pain episodes subscales. Participants respond using verbal rating scales (eg, Never, Rarely, Sometimes, Often, Always).

For each subscale, there are five items; four out of five items need to be answered in order to compute score. The sub-scales are scored by summing the values for each response and using the conversion tables in Appendix A to obtain the score [1]. In the case that only 4 out of 5 items were completed, a score can be approximated by first summing up the 4 answered items and then multiplying by 1.25. 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.

For each ASCO-Me subscale score, the observed value and the changes from baseline will be summarized by treatment group and visit. In addition, ANCOVA model mentioned in Section 8.1 will be fitted to estimate the difference in change from baseline of subscale score between each olinciguat group and the placebo group, at each visit.

8.4.3. Patient-reported Outcomes Measurement Information System (PROMIS)

The PROMIS endpoint is the PROMIS fatigue score at Week 1, 4, 8, and 12.

The Patient-reported Outcomes Measurement Information System (PROMIS) Fatigue—Short Form 7a is a self-administered questionnaire at study visit that assesses the impact and experience of fatigue in the 7 days prior to the administration of the questionnaire. Participants respond to concepts such as 'Feel Tired', 'Extreme Exhaustion', 'Out of Energy', 'Limit at Work', 'Think Clearly', 'Bath or Shower', and 'Exercise' using a verbal rating scale (eg, Never, Rarely, Sometimes, Often, and Always).

The total raw score can be derived if there are no missing data. All questions must be answered to produce a valid score. The total raw score is derived by summing the values of the response to each question; and then the total raw score will be converted to the PROMIS fatigue score by using the conversion tables in Appendix B [2]. A higher PROMIS fatigue represents more of the concept being measured. A PROMIS fatigue of 60 is one SD worse than the average United States general population and a PROMIS fatigue of 40 is one SD better than average.

For PROMIS fatigue score, the observed value and the changes from baseline will be summarized by treatment group and visit. In addition, ANCOVA model mentioned in Section 8.1 will be fitted to estimate the difference in change from baseline of PROMIS fatigue score between each olinciguat group and the placebo group, at each visit.

8.4.4. Analgesic Use

The analgesic use endpoint is the number and percentage of days with analgesic use at Week 4, 8, and 12.

Participant will be asked to record use of pain medication (names of medications) using a daily eDiary by participants.

The baseline number (percentage) of days with analgesic use will be determined based on records during the 7 days prior to randomization. The weekly number (percentage) of days with analgesic use are calculated based on the records during each week postdose (Week 1 = Day 1 to 7, Week 2 = Day 8 to 14…). If the number of days with non-missing data per period is not 7, the weekly percentage of days with analgesic use will be derived based on the records with non-missing data; the weekly number of days with analgesic use will be normalized to a 7-day period (ie, 7 * weekly percentage of days with analgesic use).

For the number (percentage) of days with analgesic use, the observed value and the changes from baseline will be summarized using descriptive statistics by treatment group and visit. In addition, the proportion of participants with any analgesic use during the week will be summarized as a responder endpoint.

8.4.5. Work and School Absences

The work and school absence endpoint is the number of days of work/school missed due to SCD symptoms at Weeks 4, 8, and 12.

Participant will be asked at each study visit to record the number of days missed from school or work due to SCD symptoms.

For the number of days of work/school missed, the observed value and the changes from baseline will be summarized using descriptive statistics by treatment group and visit.

8.4.6. EuroQol 5-Dimension 5-Level (EQ-5D-5L) Questionnaire

The EQ-5D-5L endpoint is the EQ-5D-5L at Week 12.

The EQ-5D-5L questionnaire is a generic self-administered measure of health status, at scheduled study visits.

The first component consists of 5 questions assessing the following dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problem, slight problems, moderate problems, severe problems, and extreme problems. Responses to the 5 questions that define a health state will be converted to a utility score based on the country/region information.

The second component is a visual analog scale (VAS) asking participants to rate their health from 0 (worst imaginable health state) to 100 (best imaginable health state).

For the utility score/VAS score, the observed value and the changes from baseline will be summarized by treatment group and visit.

8.4.7. Short Form Health Survey (SF-12v2)

The SF-12v2 endpoint is the change from baseline in SF-12v2 at Week 12.

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 summary (PCS) and mental component summary (MCS) scores.

For PCS/MCS score, the observed value and the changes from baseline will be summarized by treatment group and visit.

8.4.8. Patient Global Impression of Severity (PGI-S)

The PGI-S is a single-item questionnaire that assesses impression of disease severity on a 5-point verbal rating scale. For question “Overall, how would you rate your SCD symptoms over the past 7 days”, 1 out of 5 answers (1=None, 2=Mild, 3=Moderate, 4=Severe, 5=Very severe) will be selected. Participants will complete PGI-S weekly using a study-specific eDiary.

For PGI-S numeric score, the observed value and the changes from baseline will be summarized using descriptive statistics by treatment group and visit. For PGI-S categorical result, the number (percentage) of participants with each category will summarized by treatment group at each visit.

8.4.9. Patient Global Impression of Change (PGI-C)

The PGI-C 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. For question “Since the start of the study, how would you describe your overall health status”, 1 out of 7 answers (1=Very Much Worse; 2=Much Worse; 3=Minimally Worse; 4=No Change; 5=Minimally Improved; 6=Much Improved; 7= Very Much Improved) will be selected. Participants will complete this questionnaire at Week 12.

Participant 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.

For PGI-C categorical results, the number (percentage) of participants with each category will summarized by treatment group at Week 12.

9. Pharmacokinetic (PK) Analysis

The PK blood sampling will be done at predose and postdose of the following visits: Day 1, Weeks 1, 4, 8, 12, and Follow-up.

The PK plasma concentration data will be summarized at each assessed time point for PK Population by olinciguat dose level using the following descriptive statistics: n, number and percentage of values that are below the assay's limit of quantification (BLQ), mean, SD, coefficient of variation (CV) (calculated as 100*SD/mean), minimum, median and maximum.

The BLQ values will be analyzed as 0 in the table summaries. If more than 50% of values are BLQ, then only n, BLQ, n (%), minimum, median and maximum will be reported.

The following conventions will be used for the presentation of the descriptive statistics of PK plasma concentrations:

Table 11. PK Reporting Precision

Statistics	**Degree of Precision**
Minimum, Maximum	3 significant digits
Mean, Median	4 significant digits
SD	5 significant digits
CV (%)	1 decimal point

The actual sampling time of PK blood sample collection and the corresponding plasma concentration data will be listed.

10. Interim and Data Monitoring Committee Analyses

No interim analyses were conducted for this study.

DMC analyses were planned and conducted, based on a separate DMC SAP.

11. Changes from Analysis Planned in Protocol

In Protocol Section 4.2.3 (patient-reported outcomes), both number and proportion of days of work/school missed due to SCD symptoms at Weeks 4, 8, 12 were included.

However, current SAP will summarize and analyze only the number (not proportion) of days of work/school missed due to SCD symptoms at Weeks 4, 8, 12. Since each week has 7 days, the calculated proportion of days of interest doesn't provide additional information.

12. Reference List

1. San Keller, Manshu Yang, Christian Evensen, Tamika Cowans. American Institutes for Research. ASCO-Me User's Manual, December 2017.
2. HealthMeasures. PROMIS Fatigue Score Manual. 28Feb2019.

13. Programming Considerations

13.1. General Considerations

- One SAS program can create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format (.rtf).
- Numbering of tables, figures, and listings (TFLs) will follow International Conference on Harmonization (ICH) E3 guidance.

13.2. Table, Listing, and Figure Format

13.2.1. General

- All TFLs will be produced in landscape format, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified.
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2. Headers

- All output should have the following header at the top left of each page:

  Cyclerion Therapeutics C1701-202
  Draft/Final Run
- All output should have Page n of N at the top or bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

13.2.3. Display Titles

- Each TFL is identified by the designation and a numeral. (i.e., Table 14.1.1). The title is centered. The analysis set is identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
(XX Analysis Set)

13.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of participants in the analysis set.
- The order of treatments in the tables and listings will be Placebo first in the case of placebo-controlled studies and Active comparators first in the case of active comparator trials, followed by a total column (if applicable).

13.2.5. Body of the Data Display

13.2.5.1. General Conventions

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified;
- Numbers containing fractional portions are decimal aligned.

13.2.5.2. Table Conventions

- Units will be included where available.
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter.
- If the categories are not ordered (eg, medical history, reasons for discontinuation), only those categories for which there is at least 1 participant represented in 1 or more groups are included.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values.

- P-values are output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Every p-value less than 0.001 will be presented as <0.001. If the p-value are less than 0.0001, then present as <0.0001. If the p-value is returned as >0.999, then present as >0.999.

- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of participants in the analysis set for the treatment group will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by “(cont)” at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

13.2.5.3. Listing Conventions

- Listings will be sorted for presentation in order of treatment groups as above, participant number, visit/collection day, and visit/collection time.

- Missing data are represented on participant listings as either a hyphen (“-”) with a corresponding footnote (“- = unknown or not evaluated”), or as “N/A”, with the footnote “N/A = not applicable”, whichever is appropriate.

- Dates are printed in SAS DATE9.format (“ddMMMyyyy”: 01JUL2000). Missing portions of dates are represented on participant listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the participant are output as “N/A”, unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available.

13.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.

- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.

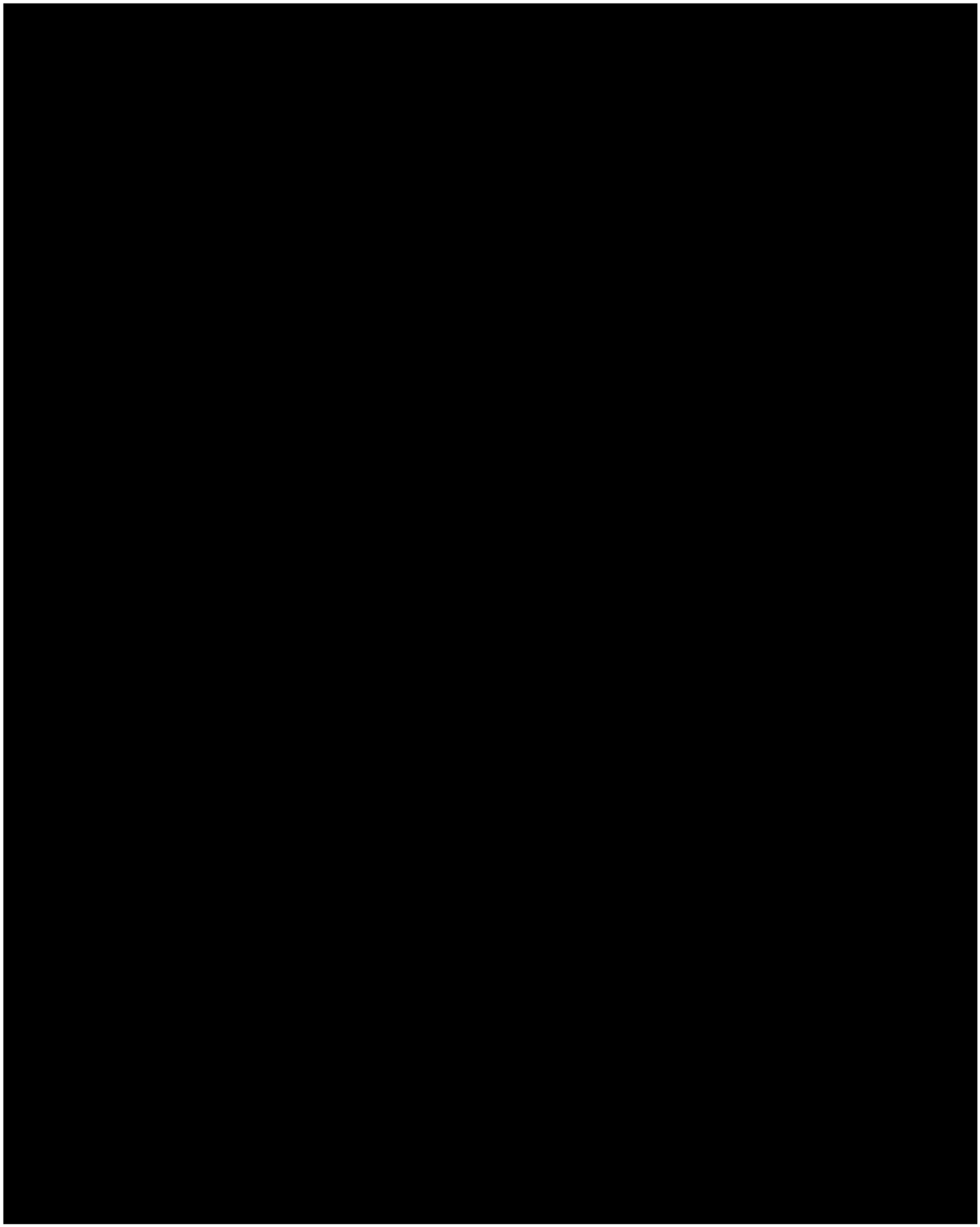
- Footnotes should always begin with “Note:” if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.

- Footnotes will be used sparingly and add value to the table, figure, or listing. If more than six lines of footnotes are planned, then a cover page is strongly recommended to be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.

- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., ‘Program : xxx.sas Table Generation: ddmmmyyyy).

14. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, and figures. [redacted] the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

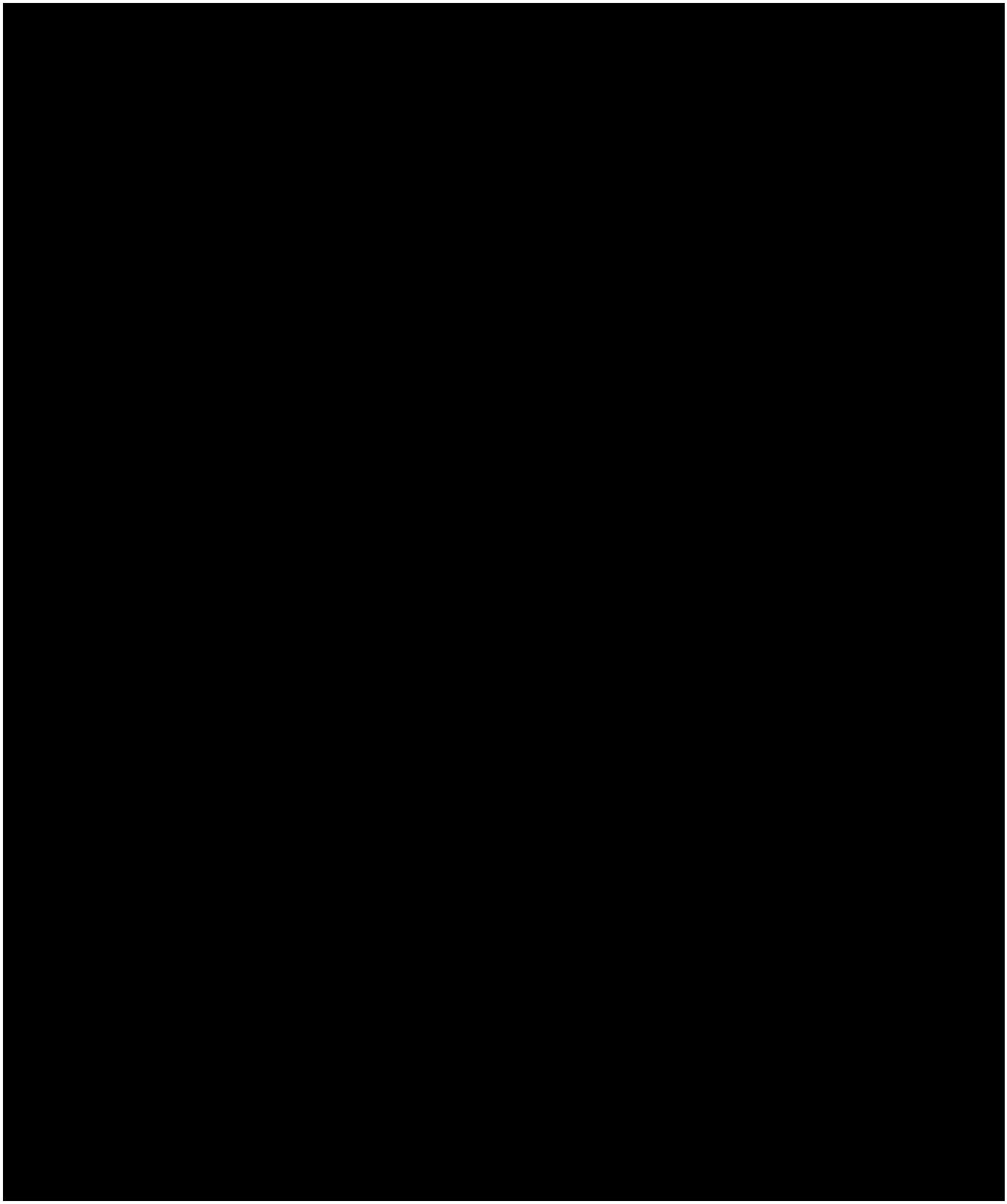


[redacted]

[redacted]

[redacted]

[redacted]



18. Appendices

Appendix A. Scoring Tables for Five Static Short Form of ASCQ-Me

Emotional Impact Short Form Conversion Table		
Raw Score	T-Score	SE[a]
5	26.8	4.5
6	30.8	3.5
7	33.3	3.1
8	35.3	2.9
9	37.0	2.8
10	38.5	2.7
11	39.9	2.6
12	41.2	2.6
13	42.5	2.6
14	43.7	2.6
15	44.9	2.6
16	46.2	2.7
17	47.4	2.7
18	48.7	2.8
19	50.1	2.8
20	51.5	3.0
21	53.3	3.3
22	55.2	3.6
23	57.3	3.8
24	60.5	4.4
25	65.6	5.8

[a]SE = Standard Error for T-Score

Social Functioning Impact Short Form Conversion Table		
Raw Score	T-Score	SE[a]
5	26.0	4.3
6	29.8	3.2
7	32.5	2.8
8	34.7	2.8
9	36.8	2.7
10	38.7	2.7
11	40.4	2.7
12	42.1	2.7
13	43.9	2.6
14	45.6	2.6
15	47.2	2.6
16	48.8	2.6
17	50.5	2.6
18	52.2	2.5
19	54.0	2.5
20	55.8	2.5
21	57.7	2.5
22	59.8	2.6
23	62.1	2.7
24	64.9	3.1
25	69.8	4.6

[a]SE = Standard Error for T-Score

Pain Short Form Conversion Table		
Raw Score	T-Score	SE[a]
5	24.8	3.9
6	28.8	2.5
7	31.0	2.2
8	33.0	2.2
9	34.9	2.2
10	36.7	2.2
11	38.3	2.2
12	39.9	2.1
13	41.5	2.1
14	43.0	2.1
15	44.4	2.1
16	45.7	2.1
17	47.1	2.1
18	48.5	2.0
19	49.9	2.0
20	51.2	2.0
21	52.5	2.0
22	54.0	2.1
23	55.8	2.3
24	58.0	2.8
25	63.8	5.2

[a]SE = Standard Error for T-Score

Stiffness Short Form Conversion Table		
Raw Score	T-Score	SE[a]
5	24.9	4.0
6	29.0	2.8
7	31.5	2.5
8	33.5	2.4
9	35.3	2.4
10	36.9	2.3
11	38.4	2.3
12	39.9	2.3
13	41.3	2.3
14	42.7	2.3
15	44.0	2.3
16	45.4	2.3
17	46.7	2.3
18	48.1	2.3
19	49.5	2.3
20	51.0	2.5
21	52.7	2.7
22	54.7	2.9
23	57.0	3.3
24	59.9	3.8
25	65.4	5.4

[a]SE = Standard Error for T-Score

Sleep Short Form Conversion Table		
Raw Score	**T-Score**	**SE[a]**
5	27.9	4.4
6	32.3	3.1
7	35.1	2.7
8	37.3	2.6
9	39.5	2.6
10	41.4	2.6
11	43.2	2.6
12	45.0	2.6
13	46.7	2.5
14	48.2	2.5
15	49.7	2.4
16	51.1	2.4
17	52.5	2.4
18	53.9	2.4
19	55.3	2.4
20	56.7	2.4
21	58.2	2.5
22	59.9	2.7
23	61.9	3.0
24	64.4	3.4
25	69.1	4.8

[a]SE = Standard Error for T-Score

Appendix B Scoring Table for PROMIS Fatigue – Short Form 7a

Fatigue 7a - Adult v1.0		
Short Form Conversion Table		
Raw Score	T-score	SE*
7	29.4	5.3
8	33.4	4.8
9	36.9	4.3
10	39.6	4.0
11	41.9	3.8
12	43.9	3.5
13	45.8	3.3
14	47.6	3.2
15	49.2	3.1
16	50.8	3.0
17	52.2	3.0
18	53.7	3.0
19	55.1	3.0
20	56.4	2.9
21	57.8	2.9
22	59.2	2.9
23	60.6	2.9
24	62.0	2.9
25	63.4	2.9
26	64.8	2.9
27	66.3	2.9
28	67.8	2.9
29	69.4	2.9
30	71.1	3.0
31	72.9	3.0
32	74.8	3.1
33	77.1	3.3
34	79.8	3.6
35	83.2	4.1

*SE = Standard Error on T-score metric